Cyclizations of *N*-Acyliminium Ions

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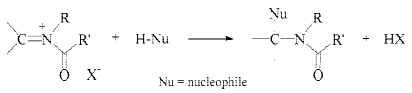
1. Introduction

Iminium ions are important, reactive species in organic synthesis for the construction of carbon−carbon and carbon−heteroatom bonds. Indeed, the well-known Mannich[1−5] and Pictet−Spengler[6−10] reactions, which have played a major role in organic chemistry for nearly 100 years, make effective use of electrophilic iminium ions. Generally speaking, these chemical processes are α-aminoalkylation reactions with the iminium ion serving as a defining reactive element. The classical Pictet−Spengler reaction is actually a subtype of the Mannich reaction involving a cyclization process, such that it represents an intramolecular α-aminoalkylation.

A further classification of iminium ion-based chemistry entails iminium species in which the nitrogen atom is acylated. Owing to the electron-attracting properties of the carbonyl group on nitrogen, the iminium carbon is now more electron-deficient, which causes such *N*-acyliminium ions to be much more reactive as electrophiles than simple *N*-alkyliminium ions. This favorable situation has spawned a large, separate area of versatile electrophilic chemistry known as α-amidoalkylation reactions, which are expressed generically in eq 1.[11−19] Here, too, the



(1)

subtype involving cyclization, i.e., the intramolecular reaction of *N*-acyliminium ions, has received considerable attention in organic chemistry, particularly with respect to the synthesis of alkaloid natural products.[15−19] Fortunately, nucleophiles that are relatively unreactive in the intramolecular Mannich

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reaction, such as unactivated benzenoids, participate effectively in cyclizations with *N*-acyliminum species.

Electron-attracting substituents other than *N*-acyl, such as *N*-sulfonyl, can also be employed in analogues of *N*-acyliminium ion reactions. However, this review will concentrate on cyclizations of the *N*-acyl type, encompassing groups such as alkanoyl, aroyl, carbalkoxy, and *N*,*N*-dialkylcarbamyl, with limited coverage of sulfonyl groups. Most significantly, this review will focus on intramolecular reactions of *N*-acyliminium ions that result in the formation of new carbon−carbon bonds, rather than new carbon−heteroatom bonds. Although β-lactam synthesis based on the cyclocondensation of imines with acid halides,

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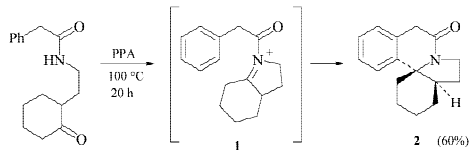
ketenes, or their equivalents can be viewed mechanistically as an *N*-acyliminium ion cyclization,[20] this process will receive just limited attention. On the other hand, we will cover the related cyclocondensation of imines with cyclic carboxylic anhydrides, which yields γ- and δ-lactams, in considerable detail. Certain specialized reaction types that potentially represent *N*-acyliminium ion cyclizations will not be addressed, namely: (1) intermolecular [4 + 2] polar cycloadditions of *N*-acyliminium ions (e.g., $[CH_2{=}N(R')C(O)R]^+$ + alkenes → 5,6-dihydro-1,3-oxazines), (2) intramolecular electrophile-induced [4 + 2] cycloadditions of *N*-acylimines (e.g., indolo-2,3-quinodimethide cycloaddition), and (3) Biginelli condensations (e.g., ArCHO + $R''CH_2C(O)CH_2CO_2R'$ + $H_2NC(O)NR_2$ → dihydropyrimidin-2-ones). Exclusion of these reaction classes is predicated on the fact that their cyclization step does not depend directly on an *N*-acyliminium ion. Additionally, this review will not deal with cyclizations of species considered to be vinylogous *N*-acyliminium ions, i.e., species with a carbon−carbon double bond conjugating an acyl group to nitrogen. Under these constraints on content, we intend to provide comprehensive coverage of *N*-acyliminium ion cyclizations over the entire course of history.[15−19] Overall, the text portion of this review will discuss the pertinent literature through 2000, with selective coverage of information published in 2001−2002. However, the tabular portion will cover all of the pertinent literature through most of 2002 comprehensively (see section 5, Comprehensive Tabular Survey of Reactions).

The earliest work on *N*-acyliminium ion cyclizations, in the 1950s, principally dealt with the synthesis of isoquinoline and indole alkaloids.[21−34] A key representative of the applications from this era is the cyclization from Belleau's erythrinane synthesis (eq 2), which afforded spirocyclic lactam **2** via acyliminium ion **1**.[21] In a subsequent paper,[23] it was suggested



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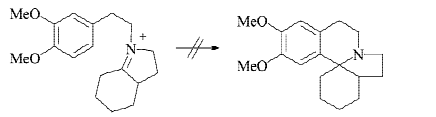
that, whereas the Pictet−Spengler approach to tetrahydroisoquinolines is limited in scope because of its sensitivity to minor structural changes around the carbonyl or aromatic groups, the *N*-acyliminium variant should, by contrast, offer tremendous potential because of the expected enhancement of electrophilic reactivity. A notable illustration of this viewpoint derives from the failure of iminium ion **3** to cyclize under "various conditions" (eq 3) compared to the successful *N*-acyliminium ion cyclization of **4** to **5** (eq 4).[23] In the 1960s through the 1980s, several



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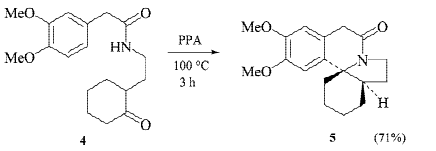

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laboratories exploited *N*-acyliminium ion cyclizations, especially for the synthesis of natural products.[15−19] This period also witnessed a spate of studies on diverse reactions, particularly those involving alkene and alkyne nucleophiles, thus spurring this field tremendously. The milestones of this chemistry have been presented in several review articles.[15−19] It is noteworthy that Belleau's early proposal[23] about the potential advantages of using *N*-acyliminium electrophiles presaged a major advance in ring formation over the next 35 years—namely, *N*-acyliminium ion cyclizations. This method has become a very effective synthetic tool in the organic chemists' armamentarium.

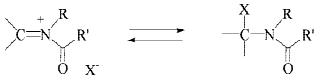
2. Mechanism and Stereochemistry

2.1. Reactive Species

N-Acyliminium ions can be generated as discrete salts, paired with non-nucleophilic anions,[15,35−40] although this is a relatively rare undertaking restricted to physicochemical studies. In synthetic transformations, the reactive species are almost exclusively produced in situ during the course of the desired reaction by a variety of useful techniques, which will be addressed in section 3, Scope and Limitations.

An *N*-acyliminium ion is most likely not generated stoichiometrically in the course of a reaction, as it

can exist in equilibrium with a covalent adduct (eq 5). The proportion of the ionic form and the covalent



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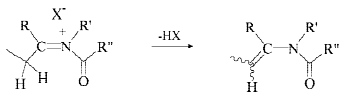
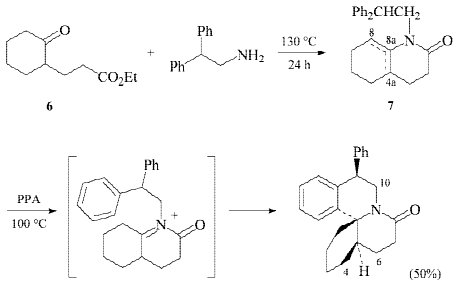
form may vary significantly depending on the nature of the anion and on experimental conditions. For example, the adducts formed from the treatment of benzaldimines with simple acid chlorides are substantially comprised of aryl α-chloro amides, rather than *N*-acyliminium salts.[41,42] Indeed, in their studies of the reaction of α-alkoxy carbamates with Lewis acids, Yamamoto et al. not only identified intermediate *N*-acyliminium ions in solution, but also characterized this type of equilibrium.[36]

N-Acyliminium ions, as carbocationic species, can suffer loss of a proton in an elimination process to yield an enamide (eq 6). The facility of enamide



(6)

generation from *N*-acyliminium ions will depend on the acidic reagent and the solvent, as well as the substrate structure.[43] Cyclic enamides can accumulate in *N*-acyliminium cyclizations that are relatively sluggish, because of a less reactive nucleophile or steric encumbrance. In many instances, especially under protic acid conditions, this side reaction can be easily reversed. This point is demonstrated by the fact that enamides serve in many situations as *N*-acyliminium ion precursors in cyclization reactions (see Scope and Limitations). For example, enamide **7** (a mixture of 4a,8a and 8,8a olefin isomers from keto ester **6**[44] and 2,2-diphenylethylamine) cleanly cyclizes to **8** with polyphosphoric acid (eq 7).[45] How-



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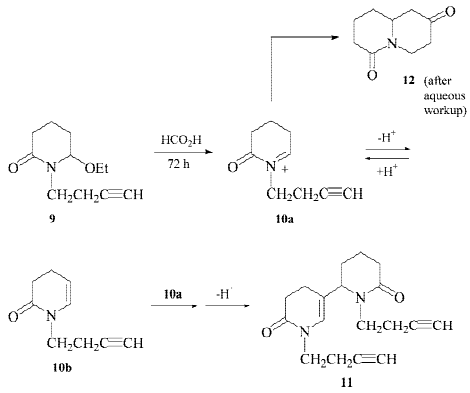
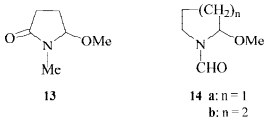
ever, effective reprotonation of an enamide in an *N*-acyliminium ion cyclization is not guaranteed, and other side reactions may then ensue. The problem of enamide protonation has arisen in cyclizations involving heteroatom-containing cyclic *N*-acyliminium ions, although it can be obviated by blocking elimination with *gem*-dimethyl substituents (see Scope and Limitations). In the context of side reactions, an enamide generated in situ can behave as a nucleophilic component, thereby combining with its *N*-acyliminium ion cognate to yield coupled, dimeric side products,[45] as exemplified in the reaction of **9** with formic acid (eq 8).[46] Substrate **9** affords dimer **11**,



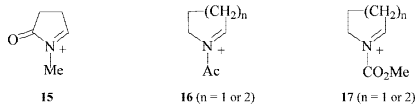
(8)

from reaction of ion **10a** and enamide **10b**, along with the expected quinolizidine **12** in a 1:5 ratio at a concentration of ca. 0.15 M. However, **12** is obtained exclusively in 89% yield under more dilute conditions (ca. 0.01 M). In general, this dimerization should pose a problem in *N*-acyliminium ion cyclizations only when the nucleophilic partner is not sufficiently reactive, such as with the acetylene group here, or when unfavorable stereoelectronic factors exist, such as in the formation of a medium-sized ring.[15−19]

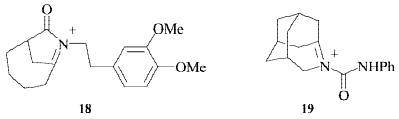
There is only limited information on the relative reactivity of different *N*-acyliminium ions. The intermolecular reaction between 1,3,5-trimethoxybenzene with four cyclic methoxy amides, promoted by aluminum(III) chloride, provides relative reactivity data that show an inverse correlation with the stability of the *N*-acyliminium ions. Thus, the rate-determining process here appears to be generation of the acyliminium species, rather than electrophilic substitution.[15,47] The five-membered-ring endocyclic amide **13** reacts more slowly than the exocyclic amide **14a** (by 7-fold), and the five-membered-ring exocyclic



amide **14a** reacts more slowly than the six-membered-ring exocyclic amide **14b** (by 4-fold), but these rate differences are not very dramatic, as they reside within 1 order of magnitude. *N*-Acyliminium ions bearing an exocyclic urethane exhibit comparatively high reactivity. For a set of cyclic *N*-acyliminium ions undergoing addition of allyltrimethylsilane in the gas phase, the relative electrophilic reactivity is **15** < **16** ≪ **17**.[48] This pattern was confirmed in an intramo-



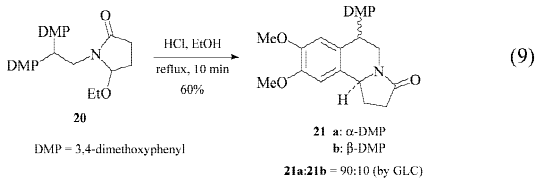
lecular competition study where an *N*-acyliminium ion with an exocyclic urethane was found to be much more reactive than one with an endocyclic amide.[49] Perhaps the most reactive *N*-acyliminium ions known are those with a bridgehead carbocation in a polycyclic system, such as **18**[50] and **19**,[51] since stabilization of the cation by the amide nitrogen is stereoelectronically disfavored according to Bredt's rule.



18 **19**

2.2. Kinetic and Thermodynamic Control

The products from *N*-acyliminium ion cyclizations are normally stable under the conditions of their formation. For instance, while certain products from the reaction of *N*-alkyliminium ions with alkenes can suffer Grob fragmentation, the corresponding products from *N*-acyliminium−olefin cyclizations are not susceptible to fragmentation.[15] Additionally, there is evidence for kinetic control in *N*-acyliminium cyclizations of benzenoid nucleophiles. Ring closures with phenyl and 3,4-dimethoxyphenyl (DMP) groups are devoid of stereochemical equilibration, as determined by a constant isomer ratio during the time course of cyclization and/or by the failure of the products to equilibrate.[45] For example, the reaction conditions used to cyclize **20** to **21a** and **21b** do not interconvert the products (eq 9).[45]

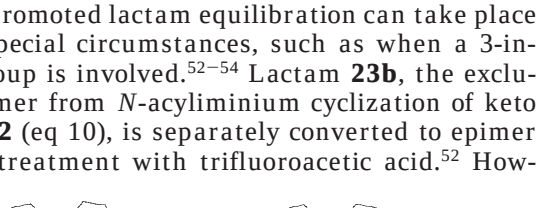


20 DMP = 3,4-dimethoxyphenyl

HCl, EtOH; reflux, 10 min; 60%

21 **a**: α-DMP; **b**: β-DMP; **21a**:**21b** = 90:10 (by GLC) (9)

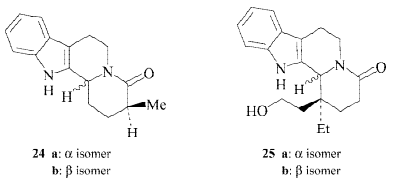
Acid-promoted lactam equilibration can take place under special circumstances, such as when a 3-indolyl group is involved.[52−54] Lactam **23b**, the exclusive isomer from *N*-acyliminium cyclization of keto amide **22** (eq 10), is separately converted to epimer **23a** on treatment with trifluoroacetic acid.[52] However, this equilibration requires harsher acidic conditions (CF_3CO_2H, >15 h, room temperature) than the cyclization of **22** (1% aqueous CF_3CO_2H, room temperature).[52] This process can proceed with even greater facility, such as with lactams **24a** and **24b**, which independently equilibrate to a 70:30 mixture with trifluoroacetic acid in 2 h at room temperature, or in 5 min at reflux.[53] Lewis acidic conditions also qualify, as in the independent equilibration of lactams **25a** and **25b** to a 1:1 mixture with boron trifluoride etherate (35−40 °C, 10 h).[54] The mechanism for lactam interchange appears to be an S_N1-like heterolytic cleavage of the carbon−nitrogen bond at the ring junction, rather than a reverse *N*-acyliminium cyclization.[53,55] Fortunately, in general practice *N*-acyliminium ion cyclizations of such π-rich heterocycles are not plagued by equilibration, probably because of the mild conditions employed and the rapidity of ring closure. To illustrate this point, there is no equilibration in the highly stereoselective, rapid cyclization of **26** to **27a** and **27b** (**a**/**b** = 92:8) with ethanolic methanesulfonic acid at room temperature.[45]



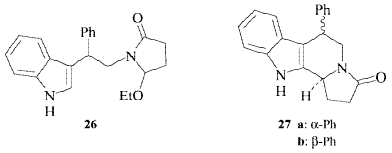
22

CF_3CO_2H; 1,4-dioxane; 24 h (10)

23 **a**: α-Me (0%); **b**: β-Me (70%)



24 **a**: α isomer; **b**: β isomer **25** **a**: α isomer; **b**: β isomer



26 **27** **a**: α-Ph; **b**: β-Ph

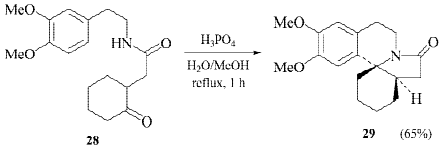
In summary, *N*-acyliminium ion cyclizations are expected to proceed under kinetic control. However, one might exercise caution in interpreting results from reactions that are conducted with π-rich heterocyclic nucleophiles under strongly acidic conditions at elevated temperatures.

2.3. Stereochemistry of Cyclizations and Mechanistic Implications

The stereochemical course of *N*-acyliminium ion cyclizations has received considerable attention over the years amidst various synthetic applications, and many types of reactions afford excellent stereoselectivity. Indeed, stereochemical control has become a hallmark for *N*-acyliminium ion cyclizations of diverse substrates containing aromatic, heterocyclic, alkene, alkyne, and keto/enol nucleophiles.[15−19] The favorable results commonly derive from straightforward stereoelectronic factors, similar to those in related cationic π-cyclizations.[56−58] Salient control elements are (1) steric approach control of the nucleophile to the iminium species, (2) steric interactions involving substituents, and, if pertinent, (3) steric interactions in the addition of nucleophiles to the new cyclic carbocation. This section will highlight key features associated with effective stereocontrol and elaborate on aspects of the reaction mechanism.

2.3.1. Benzenoid and Heterocyclic Nucleophiles

The synthesis of *Erythrina* alkaloids has served as an important arena for stereochemical observations. The "Belleau-type" *N*-acyliminium ion cyclizations in eqs 2 and 4 occur with sole formation of the *cis*-fused perhydroindole system.[23] This stereochemical outcome can be explained by steric effects that arise in the orthogonal approach of the π orbital of the arene nucleophile to the plane of the iminium ion.[23] The alternative "Mondon-type" cyclization, which has a different location of the amide carbonyl (e.g., as in **28**), is also completely stereoselective for the *cis*-fused isomer, such as **29** (eq 11),[26,27,32] and this pattern is

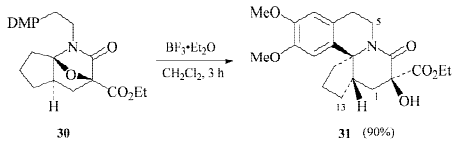


28

H_3PO_4; H_2O/MeOH; reflux, 1 h (11)

29 (65%)

general for a diversity of substrates.[27,32,33,45,59−88] The transformation of *N*-acyliminium ion precursor **30** exclusively to **31** illustrates this point in a more elaborate system (eq 12).[83,86] The stereocontrol here derives from preferential addition of the arene nucleophile to the sterically less hindered face of the *N*-acyliminium ion.



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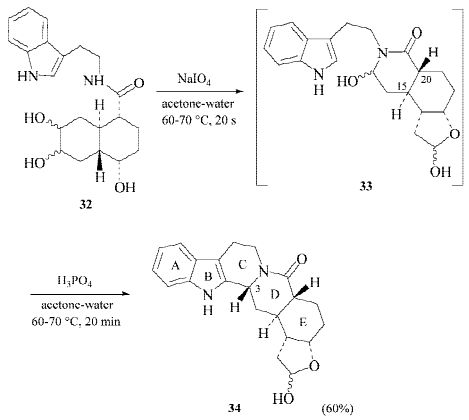
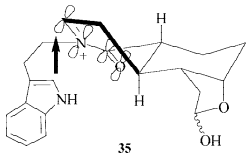
A noteworthy, diverse platform for *N*-acyliminium cyclizations of arene π-nucleophiles is found in the reactions of indoles. A classical application exists in an early total synthesis of (±)-yohimbine (eq 13).[31,89]

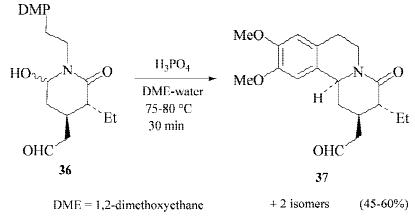


(13)

N-Acyliminium ion precursor **33**, a trapped dialdehyde from sodium metaperiodate oxidation of **32**, reacts with phosphoric acid to yield polycyclic lactam **34** (pseudoyohimbine configuration) in 60% yield with high stereoselectivity. This stereochemical outcome can be explained on the basis of preferential addition of the indole to the electrophilic carbocation center from a pseudoaxial direction in a conformationally constrained *trans*-decalin array, as depicted in **35**.

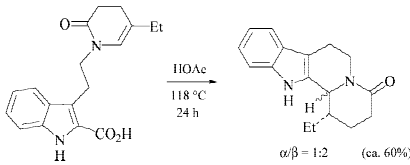


However, such stereochemical homogeneity may not arise consistently. For example, in an analogous cyclization en route to emetine, **36** leads to a mixture of three stereoisomers, including the corresponding **37** (eq 14).[90] Perhaps the difference in outcomes may relate to the greater reactivity of an indole group[91] compared to a dimethoxyphenyl group.



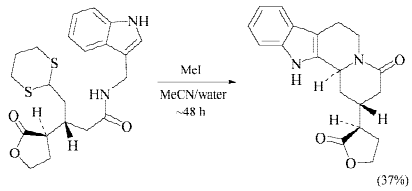
(14)

The *N*-acyliminium cyclization has been effective in the synthesis of a wide range of indole alkaloids.[15,19] In general, a tryptamine unit is condensed with a keto or aldehydo carboxylic acid derivative to give an *N*-acyliminium ion precursor that cyclizes under acidic conditions. However, there is only modest stereoselectivity in numerous syntheses, such as those of vincamine,[92−95] dihydrocleavamines,[96] quebrachamine,[51,97−99] eburnamonine,[51,99−102] and antirhine.[103] These inauspicious results could be associated with several factors: (1) an absence of steric distinction between substituents on a key stereogenic center, (2) location of the stereogenic center relative to the newly formed bond(s), (3) equilibration of product diastereomers,[52−54,99] or (4) excessive conformational flexibility. For example, a single stereogenic center adjacent (α) to the carbocation center that is generated is not conducive to good stereocontrol (e.g., eq 15[93]),[54,92,93,99−102] although certain structural con-



(15)

straints can alter this situation (eq 10).[52] In some cases a β stereogenic center fosters good stereocontrol (e.g., eq 16[105]),[104−106] whereas in others it does not (e.g., eq 17[103]).[103,107] Nevertheless, highly stereoselective *N*-acyliminium cyclizations are integral steps in the syntheses of inter alia roxburghin D,[52] eburnamonine,[100] quebrachamine,[104] antirhines,[105,106] vindorosine,[108] vindoline,[109] 20-desethylvincadifformine,[110] and geissoschizine.[111]



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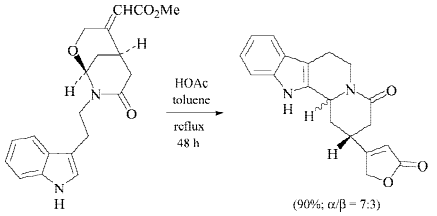
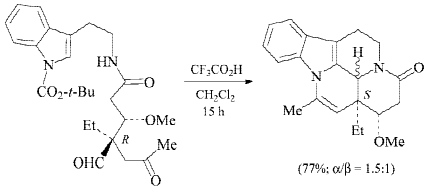


(17)

In a formal total synthesis of (+)-vincamine, three new rings are created in the *N*-acyliminium ion cyclization, but the reaction offers just a 1.5:1 ratio of isomers (eq 18).[95] However, in the analogous cyclization of **38**, an isomer ratio of 18:1 is obtained (eq 19; 7:1 at 20 °C).[100] This high stereoselectivity may originate in an electronic effect of the π-bond of the vinyl group, perhaps via a $\pi-\pi$ interaction with the indole.[100] In general, such indole-based cyclizations with substituents on the stereogenic center α to the carbocation in a six-membered-ring *N*-acyliminium ion deliver marginal stereoselectivities, in the area of 1:1.[53,92,93,99−102]



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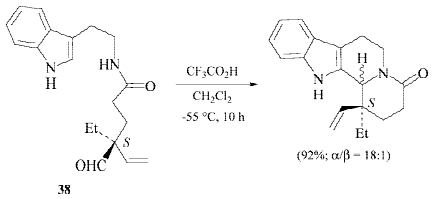
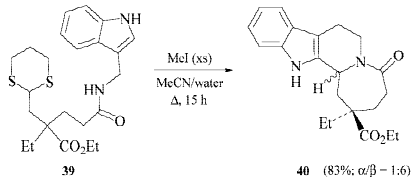


(19)

38

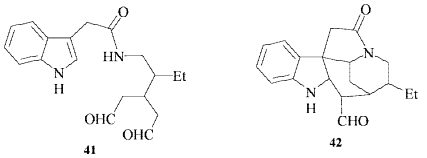
The issue of kinetic vs thermodynamic control (vide supra) can occasionally impact the stereochemical outcome. Although the *N*-acyliminium cyclization in eq 16 yields one major product,[105] when the reaction is heated at reflux to shorten the duration, the other lactam isomer (not shown) predominates, presumably due to acid-catalyzed equilibration. A thermodynamic product composition is also probable in the cyclization of **39** to **40** (eq 20; α/β = 1:6) since the α isomer equilibrates to a 1:4 α/β mixture on heating with *p*-toluenesulfonic acid.[104]



(20)

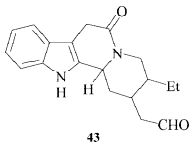
39 **40**

In rare instances *N*-acyliminium ion attack can take place at the indole 3-position to effect spirocyclization (so-called β-cyclization).[91,108−110] This type of indole cyclization is also seen with related Pictet−Spengler reactions.[7,112] The cyclization of amide dialdehyde **41** to **42**, which possesses a strychnine



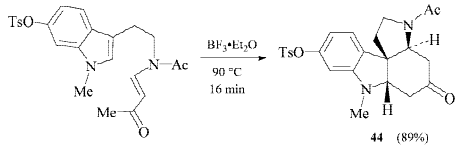
41 **42**

skeleton, proceeds by electrophilic attack at the indole 3-position (HOAc/NaOAc with heating).[91] Later, it was found that the β-cyclization product arises from an initially formed α-cyclization product;[113] indeed, under the milder conditions of aqueous HOAc at room temperature, **41** gives the α-cyclization product **43** in ca. 35% yield as a mixture of diastereomers. Such *N*-acyliminium spirocyclizations can



43

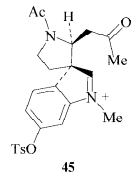
establish three to five stereogenic centers at once.[108−110] For example, tetracycle **44** is obtained with high stereoselectivity for the three stereogenic centers at the ring junctions (eq 21).[108,109] The *p*-tosyloxy sub-



(21)

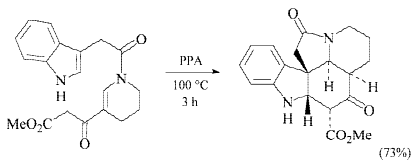
44 (89%)

stituent promotes formation of the spirocyclic product via β-cyclization over the β-carboline via α-cyclization, although the α-cyclization is favored by a more electron-releasing methoxy group. This spirocyclization involves a spiroindolenium ion (viz. **45**), prefer-



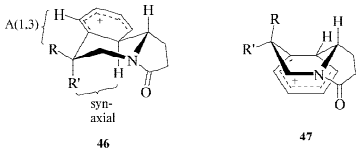
45

entially generated with the *cis* configuration (shown), which cyclizes from the α-face to yield the observed product **44**. A related reaction that generates five stereogenic centers simultaneously (eq 22) furnishes a 5:1 isomeric mixture with the major product having the same "*cis*−*cis*" configuration at the ring junctions.[110]



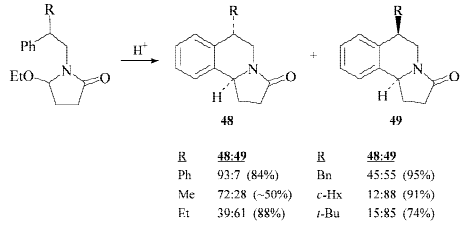
(22)

Substituents on the chain linking an arene π-nucleophile to the amide nitrogen create the potential for diastereoselection.[45,67,114−116] Two examples with substituents β to the nitrogen are shown in eqs 7 and 9. For various cases, ≥90:10 stereoselectivity in favor of the *cis* configuration (α aryl and α angular substituent at the ring junction) is obtained. This stereochemical outcome hinges on preferential formation of a chairlike arenium ion intermediate, such as **46**, which favors the larger of R and R′ in a quasi-equatorial position, rather than a strained boatlike intermediate, such as **47**. The axial proton at the ring



46 **47**

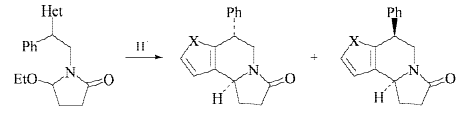
junction (angular position) in **46** is crucial for achieving the high stereoselectivity because of the 1,3-*syn*-axial interaction. Other steric factors can intervene to complicate this picture, as in the formation of **48** and **49** (eq 23).[114,115] The dramatic reversal of stereoselectivity with cyclohexyl and *tert*-butyl groups, relative to the corresponding phenyl group, is attributable to competing steric factors.[114] Specifically, a bulky aliphatic substituent would experience significant A(1,3) and gauche-butane interactions, thereby biasing the bulky substituent into a β orientation. There is also competition between different steric interactions in the cyclizations of *N*-



R	48:49	R	48:49
Ph	93:7 (84%)	Bn	45:55 (95%)
Me	72:28 (~50%)	*c*-Hx	12:88 (91%)
Et	39:61 (88%)	*t*-Bu	15:85 (74%)

(23)

methylpyrrole and thiophene substrates (eq 24), which results in α/β product ratios of 74:26 and 96:4, respectively,[45] presumably because of A(1,3) strain between the *N*-methyl and phenyl groups.

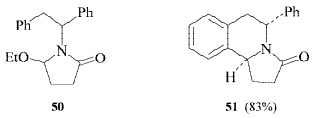


Het = 2-(1-Me-pyrrolyl) or 2-thienyl

X = NMe 74:26 (96%)
X = S 96:4 (47%)

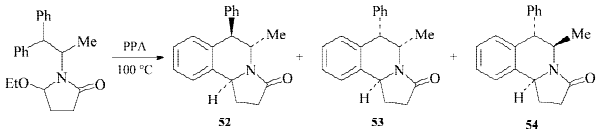
(24)

When substituents on the linking chain are α to the amide nitrogen, A(1,3) strain becomes a decisive control element. Cyclization of **50**, with a phenyl substituent adjacent to nitrogen, leads exclusively to **51**, the product with a pseudoaxial phenyl, because



50 **51** (83%)

of severe A(1,3) strain between a pseudoequatorial phenyl and the amide carbonyl in the competing transition structures.[45] However, it is more complicated when two stereogenic determinants are on the linking chain, as in eq 25, where three out of the four possible lactams are formed in a ratio of 4:2:1.[116] A balance of steric interactions is responsible for the distribution of lactams **52**−**54**.



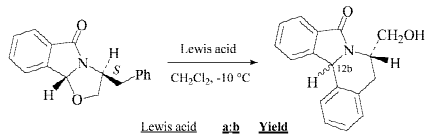
52 **53** **54**

52:**53**:**54** = 4:2:1
(68%)

(25)

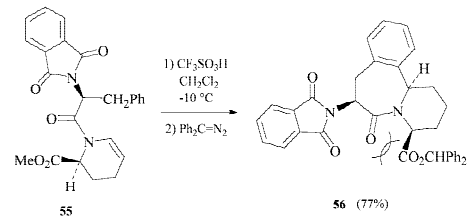
Two unusual examples of *N*-acyliminium cyclizations involving A(1,3) strain are illustrated in eqs 26[117] and 27.[118] In eq 26, the ratio of isomeric products (**a**:**b**) depends on the Lewis acid; as indicated, trimethylsilyl triflate affords outstanding stereoselectivity.[117] Nevertheless, the A(1,3) strain of the trimethylsilyl triflate reaction appears to be counteracted by chelation in the other cases. In eq 27, although a phthalimido group would normally favor an equatorial orientation on a seven-membered ring, A(1,3) strain between the lactam carbonyl and the carbomethoxy group intervenes in the transition state for arenium ion formation, causing the ester group to strongly favor an axial orientation.[118] In fact, this steric effect is responsible for the failure of the α carbomethoxy epimer of **55** to cyclize.[118]

Substituents on the lactam ring that contains the iminium center can be stereochemically influential.[119,120,121] For example, the cyclization of **57** with



Lewis acid	a:b	Yield
$SnCl_4$	2:1	98%
BF_3•Et_2O	3:1	99
H_2SO_4	6:1	80
Me_3SiOTf	≥49:1	97

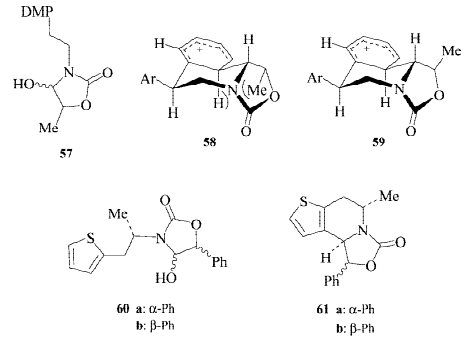
(26)



55 **56** (77%)

(27)

formic acid yields a preponderance of one stereoisomeric product (>98% *cis*), that from the arene nucleophile approaching the *N*-acyliminium ion from the side opposite to the adjacent substituent.[119] Considering the arenium ion intermediates **58** and **59**, the pseudoaxial methyl group in **58** would interact adversely with the angular bridgehead hydrogen; however, this interaction is absent in **59**. Allylic



57 **58** **59**

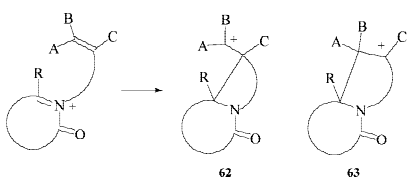
60 **a**: α-Ph
b: β-Ph

61 **a**: α-Ph
b: β-Ph

A(1,3) strain can counterbalance this steric effect as in the cyclizations of **60a** and **60b**.[121] The low 8% yield of **61b** from **60b** compared with the 80% yield of **61a** from **60a** relates to A(1,3) strain compelling the thiophene to add from the *same side* as the phenyl substituent.[121]

2.3.2. Alkenes as Nucleophiles

Cationic π-cyclizations involving alkene nucleophiles and *N*-acyliminium ions have broad utility in the synthesis of cyclic systems. Cyclization of a nitrogen-tethered, proximal alkene (for instance) can occur by two different modes of attack to furnish products with two different ring sizes, via exocyclic (**62**) [*n-exo*-trig ring closure] or endocyclic (**63**) [(*n* + 1)-*endo*-trig ring closure] carbocation intermediates (eq 28).[122] Subsequently, these carbocations could



62 **63**
size of newly formed ring: n n + 1

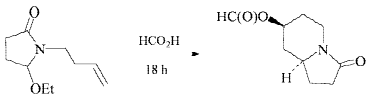
(28)

undergo standard transformations, such as solvent capture, addition of nucleophiles, elimination, or

rearrangement, to yield the final reaction products. In eq 28, the alkene is linked to the *N*-acyliminium species by the nitrogen atom, although it could just as well be connected to other positions. The reaction outcome will depend on various features, such as reactivity of the *N*-acyliminium ion, reaction conditions, types of substituents on the alkene, length of the tether, and position of the tether. Mechanistically, attack of an *N*-acyliminium ion on an alkene can be viewed in terms of antiperiplanar addition. For a concerted pathway, which is frequently seen in cationic polyene cyclizations,[56−58] the stereochemistry will be determined under kinetic control by conformational and stereoelectronic factors in the transition state. Under such conditions, the alkene configuration would be preserved in the product(s). A stepwise pathway involving a discrete carbocation intermediate is also possible. In this case, thermodynamic control and/or carbocation-derived byproducts could intervene.

Although the first *N*-acyliminium cyclization with an alkene π-nucleophile was described in 1957,[25] two decades elapsed before this reaction class was seriously explored.[15,123,124] Pioneering studies in the 1970s[15−19,123−139] set the stage for a profusion of applications to the stereoselective synthesis of alkaloid natural products. The introduction of mild cyclization conditions, such as formic acid at room temperature, was an important step forward, and this area has since burgeoned.[15,123,124]

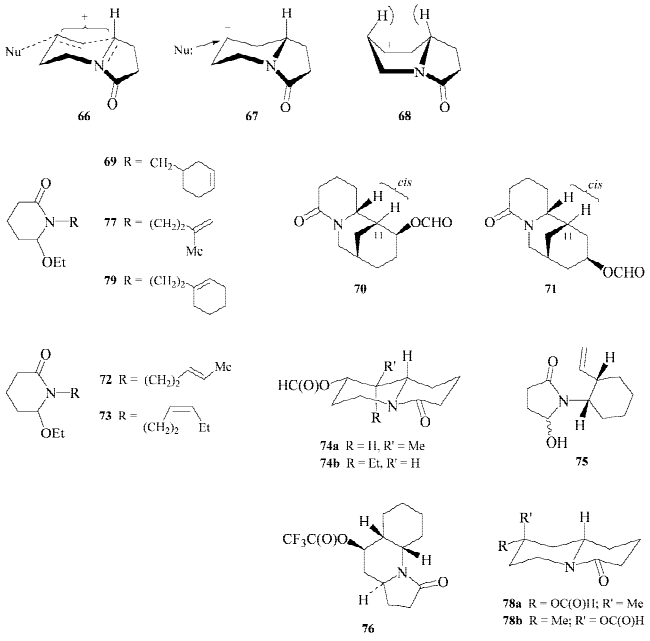
The cyclization of **64** to **65** (eq 29),[130] a prototype reaction in this area, proceeds at room temperature in nearly quantitative yield with a high degree of stereochemical control (>90%).[124] The mechanism of



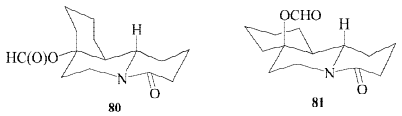
64 **65** (100%; ca. 5% of other stereoisomer present) (29)

this 6-*endo*-trig process could be concerted and involve a chairlike transition structure, such as **66**. Alternatively, it is possible to have a stepwise process involving chairlike carbocation intermediate **67**, which would be trapped by the solvent preferentially from the equatorial direction. A potentially competing pathway involving a boatlike transition state or intermediate, such as **68**, is very energetically unfavorable. The conversion of **69** to C11-*endo*-3-azabicyclo-[3.3.1]nonanes **70** and **71** (56:44 ratio) with the *cis* configuration at the ring junction (ca. 100% yield) is a direct outgrowth of a chairlike cyclization transition state with maximum overlap of the reacting π orbitals.[130] The mixture of formate regioisomers **70** and **71** arises from unusually fast 1,2-hydride migrations of the intermediate azabicyclo[3.3.1]nonyl carbocations, and the product ratios vary from 70:30 to 30:70 depending on the acid used.

A kinetically controlled process with a high degree of concertedness is supported by the fact that disubstituted alkenes of opposite stereochemistry generally cyclize with complete retention of the original configuration. For example, the conversions of *E*-isomer **72** to **74a** and *Z*-isomer **73** to **74b** occur with high

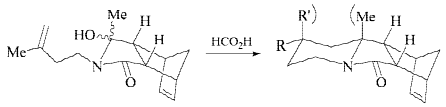


stereoselectivity and retention of alkene configuration in the products.[130] Kinetic control is also evident for the cyclization of **75** to **76** in trifluoroacetic acid in connection with trapping by triethylsilane, in that **76** did not undergo reversion.[140] The cyclization of **77** to **78a** and **78b** (tentative stereochemical assignment) in dichloroacetic acid results in a 70:30 ratio, which is kinetically controlled as suggested by the failure of a 57:43 mixture to equilibrate on exposure to dichloroacetic acid.[130] However, there are some cases of alkene cyclizations that do not proceed under kinetic control. For example, the cyclization of **79** to **80** and **81** (tentative stereochemical assignment, but



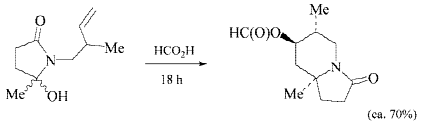
80 **81**

supported in a later study[141]) gives a 61:39 product mixture after 2 h and a 34:66 mixture after 16 h, reflecting thermodynamic control.[130] Dramatic post-cyclization equilibration occurs in the reaction of **82**, where the **83a**:**83b** ratio shifts from 60:40 at 2 min to 0:100 at 18 h (eq 30).[142]



82 **83a** R = OC(O)H; R' = Me **83b** R = Me; R' = OC(O)H (30)

Excellent stereocontrol can be obtained relative to substituents on the chain that links the alkene to the amide nitrogen. A substituent at the allylic position of the linking chain, β to the nitrogen, results in high stereoselectivity in standard (eq 31)[137] and tandem (eq 32)[124,137] cyclizations. This desirable outcome most likely arises from a strong preference of the substituent for an equatorial orientation in a product-like transition state en route to **84**, which avoids an unfavorable 1,3 R/H *syn*-axial interaction (cf. arenium ion **46**). A substituent at the homoallylic position of



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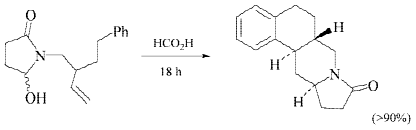
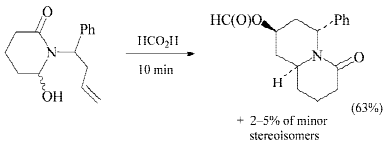


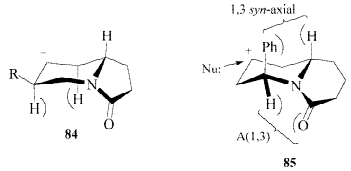
(32)

the chain, α to the nitrogen, can also exert a strong stereochemical influence (e.g., eq 33).[143] The result

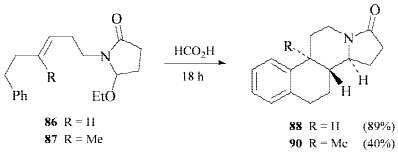


(33)

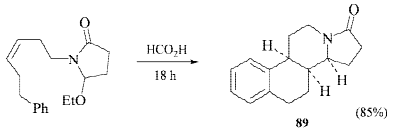
in eq 33 is attributable to cyclization via a chair (rather than a boat) conformation with the key substituent preferring an axial rather than an equatorial position, in contradistinction to related polyolefin systems.[143] Apparently, the development of unfavorable A(1,3) strain in the transition state for ring closure overrides adverse effects from 1,3-*syn*-axial interaction (viz. **85**; cf. **50** → **51**).[143] Similar steric forces operate in the highly stereoselective cyclization of **75** to **76**.[140]



Tandem cyclizations can deliver polycyclic systems in short order with high stereocontrol, under suitable conditions. For example, aza-steroids **88** and **89** are produced as single isomers in high yield with formic acid (eqs 34 and 35).[129,131] In the conversion of **87** to

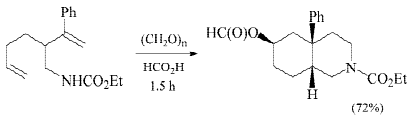


(34)



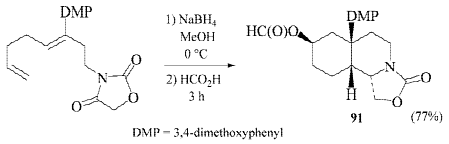
(35)

90 (major isomer) with formic acid, the yield suffers (40%) because the reaction stalls at the monocyclic stage (eq 34). Nevertheless, this conversion can be driven to completion with trifluoroacetic acid (5 °C, 30 min) to give **90** in 84% yield.[131] Tandem cyclization also offers an efficient, highly stereoselective route to *cis*-aryldecahydroisoquinolines[144−149] (e.g., eq 36;[144,146,149] relative configuration revised[146,149] from original incorrect assignment[144,145]). In forming the second ring, the stereocontrol is governed by a *cis*-fused chair−chair transition state, as opposed to a



(36)

trans-fused one, which minimizes adverse steric interactions between the 4-phenyl and 3-alkyl groups on the piperidine intermediate.[146,149] In a related tandem polyene cyclization, four stereogenic centers in tricyclic product **91** are established at once (eq 37).[148] Four stereocenters are still controlled when the alkene is unsubstituted (eq 38), but the product, **92**, now contains a *trans*-fused decahydroisoquinoline nucleus.[129]



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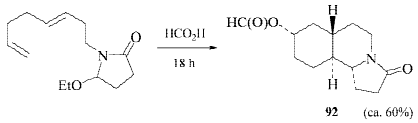
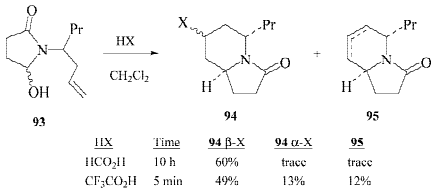


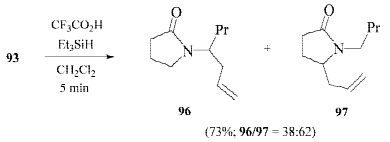
(38)

The chemistry of *N*-(2-alkenylethyl) *N*-acyliminium ions is less than straightforward because of the intervention of a 2-aza-Cope rearrangement. A "hidden" 2-aza-Cope rearrangement amidst a standard *N*-acyliminium cyclization was first revealed by trapping experiments.[150] Treatment of **93** with formic acid or trifluoroacetic acid yields two cyclized products (**94**) with high stereoselectivity relative to the CH and PrCH centers, as expected from A(1,3) strain (eq 39).[150] However, when the reaction with trifluoro-



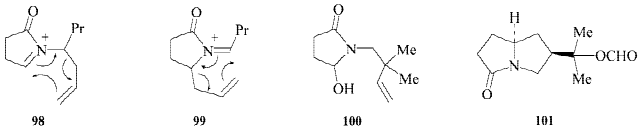
(39)

acetic acid is conducted in the presence of triethylsilane, a carbocation-trapping agent, lactam **96** and skeletally rearranged lactam **97** are obtained (eq 40).

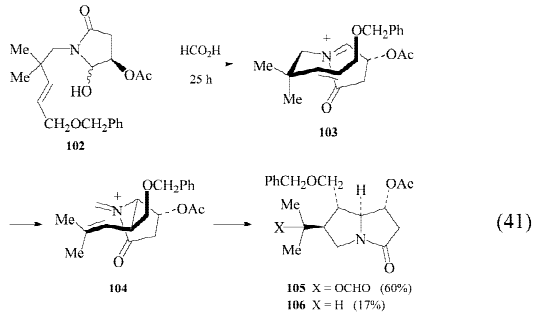


(40)

Clearly, the initial *N*-acyliminium ion **98** rearranges to the ion **99** via a 2-aza-Cope reaction as part of a rapid equilibrium; the comparatively slower reduction or cyclization then ensues. This kind of 2-aza-Cope rearrangement, which occurs in various, susceptible *N*-acyliminium systems,[151−168] can influence the cyclization products, such as whether five- or six-membered rings are generated, and the stereochemical outcome. The stereochemical control that emanates from this process has benefited the synthesis of diverse alkaloids. For example, lactam **100** cyclizes



in formic acid exclusively to pyrrolizidine **101** in 81% yield.[151] In the cyclization of complex substrate **102** to a mixture of **105** and **106**, high stereocontrol for three new stereogenic centers is dictated by geometric constraints of the [3,3] rearrangement of **103** to **104** (eq 41).[152,157] The stereocontrolled conversion of β-lactam **107** to carbapenam **110**, which is formed as a single isomer, is based on an aza-Cope *N*-acyliminium cyclization (eq 42).[165] After [3,3] allylic rearrangement on the less hindered face (viz. **108** → **109**), resultant silyl enol ether **109** cyclizes on the same face as its tether to give solely **110**.



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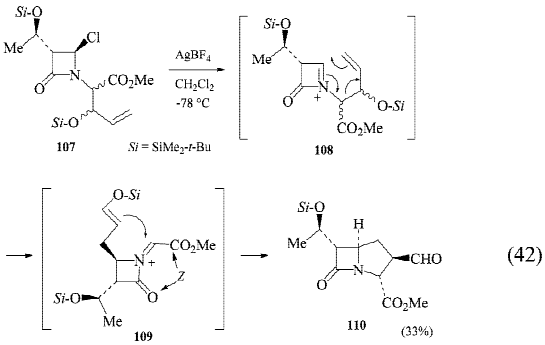
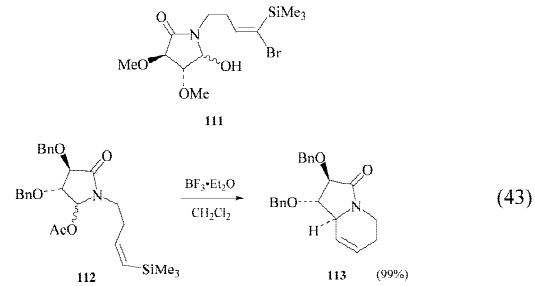
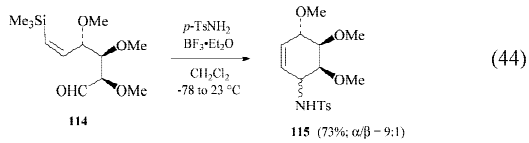


(42)

Activated alkenes, wherein the nucleophilicity is accentuated by (a) silyl,[164,167−177] (b) thioether,[178−184] (c) silylmethyl,[166,177,185−210] and (d) stannylmethyl substituents, cyclize with some interesting stereochemical aspects.[211−213] The regioselectivity of vinylsilane cyclizations is governed by generation of a carbocation β to silicon ("β-silyl effect"); therefore, the new carbon−carbon bond forms at the silicon-bearing vinyl carbon. For example, *N*-acyliminium cyclizations of vinylsilanes **111**[171] and **112**[173] are highly regioselective and stereoselective, with the α isomer **113** being formed exclusively in the latter case (eq 43). By the same token, the *N*-sulfonyliminium cyclization of **114** affords aminocyclitol **115** with a strong preference for the α isomer (eq 44).[176]

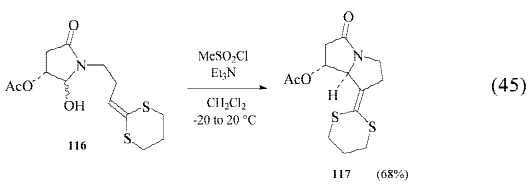


(43)



(44)

A 1,3-dithiane ketene dithioacetal facilitates the cyclization of **116** to give virtually a single product, **117** (eq 45).[179] The ketene dithioacetal confers complete control of cyclization regiochemistry via generation of a stabilized dithiocarbocation intermediate, and the acetoxy substituent directs stereochemistry by effectively blocking the α-face of the *N*-acyliminium ion. Analogous cyclizations of **118**[181] and **119**[183] are also highly stereocontrolled. In contrast, **120**, with a six-membered lactam ring, gives a 1:1 mixture of indolizidine diastereomers in 84% yield.[183] The stereoelectronic preference for axial attack on the all-equatorial half-chair *N*-acyliminium ion seems to be balanced by the steric preference for attack *anti* to the neighboring 5-benzyloxy group. A single sulfur moiety on the alkene is also viable, as in the stereoselective formation of the bridged bicyclic compound **122** from vinyl sulfide **121** (eq 46).[182]



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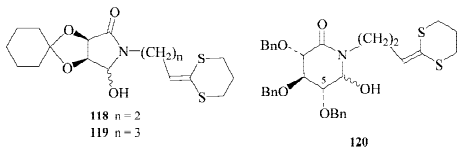
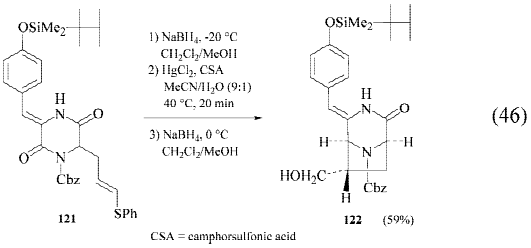
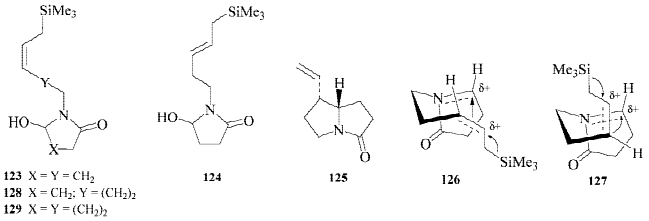


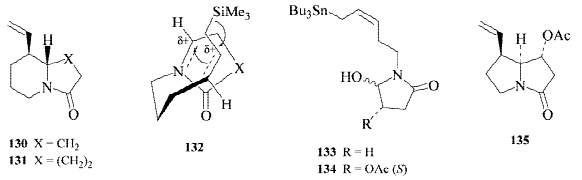


(46)

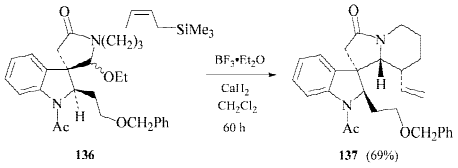
In allylsilane reactions,[166,177,185−210] the regiochemistry is governed by the β-effect of silicon; thus, new carbon−carbon bonds are formed at the vinyl carbon distal from silicon (i.e., at the γ-position). Treatment of allylsilane **123** with trifluoroacetic acid, or of **124** with formic acid, provides vinylpyrrolizidine **125**, the contrathermodynamic *endo* product, as a single isomer in good yield.[188] The absence of an effect from alkene geometry is consistent with an electrophilic addition mechanism, in which the "*syn*" (vicinal hydrogens *syn*) stereochemical preference for the new carbon−carbon bond is determined by stereoelec-



tronic factors in the cyclization step (viz. **126** and **127**).[188,214] The cyclizations of **128** and **129** with trifluoroacetic acid also produce one stereoisomer, **130** and **131**, respectively, in high yield. The source of the "*anti*" (vicinal hydrogens *anti*) stereochemical preference for the new carbon−carbon bond in **130**/**131** is depicted in **132**. Analogously, tributylstannyl

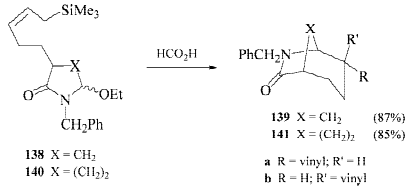


substrates **133** and **134** cyclize to **125** and **135**, respectively, with very high stereoselectivity.[211,212] In contrast, related spiro-indoline **136** gives **137** with the opposite configuration (vicinal hydrogens *syn*) (eq 47).[191]



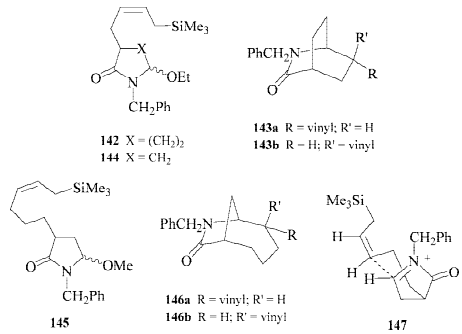
(47)

The synthesis of bridged azabicyclic molecules via allylsilane-based cyclizations is fraught with variable stereocontrol.[199−203,208,209] Reaction of ethoxypyrrolidin-2-one **138** in formic acid provides azabicyclo[3.2.1]-octanes **139** with a strong preference for an *endo* vinyl group (**a**/**b** ratio = 95:5); however, the homologous piperidin-2-one **140** affords the corresponding azabicyclo[3.2.2]nonanes **141** with little stereochemical preference (**a**/**b** ratio = 42:58) (eq 48).[202,203]

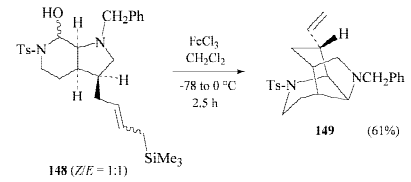


(48)

Piperidin-2-one **142**, with a one-methylene linker to the allylsilane, gives azabicyclo[2.2.2]octanes **143a** and **143b** in a 94:6 *endo*/*exo* ratio (94% yield), whereas pyrrolidin-2-one **144** gives the corresponding azabicyclo[2.2.1]heptanes (66%; not shown) with no stereochemical discrimination (*endo*/*exo* = 36:64). In sharp contrast, trimethylene-linked pyrrolidin-2-one **145** gives a strong *exo* preference in azabicyclo[4.2.1]-nonanes **146** (**a**/**b** = 8:92; 73% yield). The high *endo* selectivity for the conversion of **138** to **139** can be attributed to a chairlike transition state with the allylsilane in an equatorial orientation, as depicted

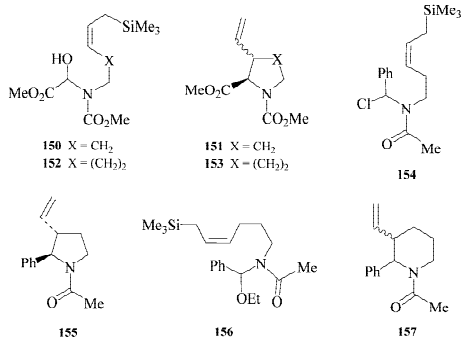


in **147**.[202] This type of stereocontrol also applies to much more complex substrates, as demonstrated by the highly stereoselective *N*-tosyliminium/allylsilane cyclizations of **148** to **149** (eq 49).[199,200]



(49)

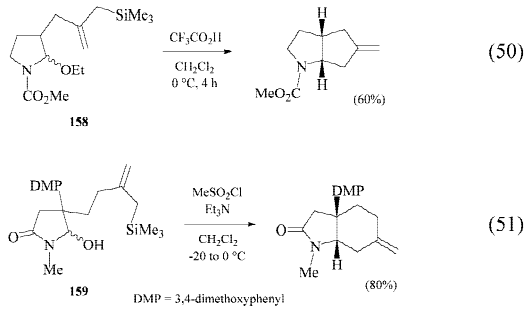
Intramolecular reactions of acyclic *N*-acyliminium ions with allylsilanes are useful for assembling vinylpiperidines and vinylpyrrolidines, with excellent stereocontrol in certain cases.[166,187,189,190,192] By means of a "glycine cation equivalent", **150** reacts with mesyl chloride and triethylamine to furnish pyrrolidine **151** with a *cis*/*trans* ratio of 11:89 (88% yield), whereas **152** furnishes piperidine **153** with a *cis*/*trans* ratio of 55:45 (79% yield).[189] Similarly, the cyclization of



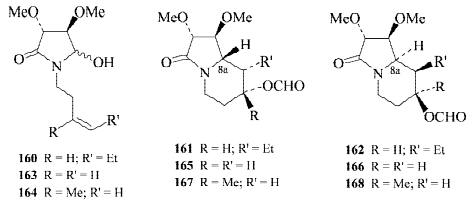
154 with diethylaluminum chloride produces pyrrolidine **155** as a single *trans* isomer in 69% yield,[187] whereas **156** produces piperidine **157** with minimal stereoselectivity (*cis*/*trans* = 2:1; 60% yield). When the glycine-cation approach is applied to alkenes devoid of special activation, complex stereochemical results arise, partially due to an intervening 2-aza-Cope rearrangement.[161,164,166,215]

Cyclizations of 2-substituted allylsilanes are also valuable.[185,186,194−198,207] *Cis*-fused hexahydrocyclopenta[*b*]pyrroles[207] and octahydroindoles[186,194] are obtained with excellent stereocontrol from pyrrolidine- and piperidine-based substrates, such as **158** and **159**, which have an allylsilane unit appended to the ring carbon adjacent to the incipient carbocation center (eqs 50[207] and 51[186,194]).

High stereocontrol can emanate from stereogenic centers on the five-membered lactam ring of cyclic

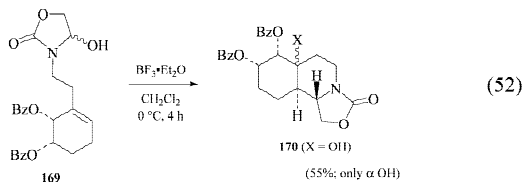


N-acyliminium ions.[138,153,157,171,173,179,181,183,210,216] In particular, cyclization of substrates with an alkoxy or acyloxy substituent adjacent to the iminium ion center may strongly favor products with a bridgehead hydrogen *syn* to the substituent, as observed in eqs 41,[153,157] 43,[173] and 45,[179] and the reactions of **111**,[171] **118**,[181] **119**,[183] and **134**.[211] In this vein, formic acid cyclization of **160** provides the 8a*S* isomer **161** exclusively in ca. 100% yield (no **162** is formed), with the 3,4-dimethoxy groups controlling the bridgehead stereochemistry of the indolizidinone product.[138] However, this type of stereocontrol can vary according to the substituents on the alkene nucleophile.[138,171,173,216]

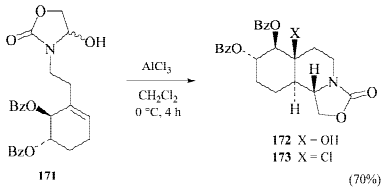


When the (*Z*)-ethyl group is removed, as in **163** or **164**, a mixture of two diastereomers is obtained with an 8a*S*:8a*R* ratio of 2:1 for **163** → **165**:**166** and 1.5:1 for **164** → **167**:**168**. This stereochemical pattern, in which the bridgehead hydrogen is *syn* to the neighboring oxygen substituent, may not carry over to the cyclization of the corresponding six-membered-rings, since a 1:1 mixture of isomeric indolizidinones is obtained from **120**.[183]

Stereogenic centers on the alkene segment can lead to high stereocontrol.[217] For example, treatment of oxazolidin-2-one **169** with boron trifluoride etherate produces **170** (X = α-OH) exclusively (eq 52).[217] The

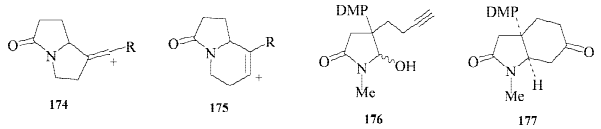


configuration of the bridgehead hydrogens is as expected from the *N*-acyliminium cyclization; however, the controlled introduction of the bridgehead hydroxyl arises from neighboring group participation of the benzoate substituent with the carbocation to form an intermediate 1,3-dioxolanium ion, which is hydrolyzed on aqueous workup. By contrast, treatment of **169** with aluminum(III) chloride affords **170** (X = Cl) as a 3.7:1 mixture of α/β chloro isomers (57% yield). On the other hand, **171** reacts with aluminum(III) chloride to yield only the β configuration, albeit as a mixture of OH and Cl species, **172** and **173** (eq 53).[217]



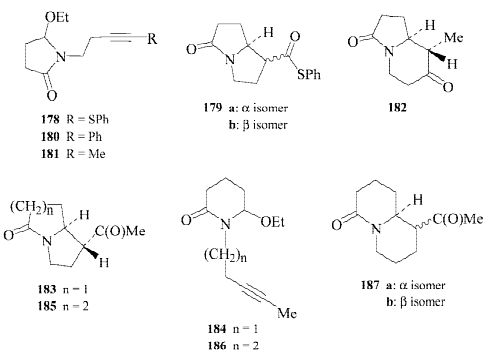
2.3.3. Alkynes as Nucleophiles

N-Acyliminium ion cyclizations of alkyne nucleophiles have received considerable attention.[15,127,133,188,189,202−205,208,218−226] Ring closure onto alkynes can proceed through an *exo* or an *endo* vinyl cation intermediate (e.g., cf. **174** and **175**, respectively). In general, *endo* cyclization is favored for terminal acetylenes, regardless of the influence of ring strain, whereas *exo* cyclization is favored with internal acetylenes, but only in the absence of ring strain.[43,46] Alkyne-based reactions, as a whole, are not



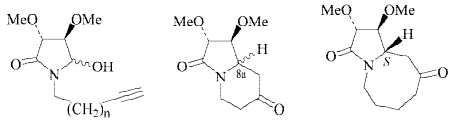
so stereochemically interesting compared with alkene-based reactions since the solvent-trapped vinyl cation in the product of the former reaction eliminates a stereogenic center. For instance, in the high-yielding formic acid cyclization of **176** to **177**, an intermediate en route to mesembrine, a ketone is generated at the site of formate addition and the configuration at the ring junction is exclusively *cis*, simply because of the ring constraint imposed by the tether to the ethenyl group.[127,132]

Stereochemical and regiochemical results are variable in the synthesis of pyrrolizidines, indolizidines, and quinolizidines. Whereas phenylthioacetylene **178** cyclizes in formic acid to a moderately biased 4:1 mixture of pyrrolizidines **179a** and **179b** (after workup with 1.5 M HCl),[218] phenylacetylene **180** cyclizes to a 1:1 mixture of related PhC(O) epimers (although the ratio may be altered by product equilibration). The regiocontrol is exclusively *exo*, probably because of better linear resonance stabilization of the *exo* vinyl cation (viz. **174**), compared with the *endo* vinyl cation (viz. **175**), by the phenylthio or phenyl substituent.[218] By contrast, treatment of **181** with



formic acid yields mostly the *endo* regioisomer **182**, rather than the *exo* regioisomer **183** (*endo*/*exo* = 90:10), but each epimer is formed with high stereoselectivity.[43,46] The one-carbon homologue **184** affords mostly the *exo* regioisomer **185** (*endo*/*exo* = 15:85), each epimer with high stereoselectivity, presumably because ring strain is less for indolizidine formation relative to pyrrolizidine formation. In fact, the cyclization of **186** shows minimal ring strain effects in yielding only *exo*-cyclized quinolizidines **187a** and **187b** with an α/β ratio of 9:1 (possibly from product equilibration).[43,46]

The presence of a stereogenic center on the lactam ring of cyclic *N*-acyliminium ions may or may not engender high stereocontrol. For example, the cyclization of enantiomerically enriched substrates **188** and **189** with formic acid yields only the *endo* products, but the stereoselectivity is very different between them.[138] Compound **188** provides a 1:1 mixture of indolizidine C8a epimers **190** (ca. 100% yield), while **189** provides **191** exclusively.[138]



188 n = 1
189 n = 3

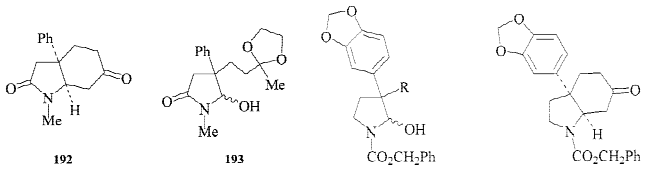
190

191

2.3.4. Carbonyl Groups as Nucleophiles via Enols and Enolates

Active methylene and methine compounds can participate effectively in *N*-acyliminium ion cyclizations, presumably via the enol or enolate forms. This subsection will deal with such reactions, as well as cyclizations of enol silyl ethers (masked enols), the cyclocondensation of imines with carboxylic acid anhydrides,[227] and the formation of β-lactams via the Staudinger reaction.[20,227]

An example of an enol cyclization with stereochemical interest is the exclusive formation of indolizidinone **192** from **193** in methanolic HCl.[127,132] *Cis*



192

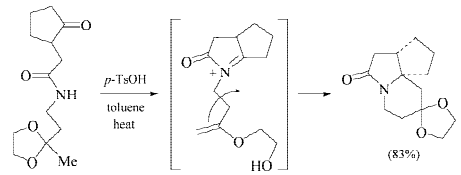
193

194 R = H
196 R = $(CH_2)_2C(O)Me$

195

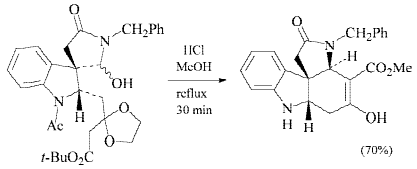
stereoselectivity is also obtained in the related cyclization of **196** to **195**, starting with **194** (methyl vinyl ketone, Triton B; HCl, MeOH),[228] and in more complex systems (eqs 54[229] and 55[230]), because ring closure occurs preferentially from the less hindered face of the *N*-acyliminium ion.

A noteworthy aspect has been the generation of complex bicyclic structures by cyclization of enol species.[231−237] The synthesis of an advanced polycyclic intermediate en route to gelsemine via the conversion of **197** to **198** is a case in point.[231,232] This reaction appears to be difficult due to the strained polycyclic ring system, which imposes a severe barrier to



(54)

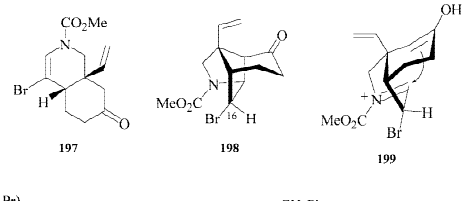
(83%)



(55)

(70%)

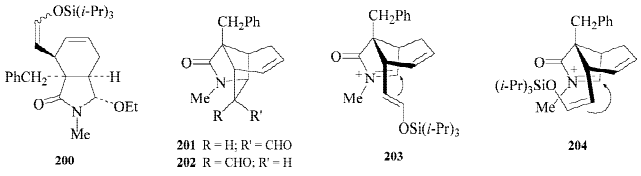
overlap of the enol and iminium π systems (viz. **199**). Nevertheless, **197** cyclizes in trifluoroacetic acid to **198** with excellent yield and stereoselectivity, even with respect to the bromine substituent. The stereochemical course is dictated by cyclization of the thermodynamically more favored ion **199**, which derives from protonation of the more hindered concave face of the ene carbamate **197**, thereby placing the bromo group *exo* in the transition state. A related approach to gelsemine involves a silyl enol ether as a masked-ketone nucleophile.[233−235] The *E* and *Z* isomers of **200** cyclize ($BF_3{\cdot}Et_2O$, CH_2Cl_2) with a remarkable stereospecificity: (*E*)-**200** (*E*/*Z* > 90:10) gives mainly the *endo* aldehyde **201** (*endo*/*exo* = ca. 90:10; 79% yield), and (*Z*)-**200** (*Z*/*E* > 90:10) gives mainly the *exo* aldehyde **202** (*endo*/*exo* = ca. 10:90; 92% yield).[233] This outcome can be rationalized by a chairlike transition state for **201** and a boatlike transition state for **202**, the latter avoiding a severe steric interaction between the silyloxy group and the cyclohexene ring (cf. **203** and **204**).[233]



197

198

199



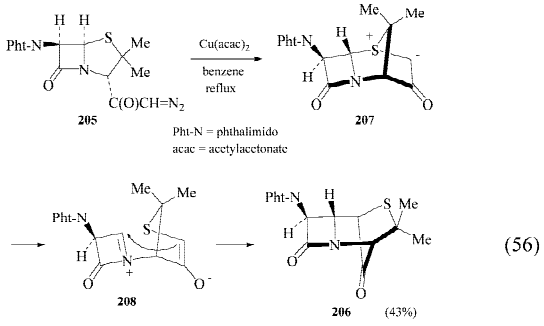
200

201 R = H; R' = CHO
202 R = CHO; R' = H

203

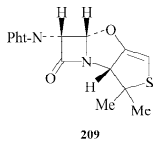
204

An unusual *N*-acyliminium cyclization of enols derives from diazo addition to an α-amido sulfide to generate a sulfonium ylide.[238−243] Cu(II)-catalyzed decomposition−rearrangement of penicillin-derived diazoketones yields a strained bicyclic product with remarkable stereochemical control (eq 56).[238] Thus, diazoketone **205** reacts with copper(II) acetylacetonate to give tricyclic ketone **206** as a single isomer in 43% yield. Mechanistically, a possible intermediate is the strained, bicyclic sulfonium ylide **207**,[238] which is cleaved to zwitterion **208**, containing an *N*-acyliminium ion and an enolate. Reclosure of **208** to the product would involve enolate addition to the *N*-acyliminium ion exclusively from the α-face, opposite to the β-oriented phthalimido group on the lactam

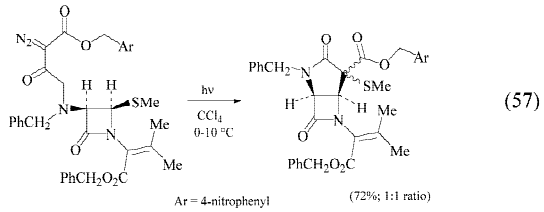


(56)

ring. Although this result suggests a steric rationale, α-face attack also takes place exclusively when the phthalimido group is α-oriented.[239] Minor byproducts from addition of the enolate oxygen to the acyliminium ion, such as **209** from the α-phthalimido isomer

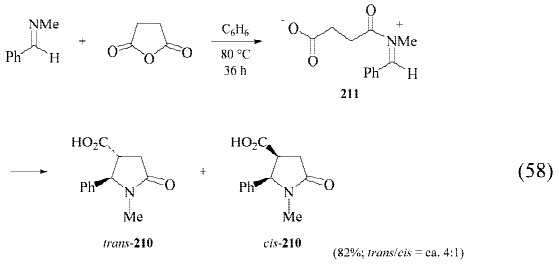


of **205**,[239] also possess the stereochemistry from α-face attack.[239,243] It is possible, however, to achieve addition from the *β*-face by tethering the diazocarbonyl group to the nitrogen substituent on the *β*-lactam ring (eq 57).[240]



(57)

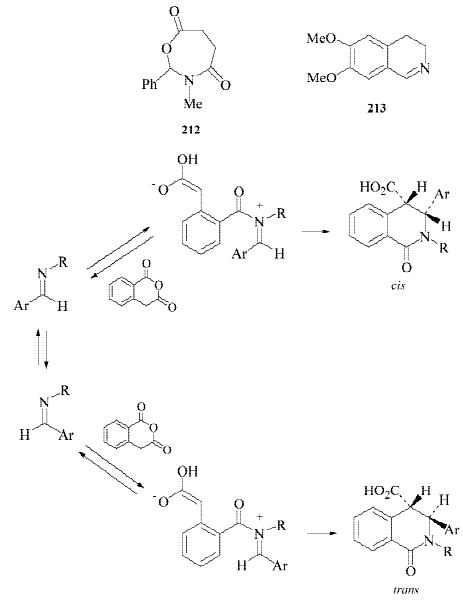
Imines can combine with cyclic anhydrides to yield cyclocondensation products that appear to arise from addition of a carboxylic acid enolate to an intermediate *N*-acyliminium species (e.g., eq 58).[227,244−276] A



(58)

prototypical reaction involving succinic anhydride and PhCH═NMe yields pyrrolidinone **210** as a mixture enriched in the *trans* isomer (eq 58).[244] Generally, succinic, glutaric, and homophthalic anhydrides condense well with benzaldimines, but just moderate stereochemical control is obtained.

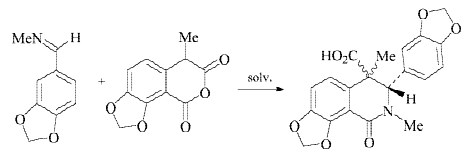
Mechanistic studies with succinic and homophthalic anhydrides support initial imine acylation by one of the anhydride carbonyls, to give species such as **211** and **212**, followed by electrophilic attack of the *N*-acyliminium carbon on the carbon adjacent to the remote carbonyl.[245,265] The stereochemical outcome under kinetic control depends on the relative distribution and reactivity of the *E* and *Z* imines (viz. eq 59).[265] The *cis*-isoquinolone would derive from



(59)

acylation of the *E* imine. Benzaldimines with larger substituents (e.g., phenyl or cyclohexyl) on nitrogen, which are inclined to favor the *E* configuration, show a stronger preference for the *cis*-isoquinolones.[265] Reactions of *N*-methylbenzaldimines with homophthalic anhydrides, in which the benzoyl carbonyl reacts preferentially, normally favor the *trans*-isoquinolones, but a significant amount of *cis* isomer is still formed.[227,265] It is noteworthy that the use of boron trifluoride etherate in this condensation results in exclusive formation of *trans*-isoquinolones, as well as an enhanced reaction scope.[273]

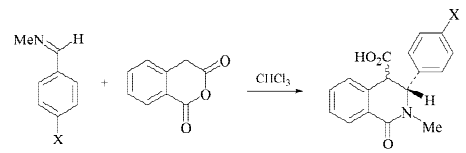
The stereochemical outcome can be significantly affected by the solvent, with polar solvents leading to a larger proportion of the *cis* isomer (eq 60).[265] With



Solvent	*trans*/*cis*
MeOH	55:45
MeCN	60:40
$CHCl_3$	77:23
benzene	92:8

(60)

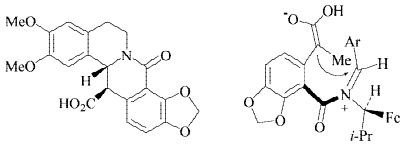
benzene, it is possible to achieve a highly biased *trans*/*cis* ratio of 92:8.[265] This ratio can also be manipulated by substituent electronic effects (eq 61).[265] In the reaction of substituted benzaldimines with homophthalic anhydride in chloroform, there is



X	*trans*/*cis*
NO_2	97:3
Cl	82:18
H	83:17
OMe	69:31
NMe_2	20:80

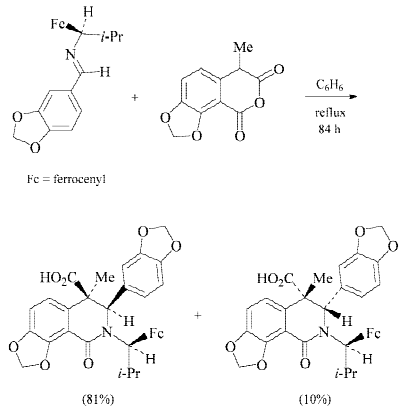
(61)

a broad range of *trans*/*cis* ratios, with the 4-nitro group affording 97:3 and the dimethylamino group affording 20:80.[265] A linear Hammett relationship between the isomer ratios and σ^+ values of the substituents indicates a higher carbocationic character in the transition state of the rate-limiting step for the *cis* product relative to the *trans* product. Thus, for the *cis* product the rate-limiting step is probably initial addition of the imine to the anhydride, whereas for the *trans* product the rate-limiting step is probably imine $E-Z$ isomerization. Imines constrained into a *Z* configuration (e.g., **213**) react with homophthalic anhydrides to yield almost exclusively *trans*-isoquinolones (e.g., **214**), as long as equilibrating conditions are avoided.[265,276] To obtain such a high preference for the *trans*-isoquinolones, one must exercise caution to maintain kinetic control in the reaction, and prevent equilibration in the workup process.[249,265,276]



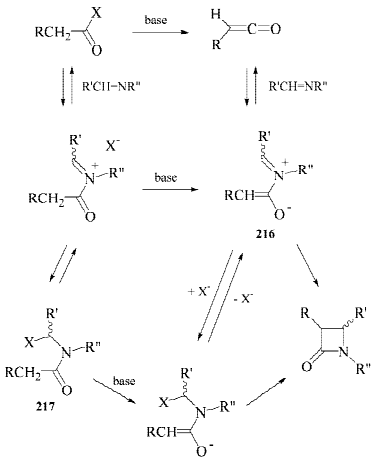
214 **215**

An intriguing example of a *trans*-isoquinolone synthesis with a nonracemic chiral imine is illustrated in eq 62.[266] The use of (*R*)-1-ferrocenyl-2-methylpropylamine as a chiral auxiliary results in a novel asymmetric synthesis with a strongly biased diastereomeric ratio of 8:1 in favor of the (3*R*,4*R*) isomer. The stereochemical outcome can be rationalized with a model of the intermediate acyliminium enolate, **215**, in which cyclization occurs by preferential addition of the carboxylate enolate to the bottom face of the iminium ion.[266]



(62)

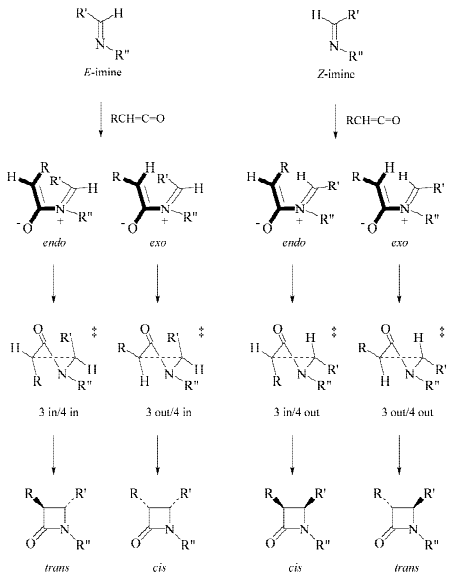
A common synthetic entrée to the β-lactam functionality is a formal [2 + 2] cycloaddition of an imine to a ketene, or its reactive equivalent.[20,277−279] While this reaction can be performed with free ketenes, synthetic practice generally depends on the use of carboxylic acid halides or other activated forms, in a process known as the Staudinger reaction. From a mechanistic standpoint, one can view the Staudinger reaction as an *N*-acyliminium ion cyclization in which a carbonyl group serves as a nucleophile via its enolate.[20,277−279] There is experimental and theoretical evidence to support a nonconcerted two-step mechanism involving a zwitterionic intermediate, such as **216**, rather than a concerted one-step pericyclic process (eq 63).[20,277−280] In fact, putative zwitterionic intermediates have been trapped as stable adducts.[20] The reaction of an acid chloride with an *N*-arylimine in the presence of a tertiary amine base can yield β-lactam products completely via a ketene intermediate, rather than via an acid chloride−imine adduct (viz. **217**).[281] However, in the absence of a base, an α-chloro amide can form, although it may not provide the β-lactam on treatment with base.[281] Reaction of phenylacetyl chloride and *N*-arylbenzaldimines without base proceeds by two competitive mechanisms: cyclization of a zwitterionic species and cyclization of an α-chloro amide.[282]



216 **217** (63)

For the Staudinger reaction, it is generally accepted that the imine attacks the central carbon of the ketene, where the LUMO has its largest coefficient, in an orthogonal manner to generate an intermediate with the planes of the two reactants more or less perpendicular (eq 64). A semiempirical theoretical (SCF-MO) study indicates the following features for the reaction: (1) it occurs in two steps; (2) the N1−C2 bond is formed first to give a zwitterionic species, and then the C3−C4 bond is formed in an *N*-acyliminium cyclization; (3) the C4 substituent is oriented inward relative to the β-lactam ring for a (*Z*)-imine and outward for an (*E*)-imine in the cyclization transition state; (4) the *trans* and *cis* stereochemistry for the substituents on C3 and C4 depends on the *exo* and *endo* approach of the ketene, respectively; and (5) generally, (*E*)-imines give *cis* β-lactams and (*Z*)-imines give *trans* β-lactams because of a steric preference for *exo* approach (eq 64).[280] Thus, the thermodynamically more stable *exo* *N*-acyliminium species undergoes conrotatory ring closure to produce the thermodynamically less stable *cis* β-lactam. Such conrotatory cyclization can best occur in a clockwise fashion since the alternative requires the ketene hydrogen and imine substituent (R′) to pass through each other.[283]

This mechanistic overview is consistent with (1) the preference for *cis* β-lactams from many acyclic aldimines, which tend to favor the *E* configuration, and (2) the preference for *trans* β-lactams from cyclic imines, which are constrained into the *Z* configura-



(64)

tion.[20] However, the stereochemical course of the Staudinger reaction is not always soundly predictable because of a dependence on conditions, most notably the order of addition of reagents.[20] In general, when an acyl chloride (or its equivalent) is added slowly to a solution containing the imine and base (usually at low temperature), the reaction follows the zwitterionic route and the *cis* β-lactam is strongly favored.[20,281] When a base is added to a mixture of the acyl chloride (or its equivalent) and the imine, the reaction leads to *cis*/*trans* mixtures, often with a predominance of the *trans* β-lactam. The latter conditions favor covalent adducts, such as **217**, which can experience bond rotation followed by intramolecular S_N2 displacement to form the β-lactam (eq 63).[20,42,281] The process is further complicated by facile interconversion of the imine and imine adduct forms (eq 63). A computational study of both pathways is in good accord with these stereochemical results.[284] However, another factor to consider is the propensity of certain *cis* β-lactams to equilibrate to *trans* β-lactams on exposure to bases,[285,286] acids,[287,288] or elevated temperatures (e.g., 230 °C).[289] An in-depth discussion of stereochemical results and asymmetric syntheses in ketene−imine cycloadditions is contained in an excellent review article.[20]

3. Scope and Limitations

N-Acyliminium ion cyclizations involve the attack of a fairly powerful electrophilic species on a suitably reactive nucleophile. This section will be concerned almost exclusively with carbon-centered nucleophiles, and the reactive components will be broadly classified into the categories of arenes, π-rich heterocycles, alkenes, and alkynes. Under the alkene topic, we will address the special nucleophiles, allenes, and enols/enolates. Another point to note is that *N*-acyliminium ion cyclizations can be performed as "unimolecular" or "bimolecular" reactions; that is, the *N*-acyliminium ion precursor can be either preconstructed or assembled in situ from two reactants. This distinction is reflected in the organization of the tables (see section 5).

There are two important advantages associated with intramolecular *N*-acyliminium ion reactions relative to the intermolecular version: (1) more facile generation of products from a substrate containing a relatively unreactive nucleophile, such as an unactivated benzenoid or alkene group, and (2) generally good stereochemical control, as discussed in the previous section.

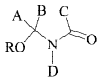
From a practical synthetic standpoint, *N*-acyliminium ion reactions conducted in strong acid media, such as polyphosphoric acid or sulfuric acid, are easier to work up relative to reactions that furnish amine or imine products because neutralization of the strong acid is frequently unnecessary to isolate the lactam products. *N*-Acyliminium ion cyclizations (e.g., eq 7) can be simply diluted with water or brine and then extracted or filtered.[45] Thus, *N*-acyliminium ion cyclizations can be particularly useful in synthesis because of the benefits gleaned from increased reactivity, good stereocontrol, and ease of reaction workup. Other favorable features are the diversity of approaches to *N*-acyliminium ion precursors and the diversity of reagents available for effecting cyclization. Also, milder reagents, such as formic acid, methanolic HCl, titanium(IV) chloride, boron trifluoride etherate, magnesium bromide, lithium perchlorate, and trimethylsilyl triflate, can often be employed. The milder conditions are especially suitable for the cyclization of more reactive substrates, such as those containing activated arenes, π-rich heterocycles, activated alkenes, and enols/enolates, as well as substrates with sensitive functionalities.

In this section, applications of *N*-acyliminium ion cyclizations in synthesis are discussed with an eye toward reaction scope and limitations. First, we briefly present an organized collection of common approaches to *N*-acyliminium ion precursors.

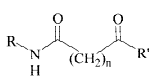
3.1. Sources of *N*-Acyliminium Ions

N-Acyliminium ions can be accessed through a variety of means; however, because of their reactivity, they are almost always generated in situ. Since the synthetic methodology in this field has been amply reviewed,[15,17,19,290] we will provide only a brief overview of useful procedures, with an emphasis on those that have been applied to cyclizations.

Numerous *N*-acyliminium ion precursors contain amides substituted on the nitrogen atom with an α-oxygenated carbon functionality, such as α-hydroxyl, α-alkoxy, or α-acyloxy alkyl groups (viz. **218**). In the case of *N*-(α-hydroxyalkyl)amides (**218**, R = H), the compounds are dissociable into secondary amide and carbonyl (aldehyde or ketone) components, but the amide adducts from electrophilic species such as chloral, formaldehyde, and glyoxylate are relatively robust. Compounds with the carbonyl and



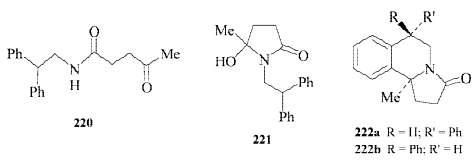
218

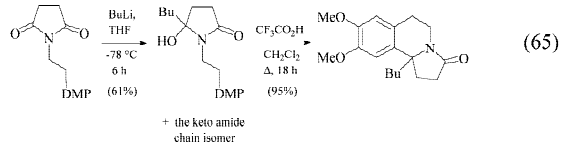


219 (n = 2 or 3)

amide units present in the same molecule, and which are able to form five- or six-membered rings within a ring-chain equilibrium, generally form very stable

adducts (viz. **219**). Regardless of whether these *N*-acyliminium ion precursors exist as a mixture of ring and chain isomers, they cyclize via *N*-acyliminium ions as though the ring-opened species were of no serious consequence. For instance, the adduct from 2,2-diphenylethylamine and α-angelicalactone, a 1:2 mixture of **220** and **221**, cleanly cyclizes in polyphosphoric acid at 100 °C to **222** (84% yield; 94:6 **a**/**b** ratio).[45,67] Another excellent example is illustrated in eq 65.[291] Clearly, both open-chain and ring-closed forms are competent substrates for *N*-acyliminium ion cyclizations. *ω*-Hydroxy lactams can serve as *N*-acyliminium precursors, or one can install another leaving group, such as alkoxy (eqs 9 and 29),[45,124] acetoxy (eq 43),[173] mesyloxy (eqs 45 and 51),[179,186,194] or halogen (eq 42).[165] In many cases, *ω*-hydroxy or *ω*-alkoxy lactam intermediates are converted directly into the *N*-acyliminium species for cyclization, rather than being isolated and purified.

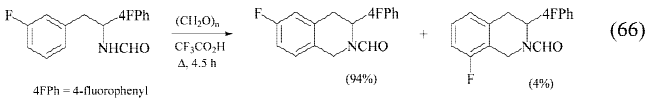




(65)

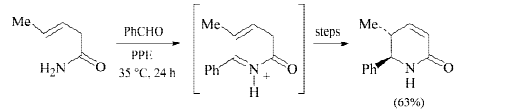
3.1.1. Reaction of Amides with Aldehydes or Ketones

Secondary amides combine with aldehydes or ketones to provide α-hydroxyalkyl derivatives, which can form the corresponding *N*-acyliminium ions on treatment with acid. In some cases, dehydration to an *N*-acyl enamine ("enamide") may take place, but that species can also cyclize effectively (e.g., eq 7).[45] This protocol is very versatile, especially for intramolecular systems, with the aldehyde or ketone entities being generated in a myriad of ways. Examples of secondary amide/aldehyde cyclizations are shown in eqs 13, 16, 18−20, and 36,[31,89,95,100,104,105,144,146,149] and examples of secondary amide/ketone cyclizations are shown in eqs 4, 7, 10, and 11.[23,26,27,45,52] Reactive aldehydes, such as formaldehyde or ethyl glyoxylate, can combine with secondary amides that bear a suitable nucleophile, under acidic conditions, to furnish cyclized products directly.[15] This reaction is featured in several tetrahydroisoquinoline syntheses[292−297] (e.g., eq 66[294]).



(66)

Primary amides react with aldehydes or ketones (or their equivalents) to form *N*-acylimines, which can then be converted to *N*-acyliminium ions by reaction at nitrogen with a suitable electrophile, particularly with protons. This approach has been applied to the synthesis of five- and six-membered lactams (e.g., eqs 67 and 68).[298−301] Depending on the acidic reagent employed, a different product is obtained due to a mechanistic divergence. More commonly, *N*-acylimines are generated from the primary amide and a highly reactive aldehyde, such as formaldehyde or ethyl glyoxylate.[14,15] However, this method is more generally applicable to cyclic systems since acyclic *N*-acylimines tend to hydrolyze to the amide and aldehyde. A valuable method for obtaining stable adducts, such as RCH(OTMS)NHCHO, is based on the condensation of aldehydes with bis-trimethylsilylformamide,[302] and these reagents undergo smooth *N*-acyliminium cyclization when a reactive nucleophile is present.[303,304] This protocol proved to be especially effective in the synthesis of pavine alkaloids (e.g., eq 69[304]).[305] Another useful procedure involves primary sulfonamides and aldehydes, whereby intermediate *N*-sulfonylimines readily cyclize onto reactive nucleophiles (eq 70).[306]



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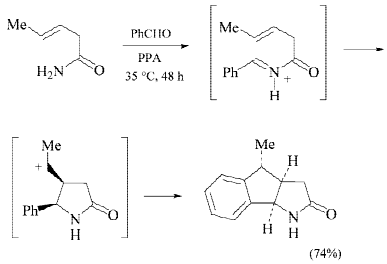

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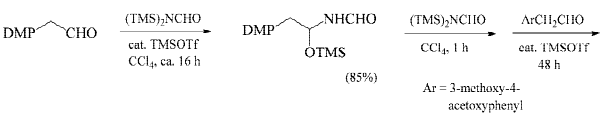

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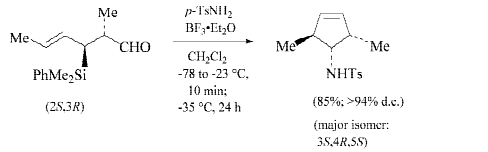

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3.1.2. Addition of Nucleophiles to Imides[15,17,19,290]

Perhaps the most successful and versatile technique for obtaining *N*-acyliminium ion precursors has been selective addition of hydride to one carbonyl of a cyclic imide.[15,307a] Although lactam diastereomers arising from the new stereocenter (at the *ω* position) are often encountered, this is inconsequential to the cyclization reaction. Various methods are available to perform this conversion without overreduction or reductive ring opening. The most common procedures

are (1) sodium borohydride in ethanol with a strong protic acid (e.g., HCl or $MeSO_3H$) at ca. 0 °C, (2) sodium borohydride in methanol between −20 and 0 °C, and (3) diisobutylaluminum hydride in toluene from −78 to −20 °C. When using sodium borohydride, the specific conditions are important to avoid reductive ring opening. Other hydride reagents, such as lithium triethylborohydride and sodium bis(2-methoxyethoxy)aluminum hydride, are also quite effective. It is especially noteworthy that the reaction of unsymmetrically substituted cyclic imides with sodium borohydride usually proceeds with high regiochemical control, such that reduction of the *sterically more hindered* imide carbonyl is strongly preferred.[15,17,307b] As a complement, reduction of unsymmetrically substituted cyclic imides with diisobutylaluminum hydride favors the less substituted carbonyl group.[15,17] For imides having both exocyclic and endocyclic carbonyls, such as *N*-acylpyrrolidin-2-ones, there can be problems from overreduction and a lack of regiochemical control, with the products being dependent on the particular substituents involved.[308]

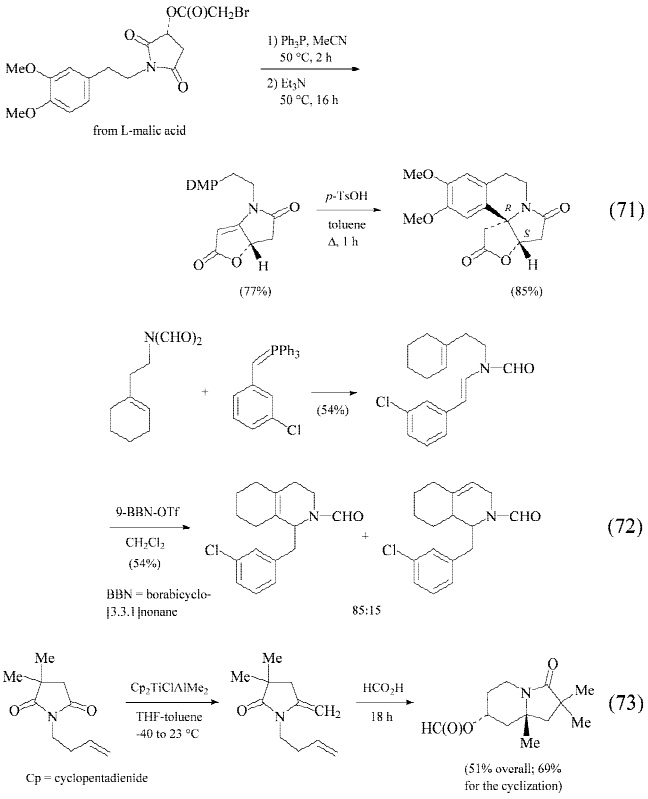
Organometallic reagents can add selectively to imides to give *N*-acyliminium ion precursors with a tertiary reactive center. Grignard and lithium reagents are useful, but care should to be exercised to avoid overaddition.[15,19,290] An example of an organolithium addition is shown in eq 65.[291] With unsymmetrically substituted cyclic imides, Grignard reagents usually add preferentially to the sterically less hindered imide carbonyl. A titanium-mediated intramolecular addition of alkenes to imides, via Kulinkovich titana-cyclopropane intermediates, shows considerable promise.[309−311] (Also, see the related Wittig and Tebbe olefinations mentioned in the next paragraph.)

3.1.3. *N*-Acyl Enamines (Enamides)

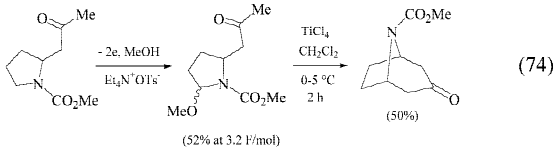
Enamides can be formed by elimination of water or an alkanol from certain ω-hydroxy or ω-alkoxy lactams (e.g., viz. eqs 7 and 8). It is not uncommon to find this intermediate stage in the thermal condensation of primary amines with aldehydo and keto acids, and their derivatives, especially for the keto case (e.g., eq 7).[45,93,312] Enamides can also result from other types of cyclization[313] or azide elimination.[314,315] Other chemical approaches provide enamide-type *N*-acyliminium ion precursors, such as *N*-acylation of enamines[68,81,108−110] (eqs 21 and 22[93−95]) or imines,[316,317] alkaline ferricyanide oxidation of isoquinolinium salts,[318,319] Wittig olefination of imides[316,320,321] (e.g., eqs 71[321] and 72[316]), and Tebbe olefination of imides (eq 73[322]). As a general rule, such enamides are competent cyclization participants; however, rare exceptions exist where enamides cyclize with difficulty, or not at all. Besides being commonly cyclized by protonation, enamides can be activated by other electrophilic reactions, such as halogenation or epoxidation.[15,290]

3.1.4. Oxidation of Amides at the Carbon α to Nitrogen

Electrochemical oxidation at the carbon α to the nitrogen of amides is a versatile method for obtaining *N*-acyliminium ion precursors for cyclization.[323,324] A



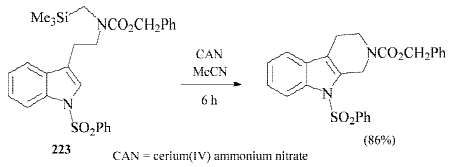
representative example is presented in eq 74. Variable results may be encountered due to the formation of oxidative byproducts.[325,326]



Chemical oxidation has also been used.[15,19,290] This method, when undirected by specific functionality, may be accompanied by problems of regiocontrol and overreaction. An interesting method is the oxidation of *N*-acylpyrrolidines or *N*-acylpiperidines with iodosylbenzene and trimethylsilyl azide to produce 2-azido derivatives, which can serve as *N*-acyliminium ion precursors.[314,315] However, there are some limitations with this procedure because of the formation of side products in the oxidation (isomers and double substitution) and in the *N*-acyliminium cyclization. A radical-based method entails diazotization of 2-aminobenzamides (in the presence of a catalytic amount of CuCl) and subsequent hydrogen-atom abstraction.[327−329] Silicon can be used to promote oxidation at a specific site, and the intermediate *N*-acyliminium ions may cyclize in situ if a reactive π-nucleophile is present.[177,330,331] A good example of this tandem sequence is the cerium(IV) oxidation of *N*-trimethylsilylmethylamide **223**, which leads directly to an efficient cyclization onto the indole 2-position (eq 75).[320]

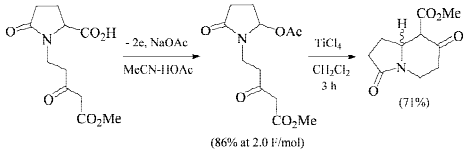
3.1.5. Decarboxylation of α-Amido Acids[290]

A related method involves the oxidative removal of a carboxylic acid group from an α-amido acid to



(75)

produce an *N*-acyliminium ion, which is usually trapped as a heteroatom adduct for subsequent use. A recent procedure is based on hypervalent iodine reagents in conjunction with iodine: $PhIO/I_2$ or $PhI(OAc)_2/I_2$.[332,333] There are also useful electrochemical oxidative decarboxylation methods.[334−336] A representative example of anodic oxidation and cyclization is illustrated in eq 76.[336] α-Amido acid chlorides easily decompose to *N*-acyliminium ions, which can then cyclize (e.g., eq 77),[337] even though the corresponding 5-methoxypyrrolidin-2-ones fail to cyclize, probably because of side reactions.[337]



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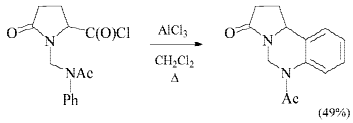
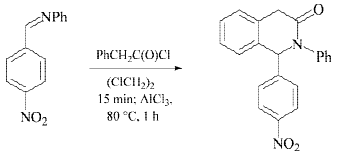


(77)

3.1.6. Acylation of N-Substituted Imines[15]

Perhaps the most direct route to *N*-acyliminium ion species is through acylation of *N*-alkyl- or *N*-arylimines.[15,338−340] The adducts formed may isomerize to enamides on exposure to moderate bases, such as triethylamine. Two different approaches for executing this reaction are illustrated in eqs 78[338] and 79.[339] Some special types of *N*-acyliminium cyclizations are dependent on this method. Imines react with cyclic anhydrides to yield cyclocondensation products via intermediate *N*-acyliminium species (e.g., eq 58)[227,244−276] and with activated carboxylic acids in a Staudinger reaction (formal [2 + 2] cycloaddition) to yield β-lactams (viz. eq 63).[20,277−279]



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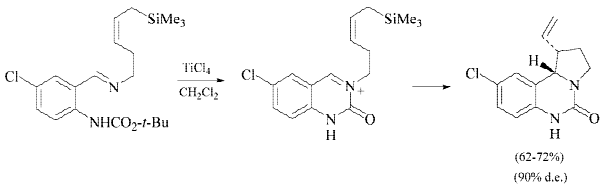
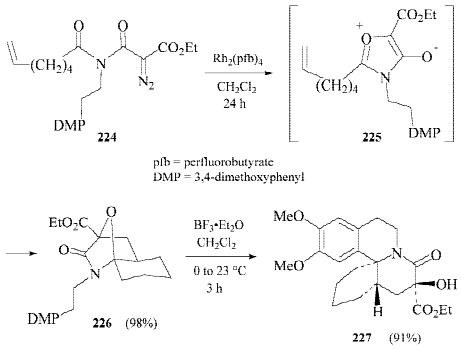


(79)

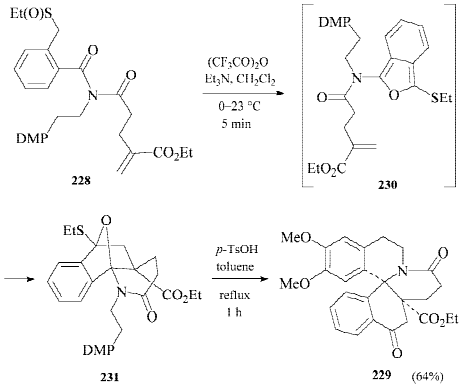
3.1.7. Cycloaddition and Cyclization Reactions

A very interesting and useful approach to *N*-acyliminium ion precursors involves dipolar cycloadditions, Diels−Alder cycloadditions, or cationic cyclizations.[88,341,342] For the purpose of illustration, each type of reaction will be briefly discussed. The first entails a tandem carbenoid cyclization/1,3-dipolar cycloaddition (eq 80).[83,86] On treatment with a catalytic quantity of the rhodium(II) catalyst, the diazo compound **224** yields isomünchnone intermediate **225**, which then undergoes intramolecular dipolar cycloaddition. The resulting polycyclic *N*-acyliminium ion precursor **226** (98% yield) readily cyclizes to **227** under mild Lewis acid catalysis. (A homologous cyclization is shown in eq 12.[83,86])



(80)

A tandem Pummerer cyclization/Diels−Alder cycloaddition/acyliminium cyclization leads to related erythrinane derivatives (e.g., eq 81).[85,87] Sulfoxide **228** is easily converted to homoerythrinane **229** (64% yield) via intramolecular Diels−Alder cycloaddition



(81)

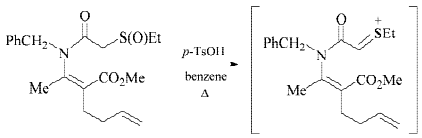
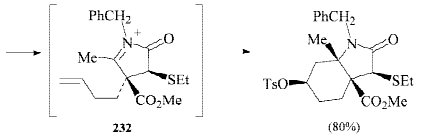
of amidofuran **230** and cyclization of the *N*-acyliminium precursor **231** (isolated and characterized). Thiacarbenium (or thionium) ions from the Pummerer reaction and other processes, such as dithioacetal dissociation, can provide different *N*-acyliminium ions (e.g., **232** and **233**) for synthetically useful cyclizations (eqs 82 and 83).[343−346]

3.2. Reactions of Benzenoid Nucleophiles

N-Acyliminium cyclizations have been widely applied to aromatic nucleophiles.[11−19,290] Unactivated benzene rings, as well as benzene rings substituted with moderate deactivating groups (e.g., fluoro[118]), can participate effectively. At the outset of this section, we will present various examples of erythrinane syntheses as a platform to illustrate the utility of benzenoid reactions.

3.2.1. Synthesis of Erythrinanes

The earliest *N*-acyliminium ion cyclizations of benzene nucleophiles exist in the syntheses of *Eryth-*

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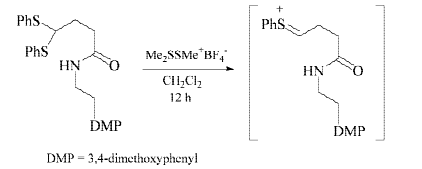
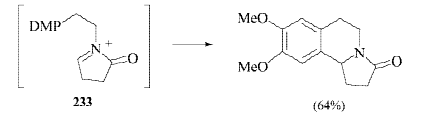
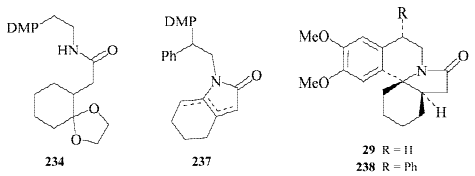
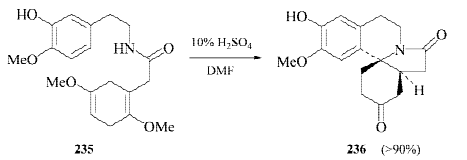




(83)

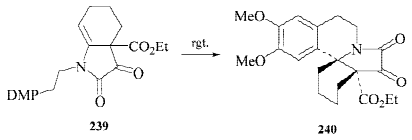
rina isoquinoline alkaloids.[21−26] Belleau demonstrated the advantage of an *N*-acyliminium variant of the Mannich reaction in the synthesis of erythrinane **5** (cf. eqs 3 and 4).[23] The effective Belleau-type (eq 4)[23] and Mondon-type (eq 11)[26,27,32] modes of cyclization differ by the position of the lactam carbonyl, but both modes supply the *cis*-fused perhydroindole configuration. These two routes work smoothly with methoxy-activated or unactivated benzene rings and tolerate various substituents on the aliphatic skeleton. In the Mondon-type cyclization, relatively mild cyclization conditions are sufficient with a 3,4-dimethoxyphenyl nucleophile (e.g., eq 11).[26,27] In fact, it is possible to convert **234** to **29** in 75% yield by using 1 N aqueous ethanolic HCl at room temperature (for 2 days).[32] Such a facile ring closure under mild conditions is relatively common when dealing with electron-rich arenes; for example, **235** readily gives **236** with 10% sulfuric acid (eq 84),[65] **30** gives **31** with boron trifluoride etherate (eq 12),[83,86] and **237** gives **238** with ethanolic HCl at reflux in just 10 min (80−90% yield).[45] For less reactive nucleophiles, more strenuous conditions are needed, such as polyphosphoric acid at 100−135 °C for 12−24 h (e.g., eq 7).[45,66]





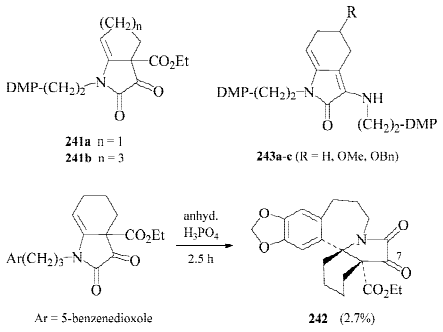
(84)

Tsuda and co-workers examined erythrinane-based cyclizations of benzenoid nucleophiles ranging from phenyl to trimethoxyphenyl to hydroxyphenyl, as well as heterocyclic species, under a variety of conditions.[68−70,75−77,80,82] Of particular note is the conversion of **239** to **240** (eq 85),[68−70,80] in which



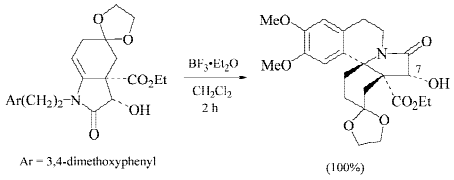
(85)

quantitative yields are obtained with polyphosphoric ester (PPE) at 90 °C in 1.5 h, boron trifluoride etherate at 23 °C in 3 h, or $AgClO_4$ in benzene at 80 °C for 0.5 h.[68,80] The use of 10% HCl in methanol at reflux is not effective in this case. Substrates with a five-membered (**241a**) or seven-membered (**241b**) ene-containing ring also cyclize well (100% H_3PO_4, 25−50 °C, 1−2 h). However, the length of the linker to the aromatic nucleophile is critical in that closure of a seven-membered ring to give **242** proceeds poorly (eq 86).[80] Derivatives with acid-sensitive moieties,



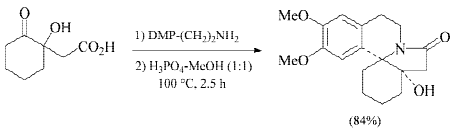
(86)

such as a free hydroxyl or a ketal, give excellent results with boron trifluoride etherate (e.g., eq 87).[80,81]



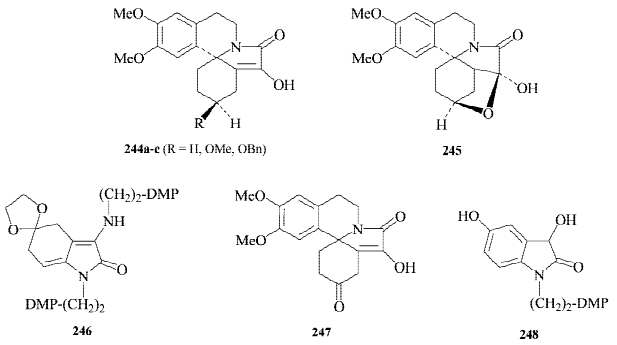
(87)

Another *N*-acyliminium cyclization that tolerates an acid-sensitive tertiary hydroxyl, if the reaction is performed carefully, is depicted in eq 88.[59] Although boron trifluoride conditions seem to be optimal with sensitive groups, they are not always trouble-free.



(88)

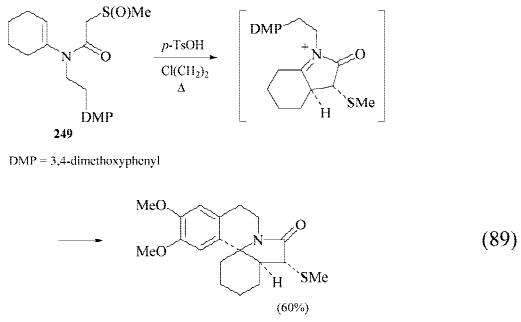
The glyoxylate approach to erythrinanes highlights a worthwhile synthetic protocol (e.g., **243** → **244**).[60,347,348] The cyclizations of **243a** and **243b** with H_3PO_4−MeOH−H_2O at reflux give **244a** (87% yield) and **244b** (74% yield).[347] However, benzyloxy substrate **243c** not only cyclizes but also experiences ether ring closure and debenzylation to give polycyclic hemiketal **245**, a transformation that is enhanced by using a phosphoric acid/formic acid mixture (61% yield).[60] In the case of ketal **246**, cyclization to **247** fails because aromatized oxindole **248** is produced.



However, a strategically placed carbethoxy substituent can prevent such aromatization (eq 87).[80]

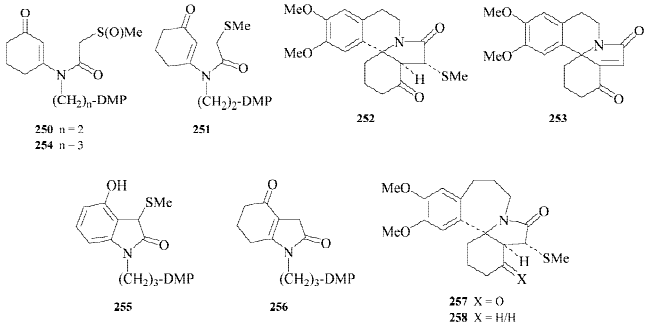
3.2.2. Tandem Reactions

The first tandem reaction sequence reported was a Pummerer cyclization/*N*-acyliminium ion cyclization to yield erythrinanes, such as that starting with **249** (eq 89[72,73]).[72−74,78,79] The analogous reaction with



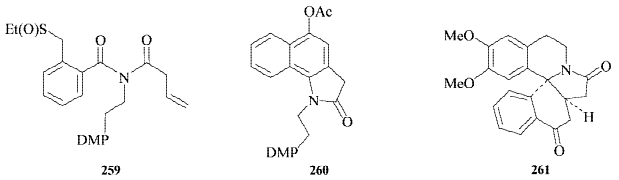
(89)

enone **250**, however, is not so straightforward. Under *p*-toluenesulfonic acid conditions, **250** only yields intermediate indolinedione **251**, which has difficulty cyclizing to erythrinane **252** because of the vinylogous amide conjugation.[74] This problem can be surmounted by using 85% phosphoric acid (80 °C, 2 h) to yield a mixture of desired **252** (53%) and byproduct **253** (15%).[349] Elimination product **253** is formed predominantly when 99% formic acid is used (reflux, 20 h).[74] By contrast, treatment of **254** with formic acid (100 °C, 20 h) does not yield any homoerythrinane product **257**; rather, **255** (47%) and **256** (16%)

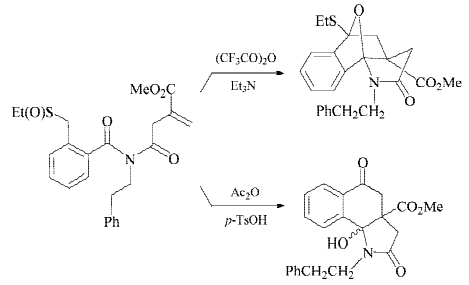


are obtained instead.[74] Formation of a seven-membered ring via an *N*-acyliminium cyclization can be problematic, as with the reaction in eq 86.[80] In a similar vein, the trimethylene analogue of the reaction in eq 89 does not give any homoerythrinane **258**.[79]

Tandem routes to erythrinane derivatives involving Pummerer cyclization, Diels−Alder cycloaddition, and *N*-acyliminium ion cyclization may be burdened by variable results.[85,87] Unlike the smooth transformation in eq 81, the reaction of **259** is complicated.

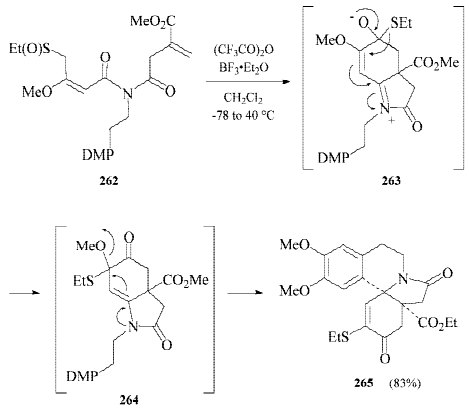


Treatment of **259** with acetic anhydride, followed by *p*-toluenesulfonic acid (xylenes, reflux), produces benzindolinone **260** instead of erythrinane **261**.[85,87] Thus, a bridgehead substituent in the intermediate *N*-acyliminium ion precursor (viz. **231**) is crucial. A successful *N*-acyliminium cyclization also requires a suitably activated aromatic ring. In fact, no erythrinane products are isolated when the substrate contains a plain benzene ring (eq 90). The practicality



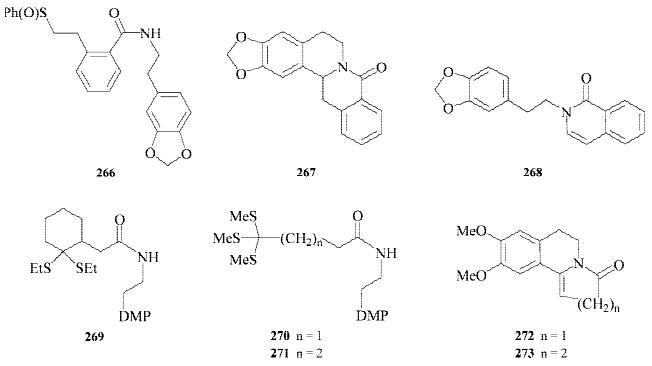
(90)

of this tandem method was effectively realized in a triple-cascade process en route to erysotramidine.[87] A key step in the conversion of **262** to **265** involves *N*-acyliminium ion **263**, which, prior to cyclization, undergoes a 1,2-shift of the ethylthio group and expulsion of methoxide, as delineated in **264** (eq 91).

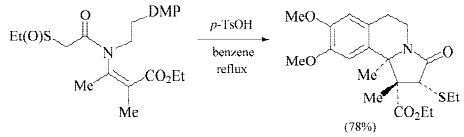


(91)

Thiacarbenium ions from the Pummerer reaction, or from dithioacetal dissociation, can initiate diverse *N*-acyliminium ion cyclizations (eqs 82 and 83).[343−346] In secondary amide reactions, as in eq 83, an intermediate thioaminal (*ω*-thioalkoxylactam) is generated in situ as an *N*-acyliminium ion precursor. In related reactions, **266** affords berberine **267** via enamide intermediate **268** (*t*-$BuMe_2SiOC(OMe)=CH_2$ and ZnI_2, then "acidic conditions"; 47% overall yield), and **269** affords erythrinane **29** ($Me_2SSMe^+BF_4^-$, CH_2Cl_2, reflux, 12 h; 71% yield).[343,345] Although orthothioesters **270** and **271** do not cyclize with



$Me_2SSMe^+BF_4^-$, dimethyl sulfate successfully provides **272** (46%) and **273** (71%), respectively.[345] The tandem thionium/*N*-acyliminium reaction is useful for preparing polycyclic lactams with good stereochemical control (e.g., eqs 92 and 93).[344]



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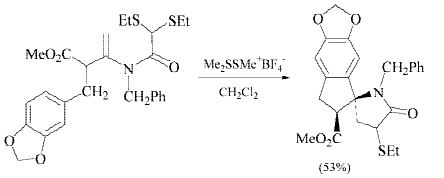
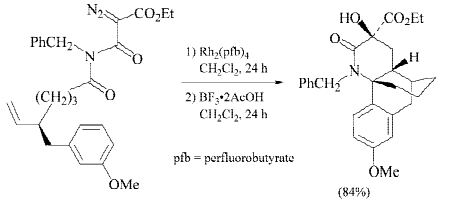


(93)

In a sequential cycloaddition/*N*-acyliminium ion cyclization process, dipolar reactants (isomünchnones), generated from diazo ketones by rhodium(II) catalysis, undergo intramolecular dipolar cycloaddition to yield oxabicyclic species, which constitute masked *N*-acyliminium ions.[83,86,88,350] A representative example is shown in eq 80. This reaction works well with a less reactive 3-methoxyphenyl group (eq 94).[350] The high regiocontrol here contrasts with other *N*-acyliminium ion cyclizations of 3-methoxybenzene-containing substrates.[325,351,352]

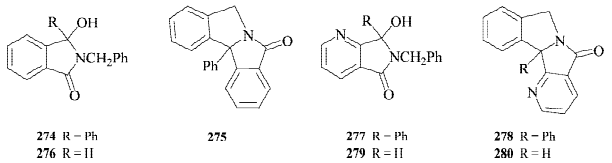


(94)

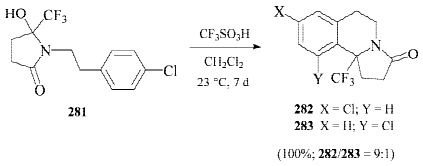
3.2.3. Effect of Substituents on the Iminium Ion

In *N*-acyliminium ion cyclizations, the nature of the substituent on the carbon or nitrogen of the iminium unit normally does not greatly impact the reaction outcome.[15,19,45,290] However, there are instances in which significant effects do occur. More reactive *N*-acyliminium species, such as those bearing electron-withdrawing groups on the carbon atom, those devoid of steric hindrance at the carbon atom, or those with more electron-deficient *N*-acyl groups, may lead to higher yields and/or allow for milder conditions.

With respect to carbon substitution, difficulties arise with conjugated carbon−carbon double or triple bonds, which result in reduced yields.[291,353] With standard substituents, such as phenyl or hydrogen, there are cases of differential reactivity, especially with ring strain in the cyclization. For certain hydroxyisoindolinones, disparate reactivity for phenyl vs hydrogen exists, in that the phenyl case succeeds and the hydrogen case fails.[354,355] For example, although **274** gives **275** in good yield, **276** reacts poorly.[354] Similarly, whereas **277** cyclizes in PPA at 135 °C to **278** in 72% yield, **279** fails to give **280**.[355]

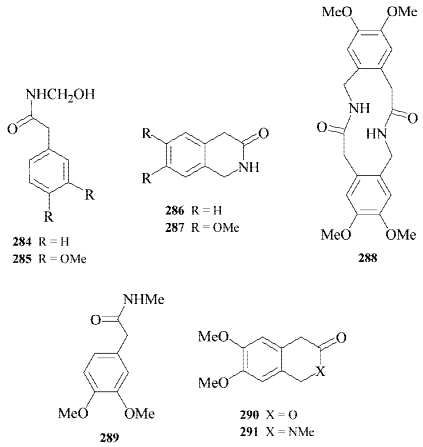


Since the corresponding cyclizations to six-membered rings supply good yields irrespective of the phenyl or hydrogen group,[354] this substituent effect is apparently accentuated by ring strain during formation of the five-membered ring.[356,357] With a trifluoromethyl group on the iminium carbon, which boosts electrophilicity, high yields are observed.[358] For example, the cyclization of **281** furnishes a 100% yield of pyrroloisoquinolines **282**/**283**, even though the arene nucleophile is a less reactive chlorophenyl group (eq 95).



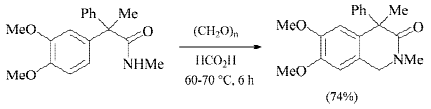
(95)

The generation of *N*-acyliminium ions with formaldehyde or glyoxylate can be very useful, especially for cyclizations of unactivated arene nucleophiles. In reactions with formaldehyde, it is important to have appropriate conditions to avoid potential side reactions. This issue surfaces with *N*-hydroxymethylphenylacetamides **284** and **285**,[359] in that **284** reacts with pyrophosphoric acid at 140−160 °C to give a 76% yield of **286**, whereas **285** reacts with pyrophosphoric



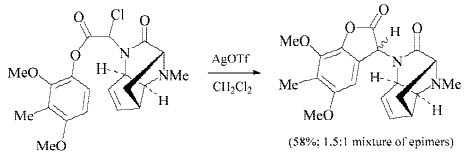
acid at 100 °C to give **287** (13%) and dimeric macrocycle **288** (16%). At 23 °C, **284** yields only intractable polymeric material and **285** yields a much higher

proportion of undesired **288** (up to 93%). In another case, phenylacetamide **289** reacts with paraformaldehyde in formic acid to yield isochromanone **290** (preemptive hydroxymethylation on the arene) rather than isoquinolinone **291** via an *N*-acyliminium cyclization.[296,360] Alternatively, α,α-disubstituted phenylacetamides cyclize by the desired *N*-acyliminium route, as exemplified in eq 96.[296] In general, side



(96)

reactions can be minimized by employing preformed *N*-hydroxymethylcarboxamide substrates. Glyoxylate-type *N*-acyliminium ions are very effective because they cyclize under relatively mild conditions,[166,361,362] as exemplified in eqs 97[361] and 98.[362]



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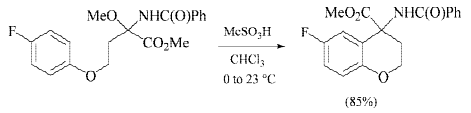
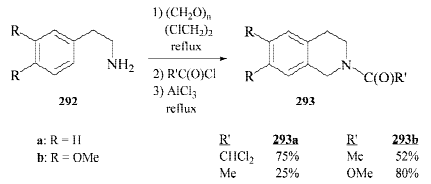


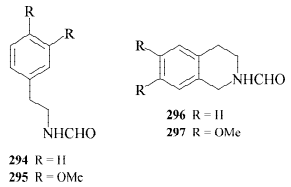
(98)

The effect of diverse *N*-acyl groups on *N*-acyliminium ion cyclizations has been assessed in the reactions of **292a** or **292b** (eq 99).[363] For the less reactive phenyl substrate, **292a**, the electron-deficient dichlo-



(99)

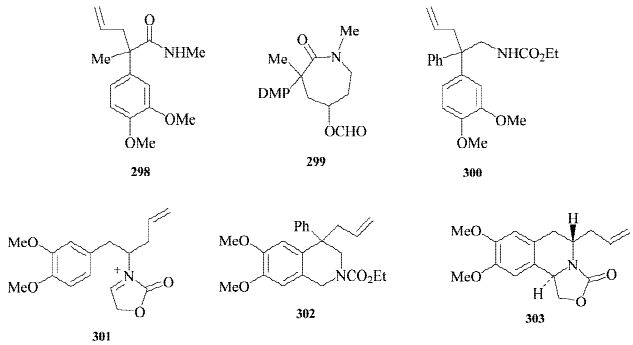
roacetyl group supplies the highest yield of tetrahydroisoquinoline **293a** (75%), and acetyl supplies the lowest yield (25%). For the more reactive dimethoxyphenyl substrate, **292b**, yields of **293b** are in the range of 52−80%, with methoxycarbonyl being optimal. Results in a related study with benzaldimines are comparable to these.[364] *N*-Formyliminium ions have proven to be synthetically versatile.[293−295] The ring closure of **294** and **295** with formaldehyde leads to **296** (57%) and **297** (73%), with a higher yield for the more reactive aromatic nucleophile.[293] Tetrahy-



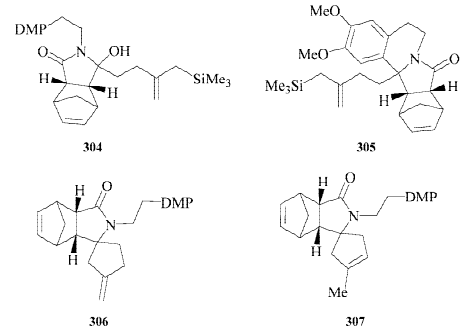
droisoquinolines are also obtained in good yields from the reaction of **294** with acetaldehyde (52%) or benzaldehyde (48%); however, the more reactive **295** results in higher yields (66% and 59%, respectively).[293] The *N*-formyliminium ion reaction is favored for the synthesis of 3-aryltetrahydroisoquinolines (e.g., eq 66) because it eschews a problem with elimination to stilbenes under harsh conditions; in fact, yields are generally good to excellent (>70%).[294,295] Another advantage is the tolerance for electron-rich 3-aryl substituents and bulky quaternary formamides, such as $PhCH_2CMe(Ph)NHCHO$.[294,295] Similarly, *N*-sulfonyliminium ion cyclizations effectively provide tetrahydroisoquinolines.[365−367] A special version of the *N*-formyliminium ion cyclization is depicted in eq 69,[304] wherein bis-aldehyde adducts of formamide, masked as trimethylsilyl ethers, double cyclize with good yields to generate the azabicyclic pavine alkaloid skeleton.[304]

3.2.4. Competition between Carbon Nucleophiles

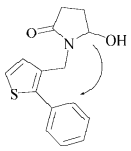
The cyclization of phenylacetamide **298** is interesting because the alkene group competes favorably with the dimethoxyphenyl group to yield azepinone **299** in 78% yield, with only a trace of the isoquinolinone.[296] Surprisingly, carbamate reactants **300** and **301** react in the opposite manner to give solely isoquinolinone products **302** (84% yield)[296] and **303** (63% yield; sole isomer), respectively.[368] Conforma-



tional effects on the cyclization geometry, by virtue of the *N*-acyliminium carbonyl being inside or outside the newly formed ring, may be responsible for this dichotomy of reactivity. A notable example of competition between arene and alkene π-nucleophiles is the cyclization of **304**,[206] which has an unusual dependency of product ratios on cyclization conditions. Treatment of **304** with trifluoroacetic acid gives a mixture of tetrahydroisoquinoline **305** (probably a single isomer) and spirocyclic compounds **306**/**307**, due to attack on the arene and allylsilane. However, when mesyl chloride and triethylamine are used, only the allylsilane unit reacts to give **306**/**307** (71% yield; 1:1 ratio).[206]



In a case of competition between phenyl and thiophene π-nucleophiles, the cyclization of **308** with trifluoroacetic acid occurred exclusively on the phenyl ring to form a new seven-membered ring (80% yield),



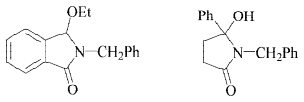
308

rather than on the thiophene ring (at the 4-position) to form a new five-membered ring.[369] This result reflects the difficulty in forming a new five-membered ring, especially for a 5,5-fused product (vide infra).[370]

In competition between phenyl and keto/enol groups, as in the aluminum(III) chloride-promoted reaction of adducts from *N*-phenylbenzaldimines and arylacetyl chlorides (i.e., α-chloro amides),[371] electron-rich aryl groups tend to yield *N*-phenyl-1-aryltetrahydroisoquinolin-3-ones via the *N*-acyliminium ion cyclization. However, other aryl groups tend to yield *N*-phenyl-β-lactams via the Staudinger reaction.[371] Related results arise in cyclizations of *N*-sulfonyliminium ions to benzothiazine 2,2-dioxides.[372]

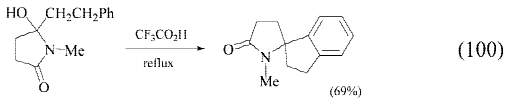
3.2.5. Formation of Five-Membered and Seven-Membered Rings

The formation of five-membered rings by *N*-acyliminium ion cyclization onto arenes can be problematic. For example, as mentioned above, **274** and **277** produce **275** and **278** in good yield, but **276** and **279** react quite poorly.[354,355] The corresponding cyclizations to six-membered rings occur with good yields for both phenyl and hydrogen substitution.[354] The difficulty in forming five-membered rings is also illustrated by the failure of **309** and **310** to cyclize under various acidic conditions,[373] as well as the



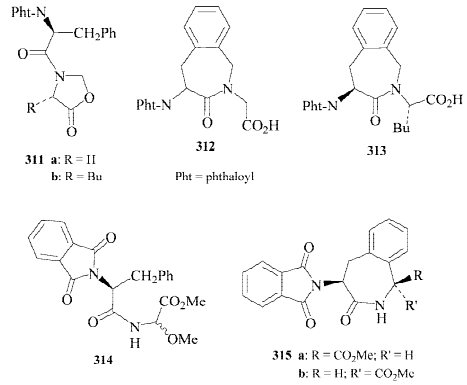
309 **310**

propensity of **308** to cyclize to a seven-membered-ring product instead of a five-membered-ring product.[369] On the other hand, five-membered rings are formed more readily from spirocyclization (e.g., eq 100[374])[374−376] and from the cyclization of *N*-arylglycinamide-based ions to 3-aminoindolin-2-ones.[377]



(100)

Formation of seven-membered rings in arene cyclizations can be troublesome,[72,77,78,313] but there are several successful examples,[118,330,369,377−390] two of which are the cyclization of **308**[369] and the reaction in eq 27.[118] Excellent results are obtained for the conversion of enantiomerically pure **311a** to benzazepine **312** with PPA, methanesulfonic acid, triflic acid, or trimethylsilyl triflate (80−94% yield), although stereoisomerization takes place at the phthalimide-bearing carbon.[378] However, there is just



311 **a**: R = H
b: R = Bu

312

Pht = phthaloyl

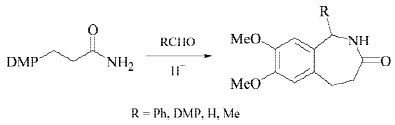
313

314

315 **a**: R = CO_2Me; R' = H
b: R = H; R' = CO_2Me

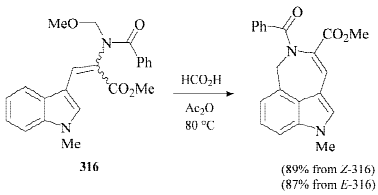
10% epimerization in the cyclization of **311b** to benzazepine **313** with triflic acid (96% yield),[380] and presumably no stereoisomerization in the cyclization of **314** to **315a** and **315b** with triflic acid (75% yield; 10:1 mixture).[378]

Some other notable examples of seven-membered-ring generation follow. (1) A series of benzazepinones is obtained from (dimethoxyphenyl)propanamide and benzaldehydes (R = Ph and DMP) in good yields, although formaldehyde (R = H) causes difficulties (eq 101).[388] (2) Azepinoindoles can be efficiently pre-



(101)

R = Ph, DMP, H, Me

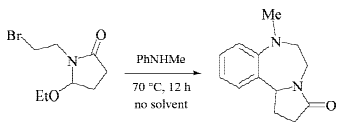


316

(89% from *Z*-316)
(87% from *E*-316)

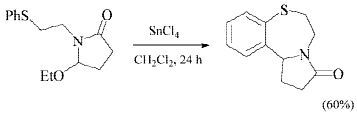
(102)

pared,[381−383] as exemplified in eq 102.[383] It is interesting that enamide **316**, as the *Z* or *E* isomer, cyclizes exclusively at the indole 4-position to give the azepinoindole, even though the reactive indole 2-position is available for six-membered-ring formation (eq 102).[383] The unusual nature of this regiochemistry is underscored by the fact that the tryptophan analogue of **316** (double bond is saturated) cyclizes only at the 2-position to give a β-carboline derivative. (3) Benzodiazepines and benzothiazepines can be efficiently prepared (eqs 103 and 104),[384] with the former reaction being unusual because the necessary acid catalyst, HBr, is produced from bromide displacement by the amine.



(103)

(65%)

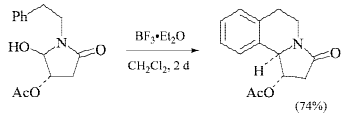


(104)

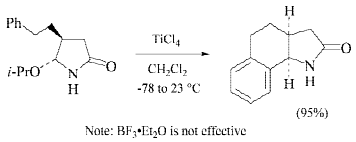
(60%)

3.2.6. Enantiospecific Synthesis

Numerous *N*-acyliminium ion cyclizations of nonracemic substrates afford enantiomerically enriched products.[117,118,320,321,381,391−399] Two examples of diastereoselective, enantiospecific conversions are shown in eqs 105[391] and 106,[396] while some others are noted in eqs 26,[117] 27,[118] and 71.[320,321] Benzyl urethane

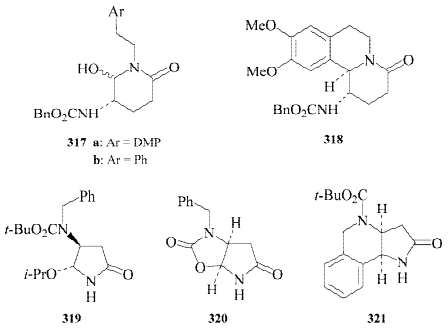


(105)



(106)

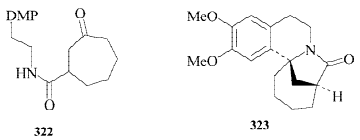
317a, with an electron-rich 3,4-dimethoxyphenyl group, cyclizes exclusively to **318** in 94% yield with >95% enantiomeric purity (BF_3·Et_2O, MeCN, −78 to −10 °C).[397] The arene adds from the less hindered face of the *N*-acyliminium ion, and the high enantiomeric purity indicates an absence of racemization via an enamide intermediate. Cyclization of phenyl



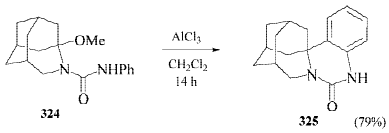
analogue **317b** is unsuccessful,[397] possibly because the urethane group competes for the *N*-acyliminium ion in the absence of a suitably nucleophilic arene, as in the conversion of *tert*-butyl urethane **319** to **320** instead of **321** (with $TiCl_4$).[394]

3.2.7. Bicyclic Bridgehead Iminium Ions

Cyclic keto amide **322** cyclizes with HF to polycycle **323** in 70% yield.[50] This reaction is impressive because it creates considerable molecular complexity



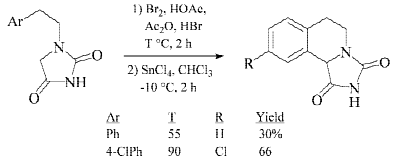
in a single step and involves a bicyclic bridgehead *N*-acyliminium ion, **18**, in which stabilization of the cation by the amide nitrogen is stereoelectronically disfavored according to Bredt's rule. Therefore, this *N*-acyliminium ion is likely to possess extraordinary reactivity. In a similar vein, the cyclization of azahomoadamantane **324** produces polycyclic quinazoline **325** in 79% isolated yield (eq 107) via bicyclic bridgehead *N*-acyliminium ion **19**.[51]



(107)

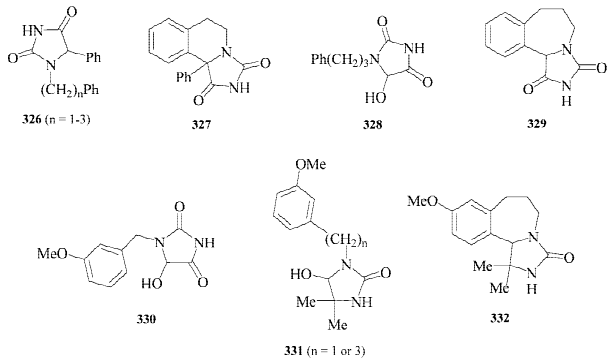
3.2.8. Cyclic Ions Containing Additional Heteroatoms

There is a large body of practical synthetic chemistry involving cyclic *N*-acyliminium ions that contain additional heteroatoms.[400−434] A notable example is the hydantoin-based *N*-acyliminium ion cyclization illustrated in eq 108.[400] In the bromination of the

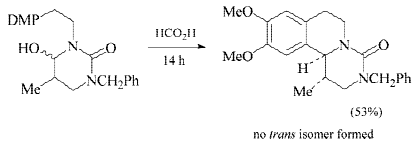


(108)

5-phenyl derivative **326** ($n = 2$), the tricyclic product **327** forms spontaneously in 90% yield; there is no need for a Lewis acid such as tin(IV) chloride to generate the requisite *N*-acyliminium ion. However, no tricyclic products are obtained from **326** ($n = 1$) or **326** ($n = 3$) either with or without the agency of tin(IV) chloride. It is possible to close a seven-membered ring to obtain tricyclic compounds, such as in the production of **329** from **328** in modest yield (CF_3CO_2H, trifluoroacetic anhydride).[401] However,

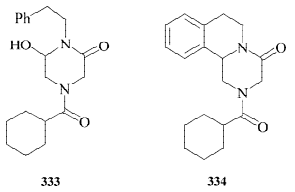


the formation of a five-membered ring is difficult, as can be appreciated by the failure of **330** to cyclize even though an activating methoxy substituent is present.[401] There is a similar dichotomy with respect to ring size in the cyclization of imidazolidin-2-ones **331** ($n = 3$) and **331** ($n = 1$), with the former supplying **332** in 68% yield and the latter failing.[402] The successful cyclization of imidazolidin-2-ones demands the absence of a hydrogen at the 4-position; otherwise, dehydrative elimination occurs to give imidazolin-2-ones, which fail to participate in the *N*-acyliminium ion cyclization.[401−404] However, this issue is surprisingly inconsequential in the cyclization of analogous pyrimidin-2-ones (e.g., eq 109).[405,406]

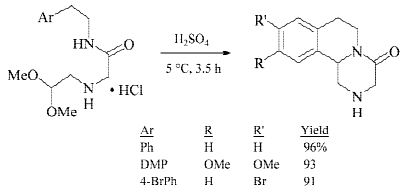


(109)

Piperazinones cyclize to isoquinoline tricycles generally with excellent yields.[404,407−410] For instance, treatment of **333** with 12 N HCl at 0 °C affords the

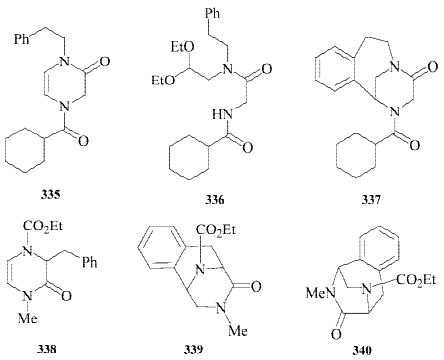


drug praziquantel, **334**, in 95% yield.[407] An unprotected nitrogen is well tolerated in this type of cyclization (eq 110).[408] It is also possible to obtain **334**

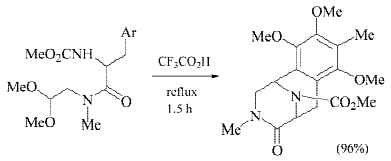


(110)

from ene diamide **335** in quantitative yield with concentrated sulfuric acid and from **336** with methanesulfonic acid (73% yield).[409] Interestingly, although **335** can lead to two different *N*-acyliminium ions on protonation of the alkene, only a single reaction path transpires, that to **334**; no alternative bridged product **337** is formed. In considering such dual reactivity, it is remarkable that **338** cyclizes exclusively to diazabicyclo[3.3.1]nonane **339** in 100% yield (trifluoroacetic acid) via the *N*-carbamoyliminium ion, with no diazabicyclo[3.2.2]nonane **340** being formed.[410]



A double-cyclization protocol has surfaced as an important synthetic tool for obtaining the 3,9-diazabicyclo[3.3.1]nonane system, which is present in several complex bis-isoquinoline alkaloids, such as saframycin, ecteinascidin, and phthalascidin.[411−426] In this process, steric issues can become quite critical. Two different, direct approaches to the right-hand portion of saframycin are depicted in eqs 111[411] and 112.[412] In the latter case, the *N*-acyliminium cyclization of **341** gives a single product, **343**, in good yield despite the necessity for **341** to isomerize via proto-



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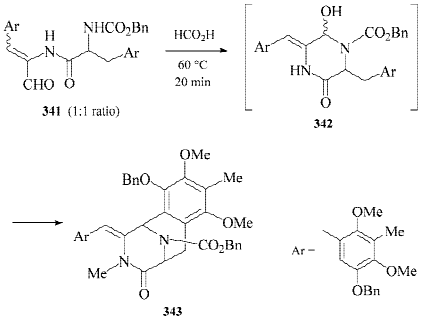
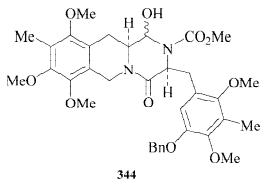
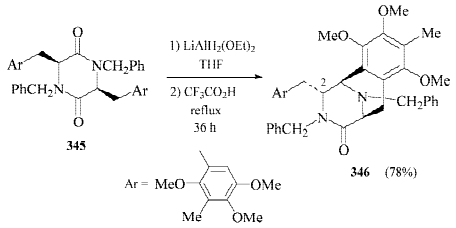


(112)

nation−deprotonation, such that only the *Z* isomer **342** is converted. Under the same conditions, **344** does not cyclize to the 3,9-diazabicyclo[3.3.1]nonane,

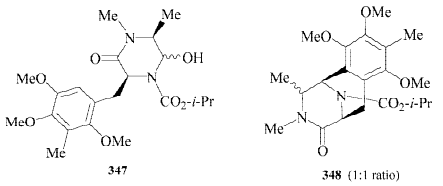


whereas the corresponding *trans* isomer does, because of a significant steric effect.[412] Steric factors arise in the conversion of **345** to **346**, wherein the unnatural C2 stereochemistry is obtained (eq 113).[426]



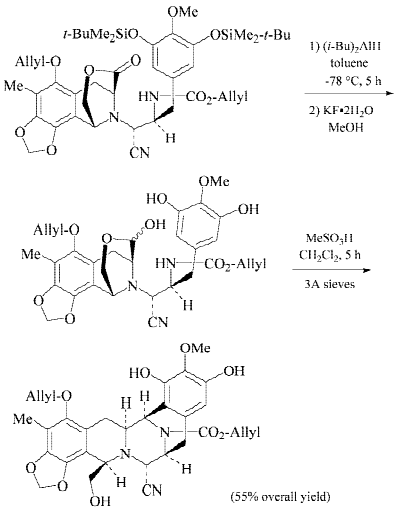
(113)

(This stereochemical inversion probably results from iminium−enamine equilibration.[426]) Stereomutation also occurs in the cyclization of **347** to **348** with



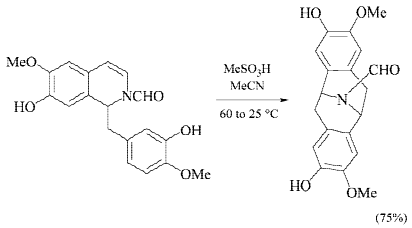
trifluoroacetic acid (51% yield).[421] The power of this double-cyclization method is beautifully expressed in Corey's enantioselective total syntheses of ecteinascidin 743 (e.g., eq 114).[417,425]

Related *N*-acyliminium ion cyclizations have been applied to the 9-azabicyclo[3.3.1]nonane system, a hallmark of the pavine alkaloids.[304,305] For example, argemonine derivatives are obtained via single-cyclization (eq 115)[305] and double-cyclization methods (eq 69).[304] Additionally, an *N*-acylhydrazonium ion



(114)

cyclization of pyrazin-3-one substrates[427] yields 1,8-diazabicyclo[3.2.1]octanes in high yields (e.g., eq 116).[205,428]



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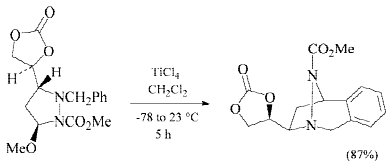
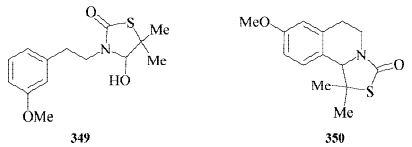


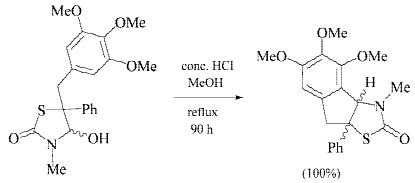
(116)

N-Acyliminium ions based on oxazolidin-2-ones[119,120,121,291,368,398,404] and thiazolidin-2-ones[148,291,429−433] cyclize in fairly standard fashion. A thiazolidinone example is represented by the quantitative conversion of **349** to **350** with formic acid.[429]



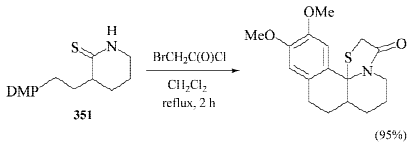
349 **350**

It is important to note that there is no cyclization in the absence of *gem*-dimethyl substitution because of dehydration to an unreactive 1,3-thiazolin-2-one (enamide).[429] With *N*-acyliminium ions based on a dimethyl-1,3-thiazolin-2-one subunit, one can form normally difficult five-membered rings in high yields, although a very reactive 3,4,5-trimethoxyphenyl group is required (e.g., eq 117[429]).[156,429]



(117)

Sulfur-containing *N*-acyliminium ions are integral to a useful one-pot bicycloannulation procedure (eq 118).[430,431] A secondary thioamide reacts with bromoacetyl chloride to generate a 1,3-thiazolinium-4-

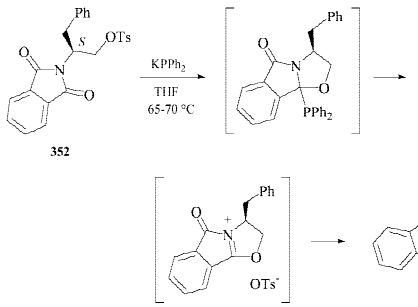


351

(118)

one, an *N*-acyliminium ion that attacks a tethered nucleophile to yield a polycyclic 1,3-thiazolidin-4-one product. With a less reactive arene, such as phenyl, a Lewis acid catalyst like aluminum(III) chloride is needed, and the yield suffers.[431] For example, a one-pot cyclization of the phenyl analogue of **351** gives the bis-desmethoxy product in 31% yield.

An intriguing *N*-acyliminium cyclization is found in the treatment of **352** with potassium diphenylphosphide, which yields polycycle **353** (eq 119).[434] This reaction probably proceeds as follows: the



352

353 (72%)

(119)

phosphide adds to the imide to generate a transient α-oxidophosphine, which is rapidly trapped by intramolecular alkylation on oxygen to give an oxazolidine intermediate that dissociates to a cyclic alkoxy *N*-acyliminium species, which cyclizes onto the phenyl group to give **353**. The high yield of **353** is remarkable, especially given the absence of acidic reagents.

3.3. Reactions of Heterocyclic Nucleophiles

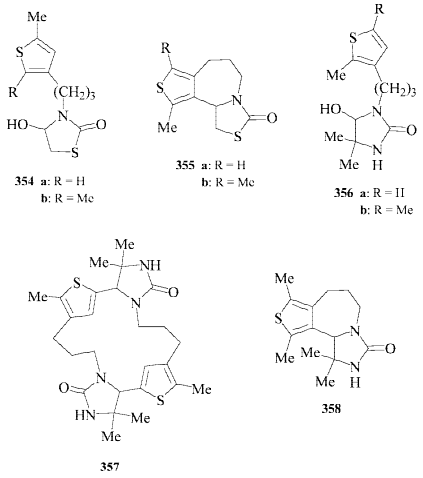
For the most part, *N*-acyliminium ion cyclizations of heterocyclic nucleophiles mirror the reactions of benzenoid nucleophiles. π-Rich heterocycles like furan, pyrrole, and indole are at the higher end of the reactivity spectrum, comparable to a phenyl bearing one or two methoxy substituents. The reactivities of π-deficient heterocycles, such as pyridine, are significantly attenuated. Given the similarity of *N*-acyliminium ion cyclizations of heterocyclic and benzenoid nucleophiles, we will emphasize the more interesting features and distinct differences.

3.3.1. Furans and Thiophenes

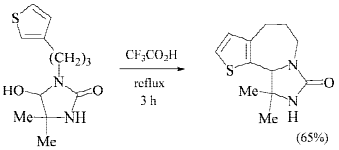
Although several examples of *N*-acyliminium cyclizations with furan[68,80,435−437] or thiophene[45,66,115,119−121,321,354,358,370,406,438−443] nucleophiles exist, this area is much less developed than that of benzenoid nucleophiles. These π-rich heterocycles show reasonable reactivity, behaving more or less like activated benzene systems. In comparing reactions

of similar substrates with thiophene and phenyl nucleophiles, it is found that thiophene is more reactive when its α position is involved. Regiochemistry can be a significant issue for cyclizations of furan or thiophene when the heterocycle is linked to an *N*-acyliminium segment by its 3-position, although attack at the 2-position would normally predominate over attack at the 4-position. Examples that address comparative reactivity and regiochemistry will be mentioned.

Thiophene cyclizations are usually straightforward, with reaction being favored at the α position. On treatment of thiazolidin-2-ones **354a** and **354b** with trifluoroacetic acid, seven-membered-ring products **355a** and **355b** are obtained in ca. 60% yield.[442] In



this case, formic acid is not useful because it leads to dehydration products (thiazolin-2-ones) that do not cyclize. Contrary to the reactivity of **354a**, imidazolidin-2-one **356a** just yields the dimeric product **357**, a thiophene-metacyclophane.[442] By blocking the thiophene 5-position, it is possible to prepare **358** from **356b** in 55% yield. When the thiophene 2-position is available, cyclization readily occurs at that site, regiospecifically (eq 120).[441] A seven-membered-ring product is also accessible by cyclization of a benzothiophene (eq 121).[441] A comparison between



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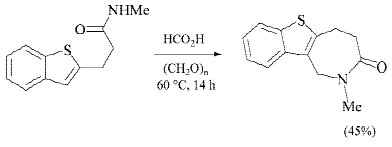
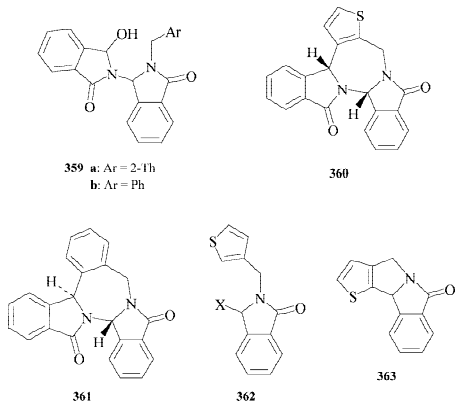


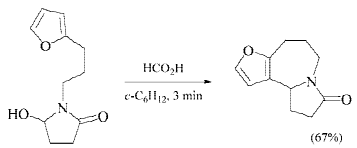
(121)

2-thienyl and phenyl in seven-membered-ring formation reflects the greater reactivity of thiophene.[439] For example, the reaction of **359a** (thiophene case) proceeds in trifluoroacetic acid at 23 °C to **360** in 99% yield, whereas **359b** (phenyl case) does not react; however, **359b** does cyclize to **361** in high yield at 73 °C. It is interesting that different diastereomers are formed from the thiophene and phenyl systems.



Cyclizations to five-membered-ring products can present some difficulties. Although the conversion of **362** (X = OH) to **363** proceeds in trifluoroacetic acid in 58% yield, cyclization does not take place when only the less reactive thiophene β position is available for reaction.[370,444] Also, this *N*-acyliminium cyclization fails when ethyl or phenyl substituents are present on the cationic center, probably because of steric hindrance. Although **362** (X = Cl or OEt) cyclizes under Lewis acid catalysis, such reactions fail when the cyclization is restricted to the thiophene β position. In sharp contrast, thiophene cyclizations that generate a new six-membered ring are very tolerant of structural variations (e.g., eq 24),[45,119,370] and these cyclizations often proceed better than their phenyl counterparts.[45,119,354,358,438,440] An *N*-acyliminium cyclization that would engender a new five-membered ring is subject to strain in the transition state for ring closure, such that only reactive nucleophiles participate effectively. Relative to competition between phenyl and thiophene nucleophiles,[369] the cyclization of **308** does not occur on the thiophene (at the 4-position) but rather on the phenyl to form a new seven-membered ring,[369] reflecting the difficulty for thiophene to react at its β position to yield a new five-membered ring.

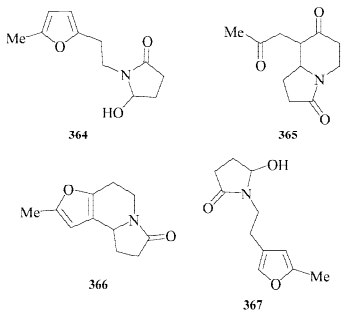
In furan-based *N*-acyliminium cyclizations, the products depend on the position of the furan tether (2 vs 3), the tether length, and the substituent on the furan 5-position.[436] Furans linked at the 3-position cyclize to six- and seven-membered rings in good yields under mild conditions (eq 122); however, furans linked at the 2-position cyclize to six-membered rings only in good yields.[436] This outcome



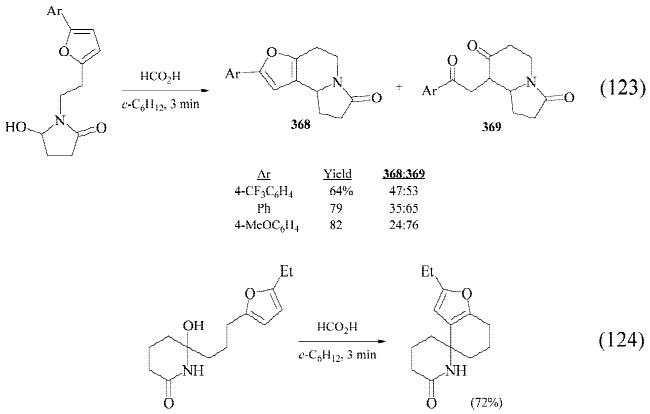
(122)

reflects the lower nucleophilicity of the furan β position relative to the α position. Furan reactions can be problematic due to degradation of the product by the acidic conditions needed for cyclization. For example, in eq 122 a short reaction time is critical to avoid a reduced yield and the generation of side products. There can be a specific problem of ring opening of the furan during the *N*-acyliminium

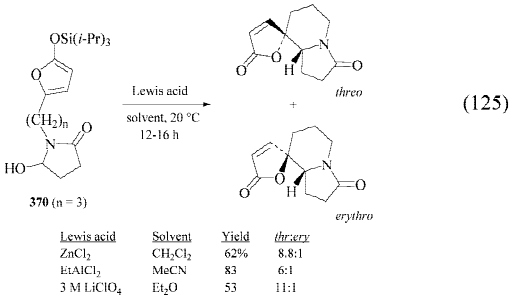
cyclization in formic acid, as seen in the cyclization of **364**,[436] which affords **365** in 75% yield. The desired



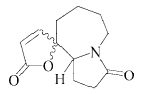
tricyclic product, **366**, is garnered by treating **364** with mesyl chloride and triethylamine instead. Furan ring opening does not ensue in the cyclization of **367**, wherein the expected tricyclic product is formed by attack at the 2-position (87% yield). 5-Aryl furan substrates provide mixtures of tricyclic compounds **368** and diketones **369**, with an emphasis on the latter products (eq 123). In a furan-based *N*-acyliminium ion spirocyclization with formic acid (eq 124), the furan does not suffer ring opening to a diketone.[435]



5-Silyloxyfurans provide spirocyclic butenolides with newly formed six- and seven-membered rings (e.g., eq 125).[437] In the case of forming a six-membered ring, the *threo* configuration is strongly favored with lithium perchlorate as the Lewis acid catalyst (eq 125); however, homologue **370** ($n = 4$)

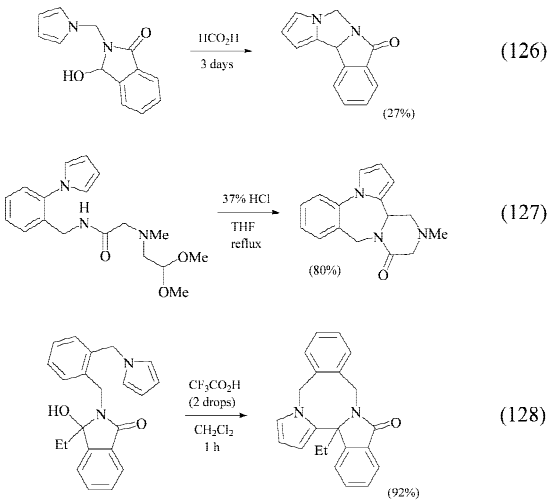


gives the seven-membered-ring product **371** as a mixture of isomers (ca. 1:1). Cyclizations of other types of 2-position-linked furans may actually undergo spirocyclic α attack prior to the observed β attack, presuming that addition of the electrophile is reversible. However, with the 5-silyloxyfuran system there is facile loss of the silyl group from the spirocyclic intermediate of *N*-acyliminium cyclization such that the spirocyclic products are produced.

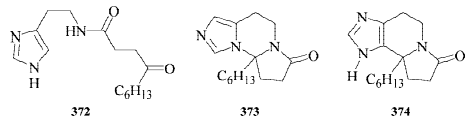


3.3.2. Pyrroles, Imidazoles, and Pyridines

N-Substituted pyrroles linked to an *N*-acyliminium ion by the pyrrole α position react cleanly at the β position (e.g., eq 24).[45,358] *N*-Acyliminium ions linked to the pyrrole nitrogen cyclize at the α position to form five-,[445] six-,[446] seven-,[446,447] and eight-membered rings[446] (e.g., eqs 126−128[445−447]). A new five-membered ring is formed with difficulty, as indicated by the low yield in eq 126.[445] In eq 128, cyclization onto the benzene ring to generate a five-membered ring does not occur; rather, the pyrrole is attacked to give a new eight-membered ring.[446] It is impressive for an *N*-acyliminium cyclization to produce a new eight-membered ring with such a high yield (92%) and with such ease (23 °C for 1 h). The high reactivity of the pyrrole nucleus must play an important role here.

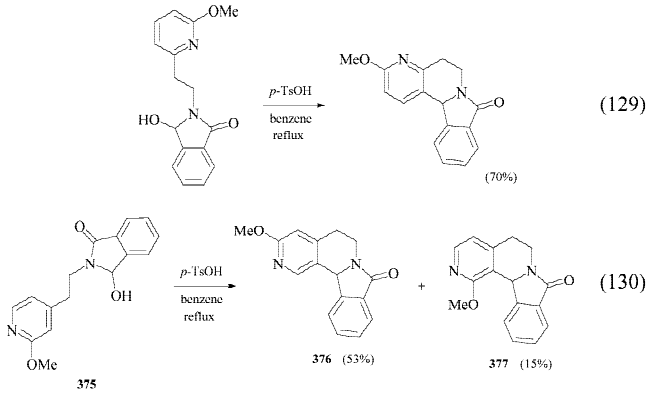


There is a reported example of an *N*-acyliminium cyclization onto an imidazole.[448] Reaction of histamine with 4-oxodecanoyl chloride in pyridine affords a mixture of amide **372** and tricyclic molecules **373** and **374**, which are acid-induced cyclization products of **372**. Prolonged heating of **373** in 10% aqueous acetic acid gives essentially pure **374** (no yield given).



Since pyridine is an electron-deficient heterocycle, one might expect it to be unreactive in *N*-acyliminium ion cyclizations. Indeed, electrophilic reactions involving pyridine, such as nitration, sulfonation, and halogenation, usually require strenuous conditions.[449] However, *N*-acyliminium cyclizations do proceed when the pyridine nucleus is activated by 2-methoxy substitution (e.g., eq 129).[450] A lower yield results when the *N*-acyliminium ion can eliminate to give

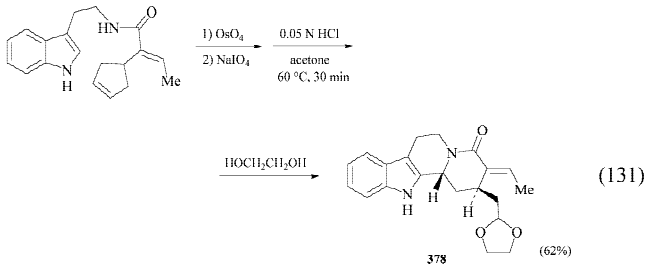
an enamide, as with a 5-hydroxypyrrolidin-2-one substrate. In the example of **375**, attack is favored *para* to the 2-methoxy, instead of *ortho*, to give a mixture of **376** and **377** (eq 130).[450]



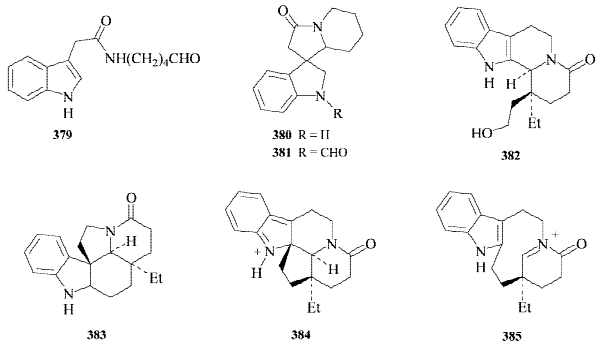
3.3.3. Cyclization of Indoles via the Pyrrole Ring

Although a wide diversity of indole-based *N*-acyliminium ion cyclizations have been reported,[15,19] a large proportion of these are ambiguous as to whether cyclization takes place by an *N*-acyliminium ion or by a standard iminium ion followed by formation of the lactam. The reactions in question generally involve direct thermal condensation of a 2-(3-indolyl)-ethylamine species with a keto or aldehydo carboxylic acid, and derivatives thereof (e.g., esters or acetals).[54,97−99,101−103,106−108,113,312,451−463] Given the high nucleophilic reactivity of indole, most of the "thermal reactions" probably proceed by a Pictet−Spengler cyclization and subsequent lactamization, not by an *N*-acyliminium ion process.

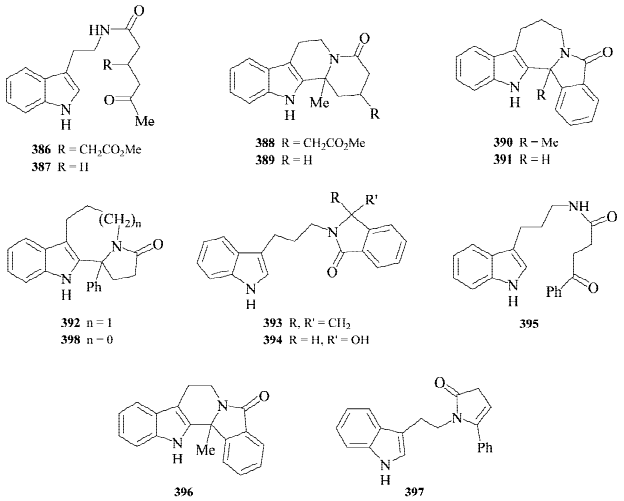
An early example of an unambiguous *N*-acyliminium ion cyclization of indole is contained within a total synthesis of yohimbine (viz. eq 13).[31,89] This approach was also exploited in a synthesis of geissoschizine, via intermediate **378** (eq 131).[111] In this



type of reaction, attack at the indole 3-position (*β*-cyclization) can occur prior to ultimate α-cyclization.[113] Indeed, amide dialdehyde **41**, in which the amide carbonyl is positioned differently than in **33**, provides **42** (HOAc/NaOAc, reflux) because the *β*-cyclization intermediate is trapped by an internal nucleophile.[91] A noteworthy illustration is provided by the cyclization of the simplified amide aldehyde **379** (HCO_2H/HCO_2Na, 100 °C), which leads to a 1:1 mixture of **380** and **381** in 78% yield.[116] Apparently, the indolenine intermediate from *β*-cyclization is captured by formate reduction in a Leuckart reaction. A particularly noteworthy *β*-cyclization occurs in the skeletal rearrangement of **382** (racemic) to **383** with either 40% sulfuric acid or boron trifluoride etherate.[460] Presumably, intermediate indolenium ion **384** fragments to *N*-acyliminium ion **385**, which then cyclizes at the *β* position to yield **383**.[464] There are some other examples of indole *β*-cyclization with *N*-acyliminium ions,[108−110] and a discussion of α- vs *β*-cyclization appears in two reviews on the Pictet−Spengler reaction of indoles.[7,112]

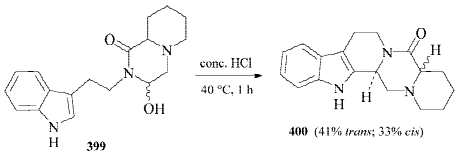


To ensure an unambiguous *N*-acyliminium ion process in indole cyclizations, the secondary amide bond should be intact before cyclization is attempted.[354,460,463,465,466] Straightforward examples are the efficient cyclizations of **386** and **387** in dilute methanolic HCl to **388** and **389**, respectively.[465] Given the high reactivity of indole, seven-membered-ring derivatives **390**−**392** are readily obtained from **393**−**395** in around 80% yield with just dilute alcoholic HCl.[463] Interestingly, the thermal condensation of 2-acetylbenzoic acid with 3-(3-aminopropyl)indole does not give lactam **390**, because enamide **393** is formed instead.[463] However, the analogous reaction with tryptamine gives **396** in 63% yield,[312] suggesting that this cyclization proceeds via a Pictet−Spengler process. Alternatively, the reaction of $PhC(O)CH_2$-CH_2CO_2H with tryptamine in refluxing toluene yields enamide **397**, an uncyclized *N*-acyliminium ion precursor,[312] although cyclization to **398** does proceed under more drastic protic conditions ($BuOCH_2CH_2$-OH, 171 °C). Thus, it is possible for the direct thermal condensation to take an *N*-acyliminium ion course.



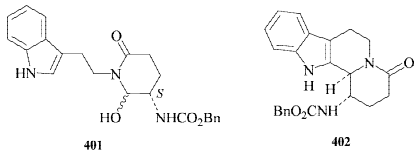
There are numerous examples of unambiguous *N*-acyliminium ion cyclizations of indoles, which are

conducted under the experimental protocols commonly employed for benzene cyclizations.[45,95,100,104,109−111,343,377,397,467−477] The conversion of **399** to 15-azayohimbane **400** in 74% yield (eq 132) is a poignant case[472] since the alternative thermal condensation method would not be viable here on account of the presence of a basic nitrogen.



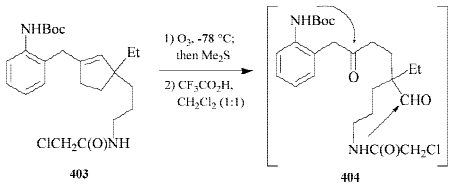
399 **400** (41% *trans*; 33% *cis*) (132)

Indole-based cyclizations with aliphatic substituents α to the carbocation center of a six-membered-ring *N*-acyliminium species generally result in poor stereoselectivity (e.g., eq 18[95]).[54,92,93,95,99−102] A notable exception exists for a vinyl substituent on the stereogenic center in the cyclization of **38** to give a product with an isomer ratio of 18:1 (eq 19).[100] A benzyl urethane substituent affords enhanced stereocontrol, with 100% diastereoselectivity and >95% enantioselectivity in the boron trifluoride etherate cyclization of **401** to **402** (−78 to −10 °C; 66% yield) (cf. **317a** → **318**).[397] However, the cyclization of **401**

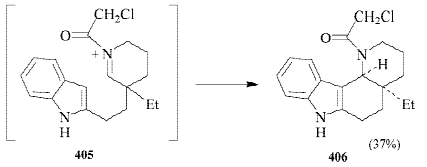


401 **402**

with a protic acid does not exhibit such excellent stereocontrol, as there is just 90% *trans* diastereoselectivity and a significant loss of enantioselectivity.[471] The extensive racemization in **402** (24% ee) is presumably caused by an enamide intermediate. In this vein, the interesting rearrangement of **382** to **383** (vide supra)[460] and the remarkable cascade reaction on going from **403** to **406** (eq 133)[477] feature highly stereoselective indole-based *N*-acyliminium cyclizations. Highly stereoselective indole-based transformations are also illustrated in eqs 21[108,109] and 22.[110]

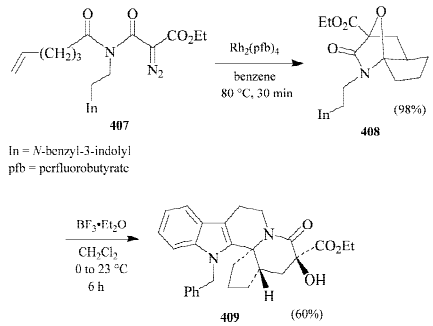


403 **404**



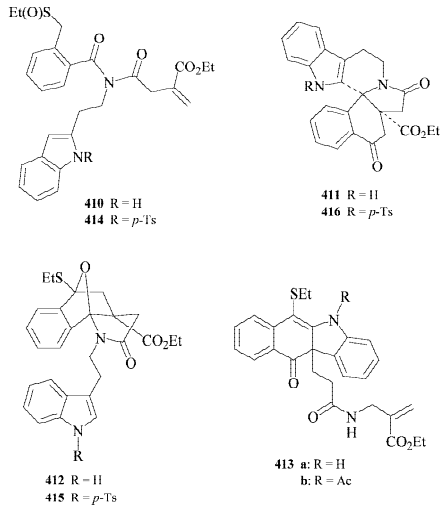
405 **406** (37%) (133)

Cascade reactions are useful in the synthesis of erythrinane-type derivatives containing an indole nucleus,[68,80,83,86,87,320] although they are basically extensions of benzenoid cyclizations.[83,86,87] The dipolar cycloaddition of **407** to oxabicycle **408**, followed by *N*-acyliminium cyclization to **409** (eq 134), compares very favorably with the benzenoid analogue in eq



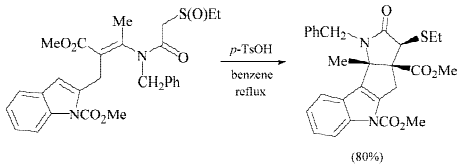
407 **408** (98%)
In = *N*-benzyl-3-indolyl
pfb = perfluorobutyrate
409 (60%) (134)

80.[83,86] However, a Pummerer-initiated tandem reaction of **410**, in analogy to **228** → **229** in eq 81, does not yield erythrinane **411** or its precursor cycloadduct, **412**.[87] Rather, a mixture of tetracyclic compounds **413a**/**b** is formed by preferential cycloaddition of the intermediate isobenzofuran to the indole π-bond (not the acrylate π-bond). Although the cy-



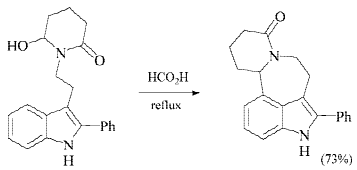
410 R = H
414 R = *p*-Ts
411 R = H
416 R = *p*-Ts
412 R = H
415 R = *p*-Ts
413 **a**: R = H
b: R = Ac

cloaddition problem can be overcome by using the *N*-tosyl derivative **414**, which leads to the cycloadduct **415** in 71% yield (TMSOTf and Et_3N),[87] the *N*-acyliminium cyclization of **415** to erythrinane **416** fails.[87] Another type of tandem process is initiated by a Pummerer reaction, as illustrated in eq 135.[344]



(80%) (135)

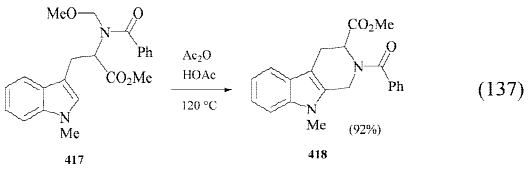
When the indole 2-position in a tryptamine derivative is substituted, *N*-acyliminium ion cyclization can occur at the 4-position to generate a new seven-membered ring (eq 136).[381,382] However, 2-carboxy is



(73%) (136)

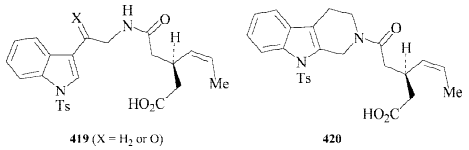
not a suitable blocking group because cyclization at the 2-position can still take place, with loss of the

carboxy group (eq 15),[93] in analogy with Pictet−Spengler reactions of tryptamine.[7,110] There can be a dichotomy of reactivity regarding indole positions 2 and 4 in that enamide **316** (*Z* or *E* isomer) cyclizes exclusively at the 4-position to give an azepinoindole, despite the availability of the more reactive 2-position (eq 102), whereas the tryptophan analogue **417** cyclizes only at the 2-position, as anticipated, to yield *β*-carboline **418** (eq 137).[383] The reaction of **419** (X = H_2) with paraformaldehyde/trifluoroacetic acid or formalin/formic acid occurs selectively at the indole 2-position to give **420** in ca. 70% yield; there is no attack at the 4-position, nor on the disubstituted (*Z*)-alkene.[475] However, the presence of a 3-acyl group on the indole, such as with **419** (X = O), is sufficiently deactivating that the alkene reaction then predominates.[475]



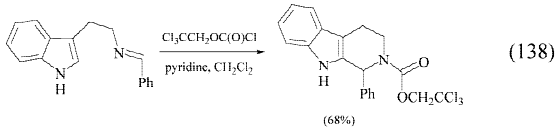
(137)

417 **418**



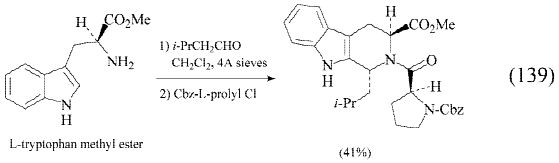
419 (X = H_2 or O) **420**

To encourage a reluctant Pictet−Spengler reaction of *N*-benzylidine tryptamine, Yamanaka et al. investigated activation by chloroformates, thereby devising a facile *N*-acyliminium ion cyclization (e.g., eq 138).[473]



(138)

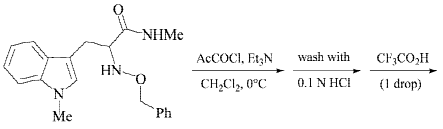
In general, acetyl chloride and ethyl chloroformate work similarly, and alkyl or electron-rich aryl substituents on the imine carbon give lower yields.[340] Activation can also be achieved with *p*-tosyl chloride in an *N*-sulfonyliminium-type cyclization.[478−480] A more complex variant entails the activation of tryptophan imines with prolyl chlorides, to arrive at pentacycles of the fumitremorgin family of natural products (eq 139).[474]

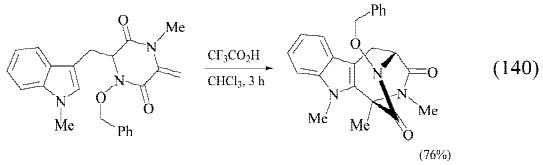


(139)

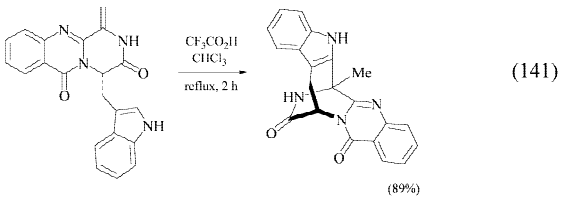
L-tryptophan methyl ester

N-Acyliminium cyclizations of indoles have provided some interesting applications in the synthesis of unusual bridged diazabicyclic products, two examples of which are illustrated in eqs 140[481] and 141.[482,483]





(140)



(141)

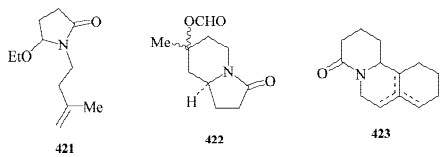
3.4. Reactions of Alkenes and Related Species

The study of the reactions of alkenes in *N*-acyliminium ion cyclizations has been a very fruitful and diverse area of research. Although Belleau reported the first examples in 1957,[24,25] this field did not receive meaningful development until nearly two decades later.[15,123,124] Speckamp and co-workers pioneered *N*-acyliminium cyclizations with alkene *π*-nucleophiles, often capitalizing on imide partial reduction to access diverse acyliminium ion precursors.[15−19,123−139,484] The introduction of mild cyclization conditions, such as formic acid at room temperature, helped to promote this area.[15,123,124] A representative example is given in eq 29.

N-Acyliminium ions are well suited to cyclization onto alkenes, and good stereochemical control is frequently realized. Cyclization of an *N*-acyliminium ion onto a tethered alkene can proceed by two different modes, exocyclic (**62**) or endocyclic (**63**), to produce two different ring sizes (eq 28).[122] The intermediate carbocation can then undergo transformations such as solvent capture, nucleophile addition, elimination, or rearrangement, to yield the reaction products. The type of products will depend on the reactivity of the *N*-acyliminium ion, reaction conditions, type of alkene nucleophile, length of the tether, and location of the tether. These issues will be dealt with in this subsection. Aspects relating to stereochemistry and mechanism were mentioned earlier, in section 2, Mechanism and Stereochemistry.

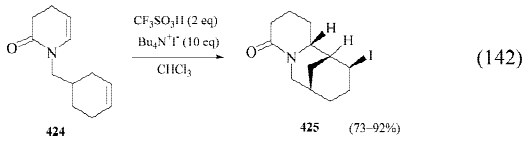
3.4.1. Standard Alkenes

Nitrogen-linked alkenes have received considerable attention, and a broad range of them have been studied.[15−19] With the formic acid method, monosubstituted (e.g., **64**) and 1,2-disubstituted alkenes (e.g., **72** and **73**) furnish single products in nearly quantitative yield in around 18 h. With 1,1-disubstituted alkenes there is a dramatic rate enhancement; for example, **421** is transformed into a mixture of cyclic formates **422** in just 15 min at 8 °C.[130] However, with



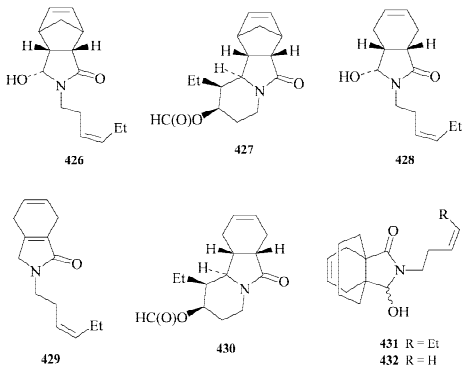
421 **422** **423**

acetic acid this type of reaction requires a much longer time, such that **421** yields a mixture of cyclic acetates corresponding to **422** in 23 h. Trisubstituted alkene **79** cyclizes to **80**/**81** (61:39 ratio) in 2 h (80% yield), as well as to a mixture of olefins, **423** (20%), due to the elimination of formate. The reaction of disubstituted alkene **69** with formic acid results in a mixture of azabicyclo[3.3.1]nonane regioisomers **70**/**71** in a 56:44 ratio (ca. 100% yield).[130] This outcome militates against the practical use of this route for the regiocontrolled elaboration en route to the *Lupine* alkaloid aloperine.[485] However, a different cyclization regime can obviate this difficulty. For example, enamide **424** reacts with triflic acid in the presence of excess iodide to provide polycyclic product **425** as a single regioisomer and single diastereomer (eq 142).[485]



424 **425** (73–92%) (142)

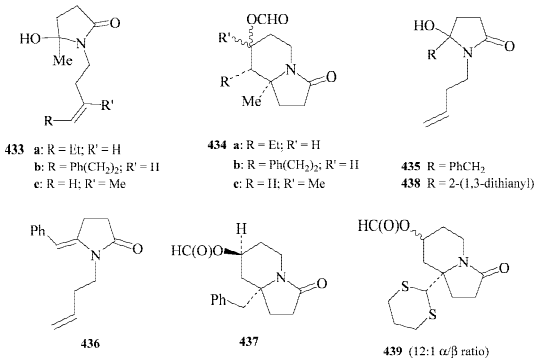
Cyclization onto a (*Z*)-alkene can sometimes be problematic, especially when steric hindrance is involved. Although **426** reacts normally in formic acid to give **427** in ca. 95% yield, **428** gives the pyrrolinone byproduct **429** (25% yield) in addition to the expected product **430** in 75% yield.[142] Steric crowding did not affect these results, but the cyclization of propellane **431** is impeded, and no desired product is formed. By contrast, cyclization of **432**, which lacks the (*Z*)-alkene, proceeds well and is complete in just 1 h.



426 **427** **428** **429** **430** **431** R = Et **432** R = H

Substitution α to nitrogen on the alkene tether can control stereochemistry by A(1,3) strain, as exemplified in eqs 33[140] and 39.[150] This steric factor has been exploited in several stereocontrolled syntheses of alkaloid natural products.[143,196−199,484,486−492] Substitution *β* to nitrogen on the alkene tether can also be an effective stereocontrol element, as exemplified in eqs 31[137] and 32.[124,137]

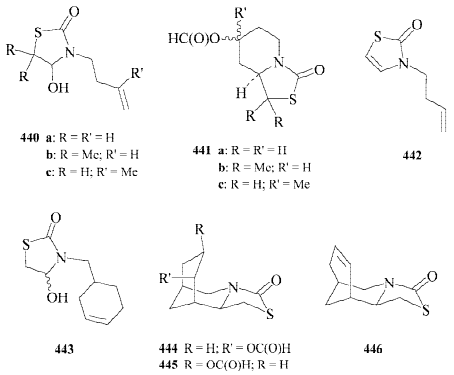
N-Acyliminium ions with non-hydrogen substituents (e.g., alkyl groups) on the iminium carbon, usually obtained from tertiary *ω*-hydroxy lactams (e.g., **433**), cyclize reasonably well, although there are some issues to consider.[136,142] The yields for this reaction type may suffer somewhat, partly because there is a lower efficiency in generating the requisite *N*-acyliminium ion precursors. Additionally, steric effects may arise, especially in cyclizations involving a (*Z*)-alkene nucleophile. For example, the cyclization of **433a** with formic acid is problematic in that indolizidines **434a** are not produced at room temperature or at 45 °C, and decomposition occurs with stronger acids.[136] The corresponding reaction of analogue **433b** did afford cyclized products **434b**, albeit in a modest 41% yield (overall from the imide). By comparison, the formic acid cyclization of 1,1-disubstituted alkene **433c** to **434c** is complete in 30 min in 85% yield. The formic acid cyclization of hydroxy lactam **435** to indolizidine **437** proceeds as well as the cyclization of enamide **436** to **437** (65% overall yield from the imide).[139] However, with a bulky 1,3-dithiane substituent present, as in **438**, formic acid cyclization to give **439** is very sluggish (7 days; 67% overall from imide).[136] Part of the problem is that **438** does not mainly exist in the ring-closed form; rather, it is composed of 50% open-chain keto amide (not shown), which cyclizes quite slowly.



433 **a**: R = Et; R′ = H **b**: R = $Ph(CH_2)_2$; R′ = H **c**: R = H; R′ = Me **434** **a**: R = Et; R′ = H **b**: R = $Ph(CH_2)_2$; R′ = H **c**: R = H; R′ = Me **435** R = $PhCH_2$ **438** R = 2-(1,3-dithianyl) **436** **437** **439** (12:1 α/β ratio)

N-Acyliminium ions based on 1,3-thiazolidin-2-ones cyclize like the corresponding carba analogues, except that the reaction rate may be retarded by dehydration of the *ω*-hydroxy or *ω*-alkoxy lactam starting material to an enamide (i.e., a thiazolin-2-one).[429,484] As a representative example, treatment of **440a** with formic acid affords **441a** in 82% yield after 142 h (ca. 6 days). This sluggishness, which contrasts with the analogous pyrrolidinone reactions, is connected with formation of intermediate enamide **442**. When the pathway to an enamide is blocked by *gem*-methyl groups, as in **440b**, the rate of ring closure is significantly enhanced, such that formic acid cyclization gives **441b** in 92% yield after just 2 h. A more nucleophilic 1,1-disubstituted alkene can overcome this sluggishness to some degree, as in the 18-h cyclization of **440c** to **441c** in ca. 70% yield, although this reaction rate is still much slower than that of the analogous pyrrolidinone case (viz. **421** → **422**). In a dramatic example of rate reduction due to dehydration, cyclohexenyl substrate **443** yields only the enamide intermediate in formic acid at room temperature. However, in refluxing formic acid, cyclized products **444** (23%), **445** (23%), and **446** (54%) are obtained.[429]

The formation of seven-membered rings in the *N*-acyliminium ion cyclization of alkenes can be effective, although difficulties may surface, such as a decrease in reaction rate and competitive formation of six-membered rings.[296,313,429,493−500] Extending the side chain of a nitrogen-linked alkene by one carbon to a pentenyl group, as in **447a** and **447b**, greatly



440 **a**: R = R' = H
b: R = Me; R' = H
c: R = H; R' = Me

441 **a**: R = R' = H
b: R = Me; R' = H
c: R = H; R' = Me

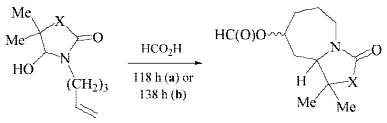
442

443

444 R = H; R' = OC(O)H
445 R = OC(O)H; R = H

446

slows the rate of cyclization (to **448a** and **448b**), although the yields are still quite acceptable (eq 143; cf. **440b** → **441b**).[429] Ring closure to seven-membered

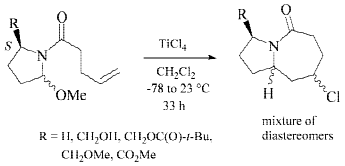


447 **a**: X = S
b: X = CH_2

448a (76%; 3:1 ratio)
448b (63%; 3:1 ratio)

(143)

rings is facilitated for monosubstituted alkenes when the *N*-acyl group is exocyclic relative to the iminium ion.[308,493−498] For example, *N*-pentenoyl-2-methoxypyrrolidine derivatives (from electrochemical anodic oxidation) cyclize in good yields to 5,7-bicyclic products (eq 144; 5−10% of 5,7-bicyclic alkenes may also be produced by elimination of HCl).[493] Surprisingly,

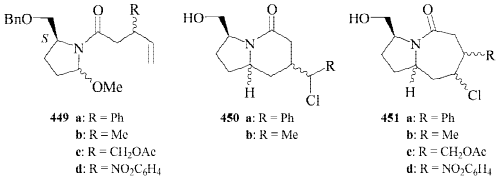


R = H, CH_2OH, $CH_2OC(O)$-*t*-Bu, CH_2OMe, CO_2Me

mixture of diastereomers

(144)

treatment of phenyl- or methyl-substituted pyrrolidine amides **449a** or **449b** with titanium(IV) chloride provides 5,6-bicyclic (debenzylated) products **450a** (90%) or **450b** (82%) exclusively, each as a mixture of diastereomers; no 5,7-bicyclic products **451a** or **451b** are formed.[494−497] Apparently, there is a rear-

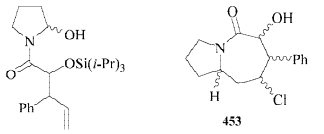


449 **a**: R = Ph
b: R = Me
c: R = CH_2OAc
d: R = $NO_2C_6H_4$

450 **a**: R = Ph
b: R = Me

451 **a**: R = Ph
b: R = Me
c: R = CH_2OAc
d: R = $NO_2C_6H_4$

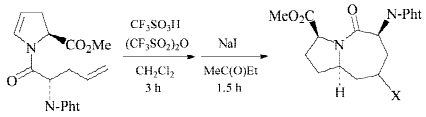
rangement that entails initial cyclization to a seven-membered-ring carbocation followed by migration of the amide α,*β* carbon−carbon bond to give a six-membered system with an exocyclic carbocation, which is trapped by a chloride ion.[495−498] In contrast, when R is an electron-withdrawing group, such as acetoxymethyl (**449c**) or 4-nitrophenyl (**449d**), only seven-membered-ring products **451c** (85%) or **451d** (61%) are obtained.[498] With this information in hand, one might suspect that the titanium(IV) chloride cyclization of **452** actually yields 5,6-fused products instead of the reported 5,7-fused products **453**.[308] A good example of exclusive generation of seven-



452

453

membered-ring products, with control of the configuration at the ring junction, is the cyclization of **454** to **455a** and **455b** (eq 145).[313] The initially formed



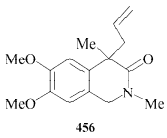
454

Pht = phthaloyl

455a X = α or β-I (58%)
455b X = β-Cl (21%)

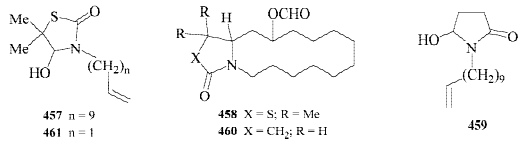
(145)

triflate is presumably converted to the ultimate halides by S_N2 displacement, with **455b** presumably arising from solvent-derived chloride. Another noteworthy case, mentioned earlier, involves phenylacetamide **298**, which has two competing nucleophiles, a 3,4-dimethoxyphenyl and an alkene. On treatment of **298** with paraformaldehyde and formic acid, the alkene reacts almost exclusively to furnish the seven-membered lactam **299** (78% yield); there is only a trace quantity of isoquinolinone **456** formed from attack on the benzene ring.[296]



456

Interestingly, it is possible to use alkene cyclizations to form macrocyclic rings under high-dilution conditions (ca. 3 mM).[156] Given a protracted reaction time of 38 days at 43 °C, 1,3-thiazolidin-2-one **457** cyclizes in formic acid to the macrobicyclic compound **458** in an impressive 84% yield (presumably a mixture of two isomers). A comparable result is obtained in the conversion of **459** to **460** (HCO_2H, 43 °C, 20 days; 82% yield).

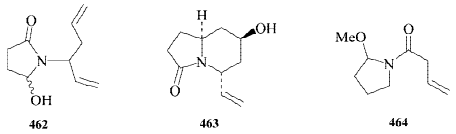


457 n = 9
461 n = 1

458 X = S; R = Me
460 X = CH_2; R = H

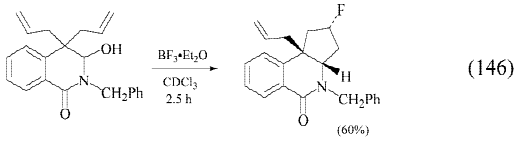
459

The formation of five-membered rings can be unpredictable since geometric constraints in the cyclization may pose an obstacle to ring closure. In general, cyclization via a 5-*endo*-trig process is problematic, while cyclization via a 5-*exo*-trig process is well behaved. For example, with simple *N*-allyl *ω*-hydroxy or *ω*-alkoxy lactams, such as **461**, the closure of a new five-membered ring is not viable, presumably because this reaction must proceed by an unfavorable 5-*endo*-trig transition state, in which the *π* orbitals of the terminal sp^2-hybridized centers are not properly aligned.[156,159,216,395,499,501] A poignant illustration is offered by substrate **462**. In the competition between allylic and homoallylic alkenes in **462**, only the homoallylic group reacts to furnish indolizidine **463** in 70% yield (HCO_2H, 23 °C, 1 h;



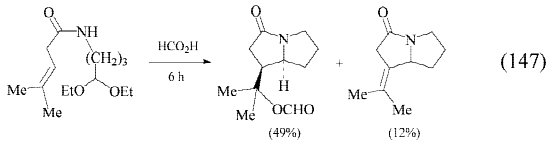
462 **463** **464**

then saponification).[159] 2-Methoxypyrrolidine **464**, in which the *N*-homoallyl group contains the amide carbonyl, does not yield any five-membered-ring pyrrolizidine products; rather, only an indolizidine product is obtained.[493] However, as indicated in eq 146, a carbon-linked allyl group can cyclize to a five-



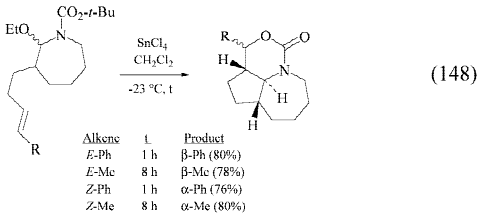
(146)

membered ring in good yield.[501] Five-membered rings are generated more consistently via *N*-acyliminium ion reactions that involve a 5-*exo*-trig geometry, especially when the alkene is activated, as noted in eqs 45 and 50.[179,188,207] A good example of a direct 5-*exo*-trig cyclization onto an unactivated alkene is shown in eq 147.[502] An interesting application of the



(147)

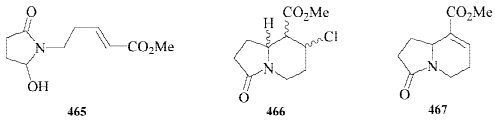
5-*exo*-trig cyclization is the conversion of *N*-Boc-2-ethoxyazepines bearing 3-homoallyl groups to tricyclic products, in which the incipient carbocation from *N*-acyliminium cyclization is captured by the urethane carbonyl (eq 148).[224] There is strict diastereoselectivity with either the (*E*)- or (*Z*)-alkenyl side chains (note: 96% *Z* → 96% α). Another approach to forming five-membered rings takes advantage of an initial aza-Cope rearrangement followed by a 5-*exo*-trig cyclization,[150−166] as portrayed in eqs 41 and 42.



Alkene	t	Product
E-Ph	1 h	β-Ph (80%)
E-Me	8 h	β-Me (78%)
Z-Ph	1 h	α-Ph (76%)
Z-Me	8 h	α-Me (80%)

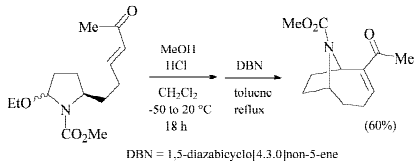
(148)

Alkenes that are deactivated, even by virtue of one halogen substituent, usually do not participate with facility in *N*-acyliminium cyclizations.[132,345,499,501,503−506] Exposure of the α,*β*-unsaturated ester **465** to tin(IV) chloride at 70 °C provides a 28% yield of chloro indolizidine **466**, en route to alkene **467**.[503] The ester



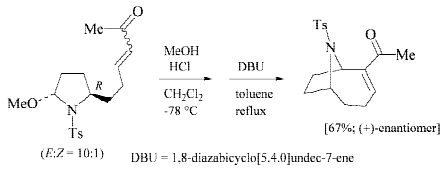
465 **466** **467**

directs a 6-*endo*-trig, as opposed to a 5-*exo*-trig, cyclization. Higher yields result in the *N*-methoxycarbonyliminium and *N*-sulfonyliminium cyclizations



DBN = 1,5-diazabicyclo[4.3.0]non-5-ene

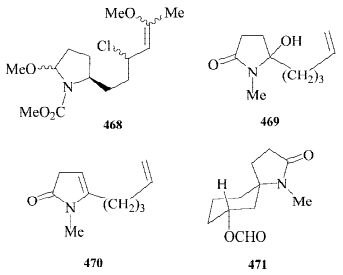
(149)



(*E*:*Z* = 10:1) DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

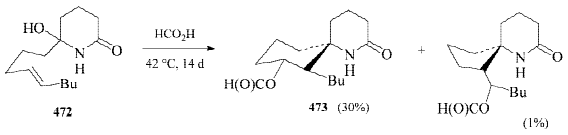
(150)

of enones outlined in eqs 149[504] and 150;[209] however, it is possible that the deactivated alkene is derivatized in situ by methanolic HCl prior to cyclization. Conjugate addition of HCl to the enone, followed by enol ether formation, would give an intermediate such as **468**,[504] cyclization of which would then involve a reactive enol ether nucleophile.



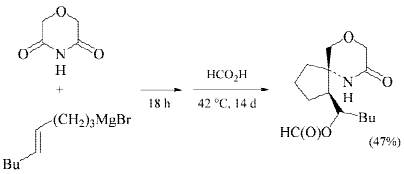
468 **469** **470** **471**

When an alkene is directly attached to the iminium carbon, *N*-acyliminium ion spirocyclization can ensue.[133−135,139,309,311,507−509] This reaction has been applied to the stereoselective formal total synthesis of perhydrohistrionicotoxin.[134,139,507,508] In a model system, treatment of hydroxy lactam **469** or enamide **470** with formic acid affords spirocyclic formate **471** in quantitative yield with high stereoselectivity;[133] however, the corresponding six-membered hydroxy lactam does not spirocyclize as well (ca. 60% yield). Although **472**, with an unsubstituted nitrogen, is transformed by a 6-*endo*-trig pathway to 6,6-azaspirane **473** with excellent stereocontrol (eq 151),[134,139]



472 **473** (30%) (1%)

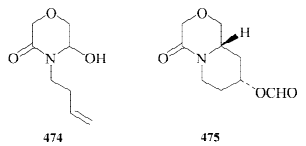
(151)



(47%)

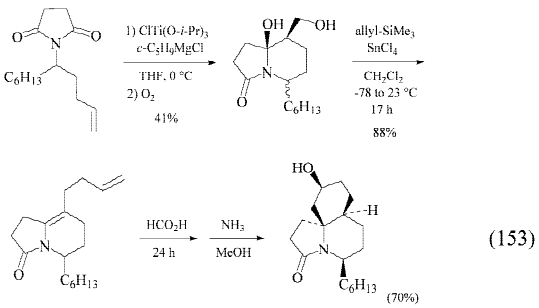
(152)

the closely related N−H morpholin-2-one substrate supplies mainly the 5,6-azaspirane by a 5-*exo*-trig pathway (eq 152).[135,139] Paradoxically, a standard 6-*endo*-trig ring closure is preferred for the nonspirocyclic reaction of morpholin-2-one **474** to **475** (80% yield).[510] An excellent foundation for *N*-acyliminium spirocyclization can be established via the Kulink-



474 **475**

ovich approach to tertiary enamides (eq 153).[309,311] Two different types of *N*-acyliminium reactions are illustrated in eqs 153[309] and 154.[311] The configuration of the product from the cyclization and formate hydrolysis in eq 153 is completely controlled, thus giving rise to the framework of the marine alkaloid lepadiformine.[309]



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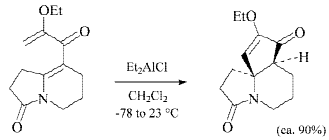
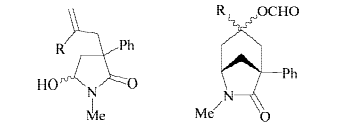


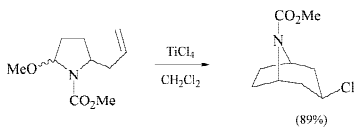
(154)

Pyrrolidines substituted with allyl or homoallyl groups at ring positions α, *β*, or *γ* to the iminium carbon lead to azabicyclic structures.[15,128,132,344,511,512] The α case: With a homoallyl group at the 4-position of a pyrrolidin-2-one substrate, 1-azabicyclo[4.3.0]-nonane (octahydroindole) derivatives are obtained,[15,132,344] as exemplified in eq 82.[344] The *β* case: 5-Hydroxypyrrolidin-2-ones substituted with an allyl group at the 3-position supply azabicyclo[3.2.1]-octanes,[128] as observed in the formic acid cyclizations of **476** to formates **477** (87 °C, 70 h) and of **478** to a single formate isomer of **479** (23 °C, 1 h; probably *β* configuration). The *γ* case: A pyrrolidine substrate with an allyl group at the 5-position delivers a 7-azabicyclo[3.2.1]octane (eq 155).[511]



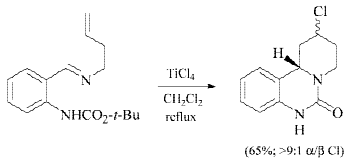
476 R = H
478 R = Me

477 R = H
479 R = Me



(155)

Tandem reactions involving alkene nucleophiles are useful in providing various polycyclic systems efficiently. Fortunately, *N*-acyliminium ion-initiated polyolefin cyclizations proceed with facility and often with high stereocontrol (e.g., eqs 32, 34−38).[129,131,137,144−149,429,513] As mentioned earlier, azasteroids **88** and **89** are produced as single isomers in high yield through formic acid cyclizations (eqs 34 and 35).[129,131] When formic acid is too sluggish, as in the conversion of **87** to **90** (major isomer, 40% yield), trifluoroacetic acid (CH_2Cl_2, 5 °C, 30 min) can be used effectively to give **90** in 84% yield.[131] (Aza-steroid derivatives have also been accessed by nontandem *N*-acyliminium ion cyclizations.[467,514]) Tandem reactions can produce other interesting polycyclic molecules (eqs 36−38,[144−149] 156,[339,515] and 157[475]). A



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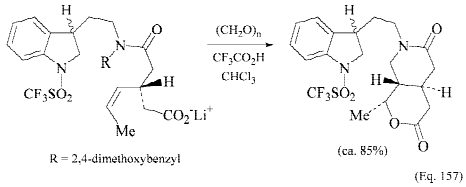
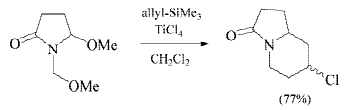


(157)

different type of tandem reaction involves allyltrimethylsilane and bis-(α-methoxy) amides in a [3 + 3] annulation (eqs 158[511] and 159;[512] cf. eq 155). A related [4 + 3] annulation between carbamate **480** and $CH_2{=}CHCH_2CH{=}C(OEt)OSiMe_3$ affords a 9-azabicyclo[4.2.1]nonane in 60% yield.[512]



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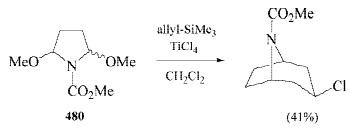
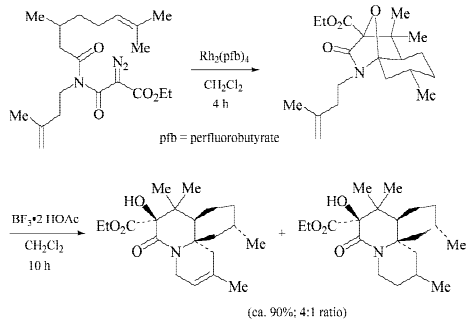


480

(159)

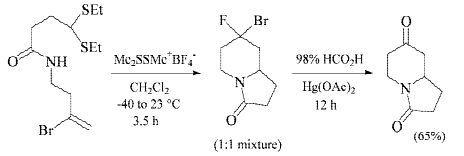
The tandem chemistry of Padwa and co-workers is designed to capitalize on reactive species, such as a carbenoid or stabilized carbocation, to generate *N*-acyliminium ions for subsequent ring closure.[83,86,343−345,430,431,516] An example of the *carbenoid method*, which entails (1) cyclization to a mesoionic heterocycle, (2) 1,3-dipolar cycloaddition to give an *N*-acyliminium ion precursor, and (3) *N*-acyliminium cyclization onto an alkene, is presented in eq 160.[86,516] The 4:1 ratio of diastereomers repre-



(160)

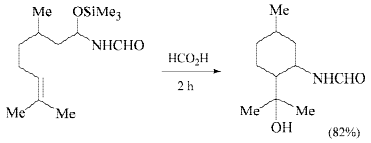
sents an equilibrium mixture since the individual isomers equilibrate on exposure to the acid catalyst.

Examples of the *thiacarbenium ion method*, which entails (1) generation of a thiacarbenium ion, (2) addition of it to an enamide double bond or the nitrogen of a secondary amide to generate an *N*-acyliminium ion, and (3) cyclization onto an alkene, are presented in eqs 82[343−345] and 161.[345]

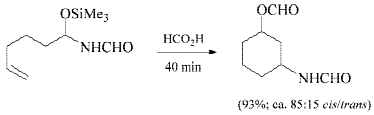


(161)

Acyclic *N*-acyliminium ions are also effective in cyclizations with alkenes (e.g., eqs 67 and 68).[161,163,164,166,298−301,303,517,518] The cyclization of α-trimethylsilyloxy formamides with alkenes generates cyclohexane products with good yields (eqs 162 and 163).[303] A related *N*-tosyliminium ion cyclization

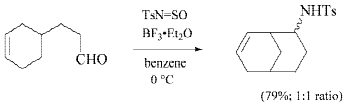


(162)

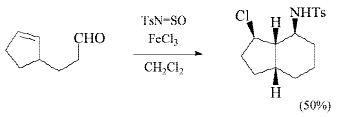


(163)

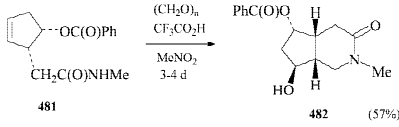
provides a ready entry into bicyclo[3.3.1]nonane and bicyclo[4.3.0]nonane systems (eqs 164 and 165);[519] it is remarkable that just a single isomer is formed in the latter reaction. Secondary carboxamide **481** cyclizes with paraformaldehyde to *cis*-fused bicyclic lactam **482** in 57% yield, exclusively with *Z* stereoselectivity (eq 166).[518]



(164)

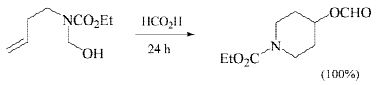


(165)

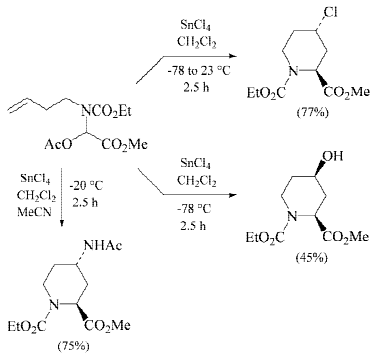


(166)

In a series of reactions of secondary carboxamides, adducts between *N*-homoallylurethanes and formaldehyde or methyl glyoxylate led to 4-formyloxypiperidines (e.g., eqs 167 and 168).[161,166,215] The glyoxylate-based cyclization, dubbed the "glycine cation method", generally results in isomeric mixtures when conducted in formic acid;[161] however, single isomers (*trans*) are obtained in some tin(IV) chloride reactions (e.g., eq 168).[166] Interestingly, two different products can arise depending on how the tin(IV) chloride reaction is performed and quenched. If the reaction is warmed to 23 °C before quenching with aqueous

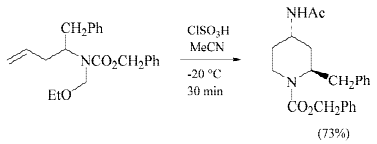


(167)



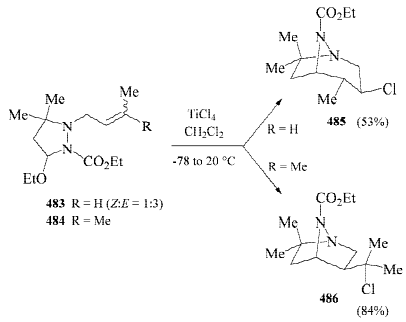
(168)

sodium bicarbonate, then it gives mainly the *trans*-4-chloropipecolic acid ester, whereas if the reaction is quenched at −78 °C, then it usually gives a *cis*-hydroxypipecolic ester (eq 168). The ester group probably participates with the intermediate carbocation to generate a bicyclo[3.2.1] oxonium species that is cleaved with retention of configuration at the 4-position. Tandem *N*-acyliminium ion cyclizations/Ritter reactions with tin(IV) chloride in acetonitrile at −20 °C result in a *trans*-4-(acetamido)pipecolic acid ester (eq 168).[164,165] This protocol was applied to the synthesis of the 4-aminopiperidine core of a neurokinin-1 antagonist (eq 169).[163]



(169)

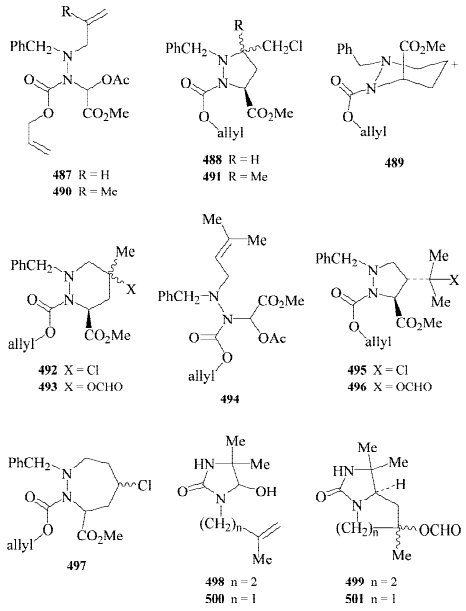
The *N*-acyliminium ion cyclization with alkenes has been applied to cyclic ions containing an additional heteroatom, particularly to *N*-acylhydrazonium[205,427,428] and imidazolidinium ions.[520] Pyrazolidine alkenes **483** and **484** cyclize well to diazabicyclic compounds **485** (6-*endo*-trig) and **486** (5-*exo*-trig), respectively (eq 170).[205] For this type of reaction,



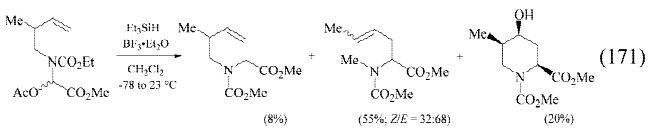
(170)

titanium(IV) chloride tends to give higher yields than tin(IV) chloride, and formic acid also works. *N*-Acylhydrazonium ion cyclizations with a carbomethoxy group on the iminium carbon can furnish pyrazolidinecarboxylate or piperazic acid derivatives.[428] In the treatment of allyl hydrazide **487** with tin(IV) chloride, pyrazolidinecarboxylate **488** is formed in 75% yield (*cis*/*trans* = 1:5) via a 6-*endo*-trig cyclization, followed by a rearrangement that arises in intermediate cyclic

carbocation **489**.[428] Methallyl substrate **490** reacts with diethylaluminum chloride to yield a mixture of pyrazolidinecarboxylate **491** (27%, *cis*/*trans* = 1:1.8) and piperazate **492** (59%, *cis*/*trans* = 1:8.8); however, with formic acid it is possible to convert **490** to only piperazate **493** (68%, *trans* only). Cyclization of trisubstituted alkene **494** with tin(IV) chloride or formic acid results in **495** in 58% yield or **496** in 66% yield, with only the *trans* configuration, via a 5-*exo*-trig process. A seven-membered-ring product, **497**, is accessible in 65% yield (1:1 isomer ratio) from the homoallyl congener of **487**. 4-Hydroxyimidazolidin-2-one **498** reacts with formic acid to give the 5,6-bicyclic compound **499** in 50% yield (1:1 ratio); however, it is not possible to cyclize **500** to **501**, even under strenuous conditions, because a 5-*endo*-trig pathway is required (in analogy with the corresponding pyrrolidinone case).[520]

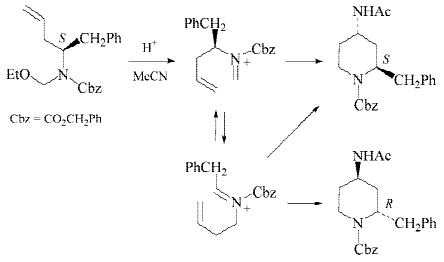


The outcome of certain cyclizations with alkene nucleophiles may be impacted by the intervention of a *2-aza-Cope rearrangement*. In particular, homoallyl cyclic *N*-acyliminium ions tend to experience this process, depending on the substitution pattern.[150−166] This [3,3] rearrangement is more prevalent when the β carbon of a nitrogen-linked homoallyl group is substituted with two alkyl groups, an aryl, or an alkoxy group, because of stabilization of an intermediate carbocation.[150−166] Acyclic *N*-acyliminium ions undergo the 2-aza-Cope rearrangement readily and it may be fast relative to the rate of cyclization,[161,163,166] as determined by product stereochemistry and trapping experiments (e.g., eq 171).[161,166]



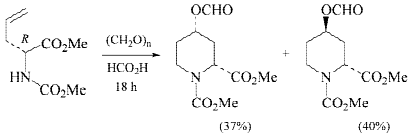
(171)

This process can be made visible through the racemization of enantiomerically enriched substrates.[163] In eq 169, enantiomerically pure (*S*) substrate leads to a product with just 42% enantiomeric excess,[163] indicating that the rate of equilibration of *N*-acyliminium ions in the aza-Cope rearrangement is not much faster than the rate of cyclization (eq 172). In



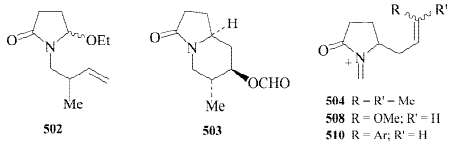
(172)

contrast, little or no racemization is observed in cyclizations of enantiomerically pure allylglycine derivatives under various conditions (e.g., eq 173),[164] indicating the absence of a competitive 2-aza-Cope rearrangement. Clearly, the ester group preserves the enantiomeric integrity. Thus, the nature of substituents can have a significant effect on the 2-aza-Cope process.

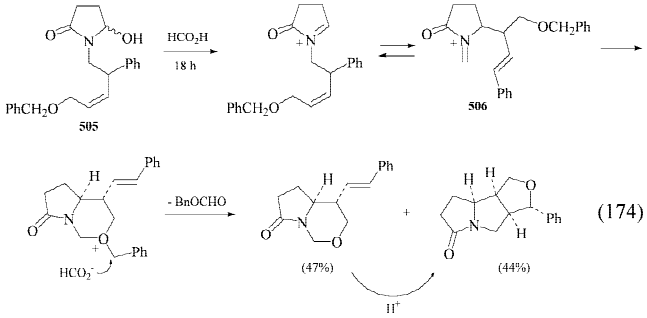


(173)

Gem-disubstitution at the β carbon of the homoallyl group distinctly accelerates the 2-aza-Cope rearrangement, and this influence causes a dramatic difference in reaction between monomethylated **502**[137] and *gem*-dimethylated **100**.[151] While **502** cyclizes in formic acid to indolizidine **503** (ca. 80% yield; 10% of three other formate isomers),[137] **100** gives pyrrolizidine **101** stereoselectively in high yield (81%;[151] 100%[154]) via rearranged *N*-acyliminium ion **504**.

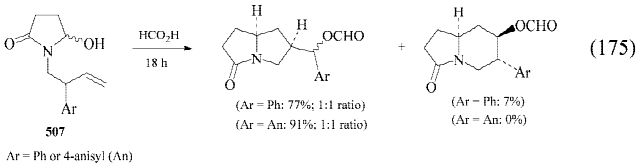


Remarkably, the conversion of hydroxypyrrolidine **100** to pyrrolizidine **101** is complete in just 5 min at room temperature.[154] Although a benzyloxy group is well behaved in the *N*-acyliminium cyclization in eq 41,[152,157] it is problematic in the cyclization of **505**, where the ether oxygen competes against the alkene to capture the rearranged *N*-acyliminium ion **506** (eq 174).[162] Perhaps the (*E*)-benzyloxy group in the rearranged ion **102** in eq 41 is not suitably disposed to react in this manner.

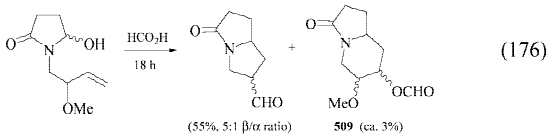


(174)

β-Monosubstituted homoallyl groups normally do not undergo the 2-aza-Cope process (e.g., eqs 31[137] and 32[124,137]) since a special driving force is required, such as a phenyl[155,160] (eqs 174 and 175) or a methoxy[154] (eq 176) substituent.[162] Indeed, aryl,[155,160]

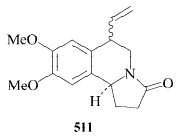


(175)



(176)

alkoxy,[154] and vinyl[159] groups are particularly conducive to this [3,3] rearrangement. The reaction in eq 176 involves mainly the rearranged *N*-acyliminium ion **508** to yield the pyrrolizidine products; there is only ca. 3% yield of indolizidines **509**.[154] The cyclization of **507** (Ar = Ph) also generates only a minor amount of indolizidine products (eq 175).[155] An electron-rich 4-methoxyphenyl group (**507**, Ar = An) depletes the indolizidines further, and pyrrolizidines are obtained exclusively (eq 175).[155] The 4-methoxyphenyl group enhances the reaction rate by approximately 20-fold.[155,160] Evidently, substituents that impart significant stabilization to the carbocation derived from the cyclization of intermediate ions **504**, **508**, or **510** (i.e., *gem*-dimethyl, methoxy, and aryl) shift the dynamic aza-Cope equilibrium between the two *N*-acyliminium ions to the right (e.g., **98** → **99**) to favor formation of new five-membered rings. The aza-Cope *N*-acyliminium ion cyclization in eq 42 is probably assisted by the strategically positioned silyloxy substituent.[165] There is a limitation on the aromatic ring with respect to its nucleophilic reactivity since ring closure could occur onto it, as observed with 3-methoxyphenyl and 3,4-dimethoxyphenyl groups [e.g., **507** (Ar = DMP) → **511**].[160]

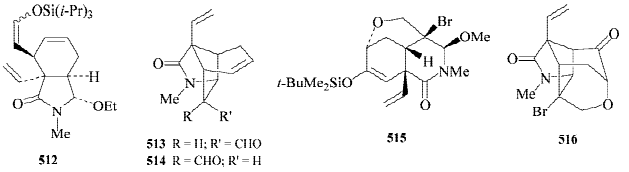


511

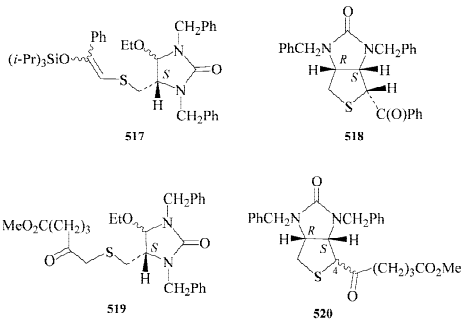
3.4.2. Vinyl Ethers and Thioethers

Cyclizations of alkenes substituted with ether[127,132,154,165,229,230,233−237,521] or thioether[178−184] groups have received relatively limited attention, although such activated alkenes have the potential to be excellent nucleophiles. There has been more interest devoted to the cyclizations of enols and enolates.

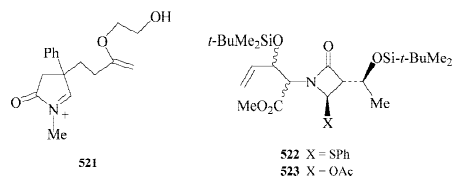
Silyl enol ethers have played a key role in total syntheses of gelsemine.[233−235,521] Treatment of (*E*)- or (*Z*)-**200** with boron trifluoride etherate for ca. 30 min gives **201** (*endo* CHO) or **202** (*exo* CHO) with high stereospecificity in good yields; a 90:10 mixture is obtained in 79% yield from (*E*)-**200** (*E*/*Z* > 90:10), and a 10:90 mixture is obtained in 92% yield from (*Z*)-**200** (*E*/*Z* < 90:10).[234] In the synthesis of (±)-gelsemine, intermediate **512** (3:1 *E*/*Z* mixture) is converted to a 3:1 mixture of *endo* and *exo* aldehydes **513** and **514** (70% yield).[233,234] Cyclization can also be accomplished effectively with trimethylsilyl triflate[235] or trifluoroacetic acid.[521] Indeed, tricyclic silyl enol ether **515** cyclizes to the gelsemine intermediate **516** in 74% yield via a difficult 5-*endo*-trig pathway (CF_3CO_2H, reflux, 15 min),[521] and this reaction proceeds with greater facility than the related enol-based ring closure of **197** to **198** (CF_3CO_2H, reflux, 8−10 h; 85% yield).[231]



N-Acyliminium cyclizations of silyl enol ethers underpin syntheses of quinocarcin[236] and biotin.[237] Cyclization of either alkene isomer of **517** produces only **518**, with the correct configuration of (+)-biotin (TMS-OTf, CH_2Cl_2, −78 °C, 1 h; 91% yield).[237] However, this favorable configuration is not maintained when the phenyl group is replaced by an alkyl group, due to enolization in the latter case. The silyl enol ether from **519**, generated in situ, cyclizes with trimethylsilyl triflate to a 2:1 mixture of (4*R*)- and (4*S*)-**520** (69% yield for two steps).[23]



The cyclization of ketal **193** to indolizidine **192** with concentrated HCl in methanol (reflux, 21 h) proceeds in 78% yield with high *cis* stereoselectivity; however, the reaction may actually involve intermediate vinyl ether **521**, derived from opening of the 1,3-dioxolane ring.[127,132] This type of *N*-acyliminium ion cyclization, based on a reactive nucleophile derived from a cyclic ketal, plays a key role in the syntheses of intermediates en route to methyl daphniphyllate (eq 54)[229] and *Aspidosperma* alkaloids (eq 55).[230]

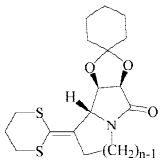


Enol ethers for *N*-acyliminium ion cyclization can be generated amidst a 2-aza-Cope rearrangement (eqs 42[165] and 176[154]), and this approach can be convenient and efficient. Interestingly, since the phenylthio and acetoxy β-lactams **522** and **523**,

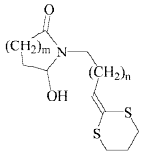
respectively, are not good substrates for *N*-acyliminium ion generation/[3,3] rearrangement/cyclization, per eq 42, it became necessary to employ the chloro substituent and silver-assisted ionization to drive the cyclization.[165]

Vinyl thioethers have been used in *N*-acyliminium ion cyclizations more commonly with the alkene activated by two sulfur groups, in the form of a 1,1-bisthioether (ketene dithioacetal). There is just a single report of a cyclization of an alkene with one sulfur group (eq 46).[182] This route relies on a regioselective sodium borohydride partial reduction of the endocyclic imide carbonyl and cyclization under special mercury(II)-assisted acidic conditions.

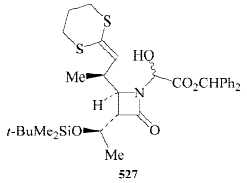
The ketene dithioacetal-terminated cyclization serves to control the regioselectivity in favor of the exocyclic mode by forming a stabilized dithiocarbocation intermediate. The reaction in eq 45 affords pyrrolizidine **117** in 68% yield by a 5-*exo*-trig cyclization, while the configuration at the bridgehead carbon (C3a) is controlled by the acetoxy group.[179] Similar cyclizations of enantiomerically pure **118**[181] and **119**[183] ($MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 to 23 °C, MeCN added at 23 °C as an accelerant) also proceed well (85% and 60% yield) by 5-*exo*-trig and 6-*exo*-trig routes to pyrrolizidine **524** and indolizidine **525**, respectively. Although dithioalkenes **526a** and **526b** cyclize in 80−85% yield by 5-*exo*-trig and 6-*exo*-trig routes, respectively,[178,180] the yield suffers for the corresponding 7-*exo*-trig reaction involving **526c** (48%).[180] This ketene dithioacetal cyclization can be quite useful for sensitive systems, as noted in the clean conversion of isomeric β-lactams **527** to carbapenams **528** in 73% yield with mesyl chloride and triethylamine (MeCN, 0 to 23 °C, then reflux for 4 h).[184]



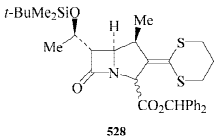
524 n = 2
525 n = 3



526 **a**: m = n = 1
b: m = n = 2
c: m = 1; n = 3



527

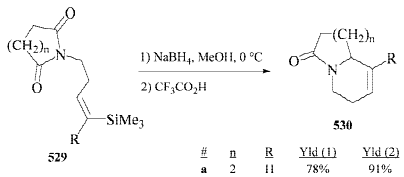


528

3.4.3. Vinylsilanes

With vinylsilane nucleophiles, the *N*-acyliminium ion cyclization is directed to the silicon-bearing alkene carbon because of stabilization of the resultant carbocation by the "β-silyl effect". Vinylsilanes are not especially reactive nucleophiles compared to allylsilanes and vinyl thioethers, so side reactions, such as proto-desilylation, sometimes intervene.

The first examples of silicon-directed cyclizations were conducted as extensions of Mannich cyclizations (eq 177).[167,169] Quinolizidine **530a** and indolizidine **530b** are readily formed from **529a** and **529b** with trifluoroacetic acid at room temperature (formic acid is much less effective).[167] The production of indolizidine **530c** from **529c** requires a higher temperature and still is not obtained in a comparable yield, presumably because the bromo substituent deactivates the alkene.[167,169]

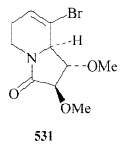


529 **530**

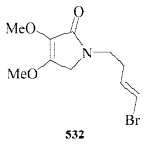
#	n	R	Yld (1)	Yld (2)
a	2	H	78%	91%
b	1	H	79	92
c	1	Br	94	70

(177)

Various alkoxy-substituted substrates cyclize with high stereoselectivity (e.g., eq 43[173]), although some reactions are problematic on account of low yields or mixed stereochemical results.[138,216] A terminal alkene substituent appears to be critical for good stereocontrol, and this condition is satisfied by the bulky (*Z*)-trimethylsilyl group.[171−173] In trifluoroacetic acid, crude **111** (from imide reduction) reacts to give **531** in 87% yield (ca. 85% purity);[171] however, in formic

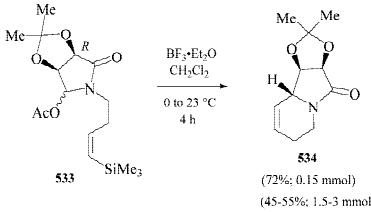


531



532

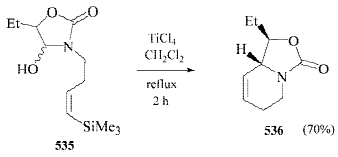
acid, proto-desilylation occurs and no cyclization product **532** is obtained.[171] With a cyclic ketal present, the cyclization of 5-acetoxy lactam **533** to **534** proceeds well with boron trifluoride etherate (eq 178), but the corresponding 5-hydroxy lactam substrate does not give **534** under various conditions.[172] Lewis



533 **534**
(72%; 0.15 mmol)
(45-55%; 1.5-3 mmol)

(178)

acids may be beneficial relative to protic acids for such vinylsilane cyclizations. Indeed, boron trifluoride etherate promotes a clean cyclization of (*Z*)-vinylsilane **112** (eq 43),[173] and titanium(IV) chloride is useful in converting **535** to **536** (eq 179).[170] Steric

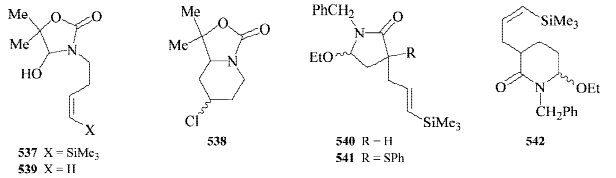


535 **536** (70%)

(179)

encumbrance in the cyclization of **537** leads to substantial proto-desilylation, such that the yield of **538** is merely 22%.[170] However, the production of **538** from the non-silyl-substituted analogue **539** is more satisfactory (65% yield).[170]

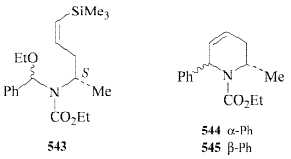
Vinylsilanes **540**−**542** do not cyclize to bridged azabicyclic compounds with formic acid (23 °C or reflux), trifluoroacetic acid, tin(IV) chloride (23 °C),



537 X = $SiMe_3$
539 X = H
538
540 R = H
541 R = SPh
542

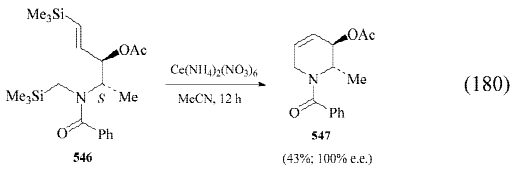
or titanium(IV) chloride (−78 or 23 °C).[522] The only identifiable products emerge from the elimination of ethanol and/or proto-desilylation. These adverse results contrast sharply with the successful formation of aza[3.2.1]bicyclooctanes from allylsilanes (e.g., **138** → **139**),[202,203] which is reflective of the limitations of vinylsilane reactivity.

N-Acyliminium cyclizations have been effected with acyclic vinylsilanes.[164,168,174,176,177] Enantiomerically pure (*Z*)-vinylsilane **543** leads to epimeric products **544** and **545** (BF_3·Et_2O, CH_2Cl_2, 0 °C; 71% yield; 1:1 ratio) without significant racemization (95% ee)[174]



543
544 α-Ph
545 β-Ph

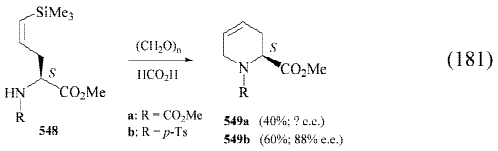
(note: first thought to give a 1:1 mixture **544** and **545**, each as a racemate[168]). (*E*)-Vinylsilane **546** also cyclizes with complete retention of relative and absolute configuration in **547** (eq 180).[177] Pipecolic



546
547 (43%; 100% e.e.)

(180)

acid derivatives **549** are obtained from *N*-acyliminium ions derived from enantiomerically pure amino acids **548** (eq 181).[164] The stereospecificity is not rigorously conserved in this process, in that **549b** has 88% ee (presumably due to minor racemization via a 2-aza-Cope rearrangement).



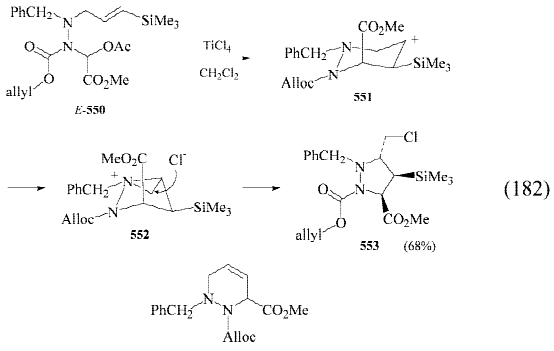
548
a: R = CO_2Me
b: R = *p*-Ts
549a (40%; ? e.e.)
549b (60%; 88% e.e.)

(181)

In *N*-acylhydrazonium ion cyclizations of vinylsilanes,[427,428] there is a dramatic difference in reactivity between the *E* and *Z* forms.[428] For example, (*E*)-**550** reacts with tin(IV) chloride via a chairlike conformer to give the β-silyl carbocation **551**, in which stabilization by the silicon atom and subsequent elimination is geometrically disfavored; consequently, ring contraction via the aziridinium ion **552** occurs to give **553** in 68% yield (eq 182).[428] On the other hand, a mixture of (*Z*)- and (*E*)-**550** (ca. 1:1 ratio) gives a mixture of **553** and **554** in 82% yield (2:3 ratio).

3.4.4. Allylsilanes and Allylstannanes[523−527]

Allylsilanes are normally exemplary participants in *N*-acyliminium cyclizations; also, they often engender excellent stereocontrol.[166,177,185−209] The β-effect of the silicon atom is a powerful determinant of the regiochemistry of allylsilane reactions with electrophiles, so the new carbon−carbon bond is formed at the vinyl carbon distal to silicon, that is, at the γ-position.

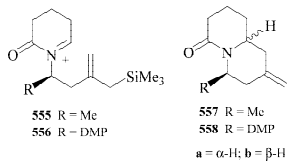


E-**550**
551
552
553 (68%)
554

(182)

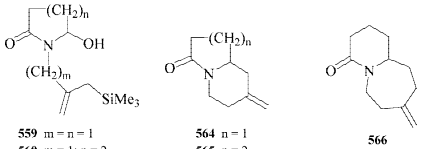
Early studies involved nitrogen-linked cyclic *N*-acyliminium ions.[188,204] Reactions of (*Z*)- and (*E*)-alkenes **123** (CF_3CO_2H) and **124** (HCO_2H) produce vinylpyrrolizidine **125** in 70−85% yield as a single "*syn*" stereoisomer (vicinal hydrogens *syn*).[188] Homologous (*Z*)-alkenes **128** and **129** give **130** and **131** with good yields, each as a single "*anti*" isomer.[188] The corresponding stannane **133** also provides **125** with high stereoselectivity in 77% yield.[211,212] The cyclization of **136** to **137** (eq 47) proceeds with high stereoselectivity in the opposite direction (vicinal hydrogens *syn*).[191] Steric bulk must interfere with the addition mode in the mechanistic model **132** to force the alkene nucleophile to add from the opposite side of the *N*-acyliminium ion.

Cyclizations of nitrogen-linked allylsilanes with a terminal alkene are useful in the synthesis of indolizidine and quinolizidine derivatives.[185,193−198] In syntheses of (+)-myrtine[198] and (−)-lasubines,[196] *N*-acyliminium ions **555** and **556** cyclize to **557**[198] and **558**,[196] both as isomeric mixtures (**a**/**b** = 3:7 and 3:1,



555 R = Me
556 R = DMP
557 R = Me
558 R = DMP
a = α-H; **b** = β-H

respectively). The product isomer ratios (**a**/**b**) in the trifluoroacetic acid cyclization of *rac*-**556** to *rac*-**558** are temperature dependent, ranging from 1:4 at −78 °C to 2:1 at 20 °C.[193,197] In general, these reactions are not very diastereoselective, in contrast to the corresponding ones without a silicon group. A limitation of this method is illustrated by the reactions of hydroxy lactams **559**−**563**.[194] The formation of five-membered rings from **559** and **560** with trifluoroacetic acid fails, as only proto-desilylation products are detected. Cyclization also fails when the ethoxy lactam of **559** is treated with titanium(IV) chloride, tin(IV) chloride, or boron trifluoride etherate. Nevertheless, **561**−**563** successfully cyclize in trifluoroacetic acid to **564**−**566** with yields of 70%, 94%, and 78%, respectively.

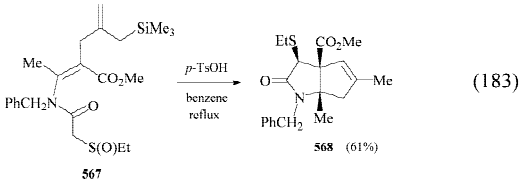


559 m = n = 1
560 m = 1; n = 2
561 m = 2; n = 1
562 m = n = 2
563 m = 3; n = 2

564 n = 1
565 n = 2

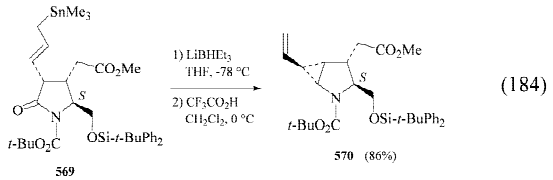
566

Pyrrolidines and piperidines with an allylsilane tethered to the ring carbon adjacent to the *N*-acyliminium carbon cyclize to hexahydrocyclopenta-[*b*]pyrroles[207] and octahydroindoles[186,194] (e.g., eq 50[207]) with *cis* stereoselectivity. This process provides a basis for a formal total synthesis of mesembrine,[186,194] wherein the cyclization is executed under nonacidic conditions to avoid isomerization of the double bond in the product (eq 51). Double bond isomerization occurs when trifluoroacetic acid is used, leading to a mixture of olefin isomers. Also, in the acid-catalyzed tandem Pummerer/*N*-acyliminium cyclization of **567** to **568**, the carbon−carbon double bond isomerizes into the ring (eq 183; position of the



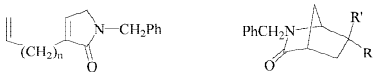
567 → (*p*-TsOH, benzene, reflux) → **568** (61%) (183)

double bond in **568** is uncertain).[344] The 1-azabicyclo-[3.1.0]pentane skeleton is nicely accessible by generating a fused cyclopropane ring via an *N*-acyliminium cyclization of an allylstannane (eq 184); **570** is obtained from **569** in good yield with the vinyl exclusively *exo*.[212]



569 → (1) $LiBHEt_3$, THF, −78 °C; (2) CF_3CO_2H, CH_2Cl_2, 0 °C → **570** (86%) (184)

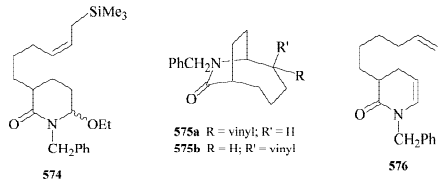
Allylsilane-based cyclizations offer a practical approach to bridged azabicyclic molecules, sometimes with good stereocontrol.[199−203,208] Reaction of ethoxypyrrolidin-2-one **138** in formic acid provides azabicyclo-[3.2.1]octanes **139** in 87% yield with a 95:5 **a**/**b** ratio, in favor of the *endo* vinyl group.[202,203] This cyclization proceeds less efficiently in trifluoroacetic acid because of a 12% yield of the proto-desilylation product **571**.



571 n = 3
573 n = 4

572a R = vinyl; R' = H
572b R = H; R' = vinyl

In contrast to the pyrrolidin-2-one, piperidin-2-one **140** gives homologous azabicyclo[3.2.2]nonanes **141** with little stereochemical bias (eq 48).[202,203] The stereochemical outcome is reversed with a one-methylene linker to the allylsilane in that piperidin-2-one **142** gives azabicyclo[2.2.2]octanes **143** in 94% yield with a strong *endo* preference (**a**/**b** = 94:6), while pyrrolidin-2-one **144** gives azabicyclo[2.2.1]-heptanes **572** in 66% yield with little stereochemical bias.[202] With a three-methylene linker, pyrrolidin-2-one **145** gives azabicyclo[4.2.1]nonanes **146** in 73% yield, mainly as the *exo* isomer (**a**/**b** = 8:92), along with side product **573** (12% yield). To form an eight-membered ring in a bridged azabicyclic compound, it is advisable to employ a Lewis acid catalyst.[202,203,222] However, in the treatment of **574** with tin(IV) chloride, azabicycle **575** is garnered in only about 20%

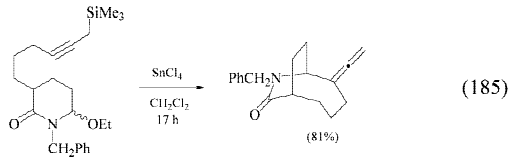


574

575a R = vinyl; R' = H
575b R = H; R' = vinyl

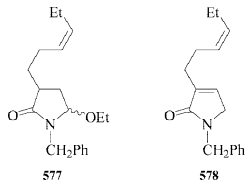
576

yield because of a substantial amount (ca. 80%) of proto-desilylation to **576**. By comparison, the analogous propargylsilane-based cyclization to a bridged eight-membered ring is much more propitious (eq 185).[203,222] Generally, good yields of azabicyclic com-



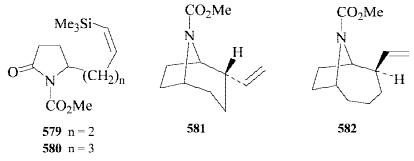
SnCl₄, CH_2Cl_2, 17 h → (81%) (185)

pounds are obtained when new five-, six-, or seven-membered rings are created, although the best yields occur in the six-membered-ring cases. The presence of an activated alkene, such as an allylsilane, is critical for the formation of bridged bicyclic molecules. For example, treatment of **577** with trifluoroacetic acid yields only the elimination product **578**.[202,203]



577 **578**

Bridged bicyclic compounds can be generated with substrates possessing exocyclic *N*-acyl or *N*-sulfonyl groups.[199−201,208] 5-Hydroxypyrrolidines from the partial reduction of **579** and **580** afford **581** (*endo*) and

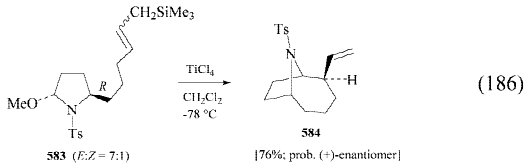


579 n = 2
580 n = 3

581

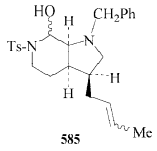
582

582 (*exo*/*endo* = 19:1) in ca. 75% yield.[208] Bicyclo-[4.2.1]nonane **584**, a precursor to anatoxin, is obtained from **583** by a titanium(IV) chloride-based *N*-tosyliminium cyclization (eq 186).[201,209] An analogous *N*-tosyliminium/allylsilane cyclization, used in the synthesis of sarain A, did not work with titanium-(IV) chloride or boron trifluoride etherate because of significant proto-desilylation, but it did proceed well

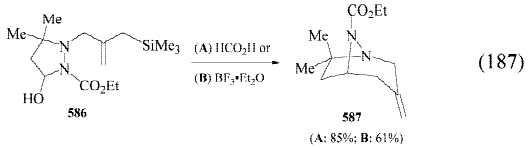


(186)

with anhydrous iron(III) chloride (eq 49).[199,200] By comparison, standard alkene **585** did not yield any

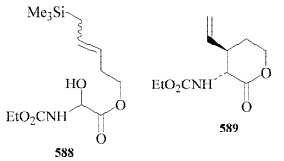


desired polycyclic material with iron(III) chloride. Bridged bicyclic hydrazides, such as **587**, are formed via the cyclization of hydrazonium ion precursors, such as **586** (eq 187).[205]

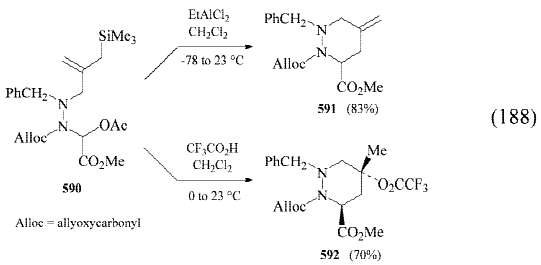


(187)

Allylsilane cyclizations of acyclic *N*-acyliminium ions can readily supply vinylpiperidines and vinylpyrrolidines, at times with excellent stereocontrol.[166,187,189,190,192] For example, treatment of **154** with diethylaluminum chloride gives only the *E*-isomer **155** in 69% yield.[187] By contrast, the trimethylene homologue **156** yields **157** with minimal stereoselectivity (Z/E = 2:1) in 60% yield. "Glycine cation equivalents" extend this method to the synthesis of proline and pipecolic acid derivatives.[189] Cyclizations of **150** and **152** (MsCl, Et_3N) afford **151** and **153** in 88% and 79% yields (Z/E = 11:89 and Z/E = 55:45, respectively).[189] Despite such positive results, a similar reaction with **588** does not yield the desired **589**.[192] The glycine-cation method with alkenes de-

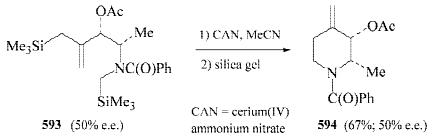


void of special activation can lead to complex stereochemical results on account of the 2-aza-Cope rearrangement.[161,164,166,215] Although hydrazide **590** cyclizes to alkene **591** or trifluoroacetate **592**, depending on reaction conditions (eq 188),[428] a ring-contrac-



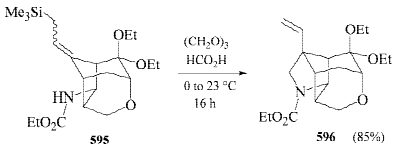
(188)

tion pathway, such as with **550** → **553**, is adopted when the silyl-directing group is missing.[447] An acyclic reaction with a more substituted substrate, **593**, gives **594** with complete stereospecificity (eq 189).[177] The cyclization of *N*-sulfonyliminium ions



(189)

from silyl-substituted (*E*)-alkenyl aldehydes proceeds efficiently to stereodefined amido cycloalkenes (eq 70).[306] From a synthetic perspective, *N*-acyliminium cyclizations of acyclic allylsilane substrates have provided key intermediates en route to gelsemine (eq 190)[190] and α-allokainic acid (eq 191).[192]



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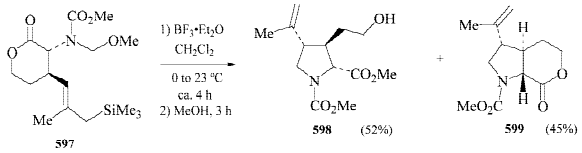
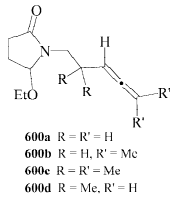


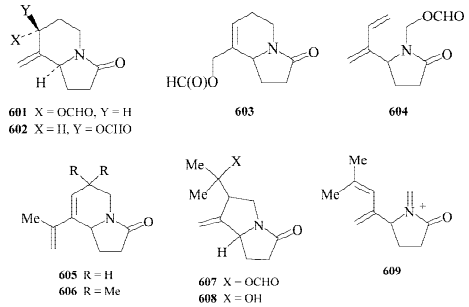
(191)

3.4.5. Allenes

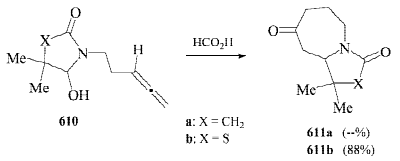
Terminal allenes can function as π-nucleophiles in *N*-acyliminium cyclizations, but only limited studies are reported in this area. The set of ethoxy lactams **600** react by two different pathways according to the substitution pattern, one leading to indolizidines and the other to pyrrolizidines.[153,429] On treatment of



600a with formic acid a new six-membered ring is formed, giving rise to indolizidines **601**−**603**, as well as some 2-aza-Cope byproduct **604** (96% yield; 2:1:1:2 ratio). A cleaner reaction ensues with **600b** and **600c** to produce indolizidines **605** and **606** in quantitative yield. However, **600d** affords a 4:1 mixture of pyrrolizidines **607** and **608** (94%) stereoselectively, both of which emerge from a 2-aza-Cope rearrangement involving the *N*-acyliminium ion **609**.[153,429]

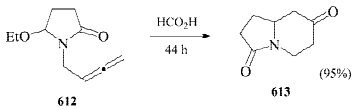


Interestingly, **610a** and **610b** furnish an entirely different type of product in seven-membered ring-fused ketones **611a** and **611b**, presumably due to the bulky dimethyl substitution, which impedes attack of the *N*-acyliminium ion on the central allene carbon (eq 192).[154,429] Thus, the reaction favors formation of



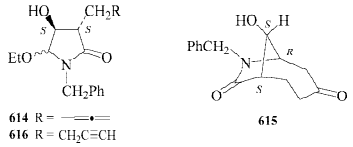
(192)

secondary products from attack at the allene terminus with subsequent solvent trapping of the intermediate vinyl carbocation. In the absence of dimethyl substitution, as in **612**, six-membered-ring closure proceeds smoothly to give **613** (eq 193).[528]

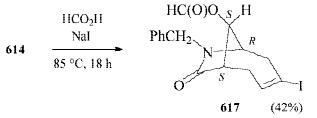


(193)

An allene-terminated *N*-acyliminium cyclization played a key role in the total synthesis of gelsedine.[528−530] Treatment of (3*S*,4*S*)-pyrrolidinone **614** with formic acid at 85 °C, followed by methanolic ammonia to hydrolyze the formate ester, supplies enantiomerically pure azabicyclic keto lactam **615** in 79% yield.[528,530] Notably, the hydroxyl does not in-



terfere with the cyclization, perhaps because it is first converted to a formate ester in situ. Although cyclization of the corresponding alkyne, **616**, is more sluggish, a 52% yield of **615** is still obtained. The introduction of suitable functionality at C4 of the 8-azabicyclo[4.2.1]nonane system is based on an iodide-terminated *N*-acyliminium cyclization,[485] such that allene **614** is readily converted to vinyl iodide **617**, albeit in just 42% yield (eq 194).[529,530]

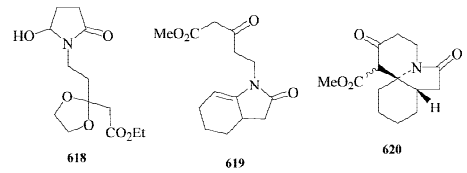


(194)

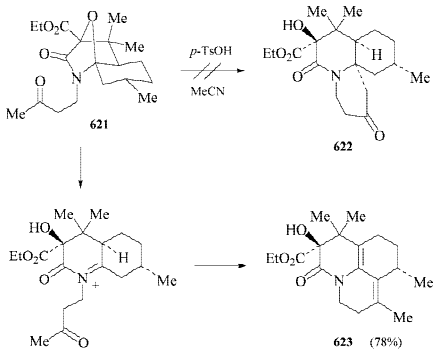
3.4.6. Enols and Enolates

Active methylene and methine groups can participate in *N*-acyliminium ion cyclizations via their enol or enolate forms. Enol nucleophiles supply products that are analogous to those from vinyl ether nucleophiles. In cases where a ketal group is being cleaved during cyclization, or where a ketone cyclization is promoted by an alcoholic mineral acid, it can be unclear as to whether an enol/enolate or a vinyl ether is the crucial reacting moiety. A vinyl ether from partial cleavage of a ketal may be a more likely reactant under nonaqueous conditions, since the ketone may not be liberated. Specialized versions of the *N*-acyliminium cyclization of enols/enolates include the cyclocondensation of imines with carboxylic anhydrides[227] and the formation of β-lactams via the Staudinger reaction.[20,227] The former will be mentioned in this subsection, but the latter will not be discussed.

There are several reports of unambiguous *N*-acyliminium ion cyclizations with ketone enols.[231,323,336,499,531−533] Representative examples involving an isolated ketone and a β-keto ester are depicted in eqs 74[323] and 76,[336] respectively. An improved 97% yield of the indolizidine product in eq 76 is obtained by treating ketal ester **618** with formic acid.[531] Although β-keto ester **619** is converted to the

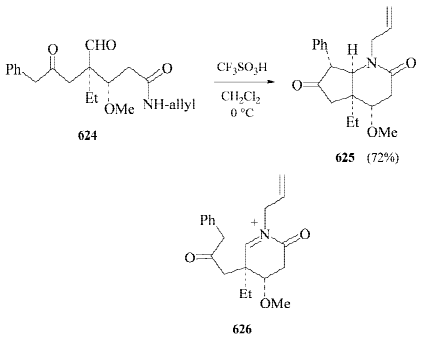


tricyclic compound **620** in 58% yield with boron trifluoride etherate,[532] the related reaction of isolated ketone **621** does not give **622**; rather, the *N*-acyliminium ion leads to an intermediate enamide that reacts at the carbonyl carbon to give **623** (eq 195).[499] The



(195)

N-acyliminium ion cyclization of an enol is capable of forming a new five-membered ring (eq 196),[534] even though this 5-*endo*-trig process is highly disfavored in the cyclization of a standard alkene (vide supra).

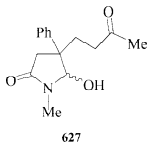


(196)

Indeed, cyclization of keto aldehyde amide **624** to *cis*-cyclopenta[*b*]pyridine **625** with triflic acid (via putative intermediate **626**) proceeds in 72% yield without interference from the *N*-allyl group, cyclization of which would occur by a 5-*endo*-trig process (note: weaker acids led to unwanted byproducts).[534] A notable ketone-based *N*-acyliminium cyclization is a key step in the synthesis of gelsemine, whereby

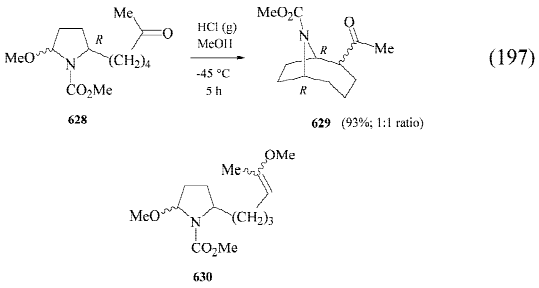
bromo enamide **197** is converted to the bridged polycycle **198** (CF_3CO_2H, 85% yield).[231]

Certain protocols for conducting enol-type *N*-acyliminium ion cyclizations may entail an enol ether from the partial opening of a ketal substrate or from addition of an alcohol to a ketone substrate, rather than a free enol/enolate form of the ketone. A case in point is the *cis*-stereoselective conversion of cyclic ketal **193** to octahydroindole **192** with concentrated HCl and methanol (reflux; 78% yield), en route to mesembrine.[127,132] Since free methyl ketone **627** cy-



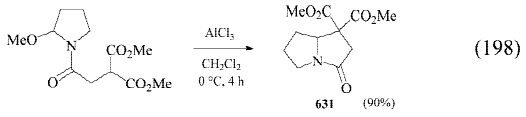
627

clizes readily in 65% sulfuric acid to **192**, along with some troublesome impurities, the one-step methanol−HCl process is more effective.[132] The cyclization of ketone **628** to 9-azabicyclo[4.2.1]nonane **629**, en route to (+)-anatoxin-a, appears to involve the enol form of **628** (eq 197);[533] however, formation of methyl vinyl ether **630** may intervene to propel the reaction (cf. eqs 74, 149, and 150).



628 **629** (93%; 1:1 ratio) **630** (197)

1,3-Diester (malonate) derivatives can also serve as good substrates for this type of *N*-acyliminium cyclization[535,536] (e.g., eq 198[536]). However, a single ester group is not sufficient to allow for an enol-type *N*-acyliminium ion cyclization.[535]



631 (90%) (198)

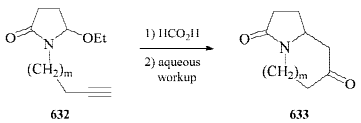
An enolate-based *N*-acyliminium cyclization that is useful in the synthesis of isoquinoline alkaloids involves the condensation of imines and cyclic anhydrides.[227,244−276] This approach is illustrated by the reaction of succinic anhydride with PhCH=NMe in eq 58.[244] The reaction transpires well with succinic, glutaric, or homophthalic anhydrides and with benzaldimines. The benzoyl carbonyl of homophthalic anhydrides reacts preferentially, thereby controlling the regiochemistry.[227,265] The *trans*/*cis* isomer ratio can vary according to the solvent employed or the benzaldimine substituents (eqs 60 and 61), with benzene giving a high proportion of *trans* isomer.[265] Boron trifluoride etherate results in exclusive formation of *trans*-isoquinolones, as well as an expanded reaction scope.[273] (*Z*)-Imines, such as **213**, give *trans*-isoquinolones, such as **214**, almost exclusively in the absence of equilibrating conditions.[265,276] An asymmetric *trans*-isoquinolone synthesis with an enantiomerically enriched chiral imine (eq 62) provides each enantiomer of corynoline with a high enantiomeric purity.[266]

3.5. Reactions of Alkynes

Alkynes are useful nucleophilic terminators for *N*-acyliminium ion cyclizations, and ring closure proceeds through an *exo* or *endo* vinyl cation intermediate (viz. **174** and **175**), which is captured by solvent or an available anion.[15,188,189,202−205,208,218−226] With oxygen-based nucleophiles, such as formate or acetate, a ketone group is usually obtained at the site of cyclization due to facile hydrolysis of the acyloxyalkene product during aqueous workup. Alkynes are generally less reactive as nucleophiles, so reaction times are often protracted (>24 h). In general, *endo* cyclization is strongly favored with terminal acetylenes.[43,46]

3.5.1. Standard Alkynes

ω-Alkoxy lactams bearing a terminal alkyne on nitrogen undergo *endo* cyclization to form new six-, seven-, eight-, and 15-membered rings within bicyclic keto lactams in good yields (eq 199).[43,46,125,136,143,156]



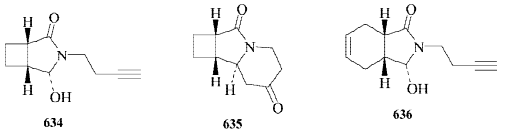
632 **633** (199)

#	m	Time	Yield
a	0	??	0%
b	1	72 h	97
c	2	5 d	90
d	3	14 d	80
e[a]	10	20 d	82

[a] 5-Hydroxy lactam; at 43 °C.

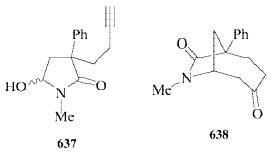
With a short linker to the acetylene group, as in **632a**, this cyclization is not viable.[46] It is noteworthy that the cyclization of 6-ethoxypyrrolidin-2-one **632b** provides an excellent 97% yield of indolizidine **633b** at ca. 0.3 M,[43,46] whereas the reaction of 6-ethoxypiperidin-2-one **9** at ca. 0.2 M leads to ca. 20% yield of dimeric byproduct **11** (viz. eq 8) in addition to desired quinolizidine **12**. At a higher dilution (ca. 0.01 M) dimer **11** vanishes and only quinolizidine **12** is obtained. The closure of seven- and eight-membered rings ($m = 2$ and 3) proceeds quite well via an *endo* pathway (eq 199). The facile formation of an eight-membered ring in **633d** is remarkable in comparison with the poor cyclization results found with the corresponding alkene substrates.[46] Treatment of methoxy-substituted pyrrolidin-2-one **189** with formic acid also generates an eight-membered-ring product, **191** (no yield reported).[138] Macrocyclization is also feasible, provided that high dilution is employed, as in the conversion of **632e** to **633e**.[156] Although bicyclic hydroxy lactam **634** cyclizes in formic acid to **635** in 84% yield, **636** fails to cyclize because of enamide formation and subsequent olefin migration.[143]

ω-Alkoxy lactams with a terminal alkyne on the lactam 3-position yield bridged bicyclic products. For example, the formic acid cyclization of **637** furnishes **638**, albeit in a modest 37% yield because a seven-



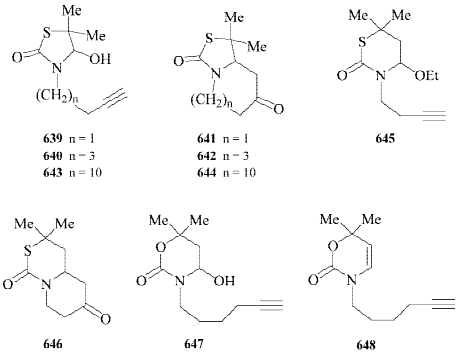
634 **635** **636**

membered ring is being formed. A six-membered ring can be generated more successfully, as in the conversion of lactam **176**, with the alkyne linked at the 3-position, to octahydroindole **177** (HCO_2H, 120 h; 85% yield; only *cis* stereochemistry).[127,132]



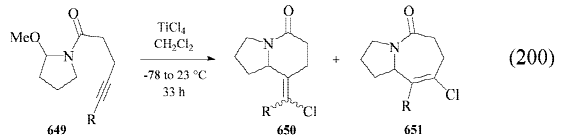
637 **638**

Heteroatom-containing *N*-acyliminium ions cyclize onto a terminal acetylene in a similar manner.[156,429,484,485,523] Thiazolidinones **639** and **640** give bicyclic ketones **641** (80% yield) and **642** (70% yield), respectively,[429,484] and **643** gives macrocycle **644** (76% yield).[156] However, the yield of **646** from 6-ethoxythiazinone **645** is reduced to 45%, presumably because of enamide formation.[485] In fact, enamide **648** is the only tractable product when oxazinone **647** is treated with formic acid (ca. 25% yield).[485]



639 n = 1; **640** n = 3; **643** n = 10
641 n = 1; **642** n = 3; **644** n = 10
645
646 **647** **648**

Internal alkyne substrates can yield *exo* or *endo* products, depending on the structural features.[43,46,218,220,223,224,493] Methyl-substituted alkyne **181** cyclizes in formic acid over 5 days to a mixture of *endo* and *exo* regioisomers **182** and **183** in 90% yield, with a strong preference for **197** (*endo*/*exo* = 90:10).[43,46] However, the piperidinone homologue **184** gives the opposite result, generating mainly the *exo* regioisomer **185** in 92% yield (*endo*/*exo* = 15:85). When the alkyne group is separated by one more methylene, as in the conversion of **186** to **187** (88% yield), only *exo* products are formed.[43,46] This *exo* preference holds for the related cyclization of **649a** to **650** (eq 200).[493] By contrast, the corresponding

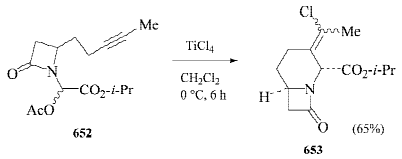


(200)

649 **650** **651**

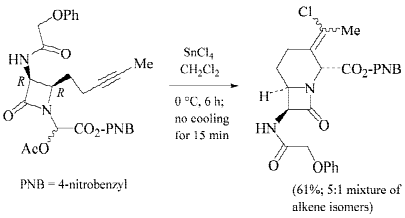
#	R	650	651
a	Me	82%	0%
b	H	0%	70%

terminal alkyne, **649b**, cyclizes exclusively by an *endo* cyclization to form a new seven-membered ring and give **651** in 70% yield (eq 200).[493] Sensitive β-lactam substrate **652**, with an internal alkyne, cyclizes via a glycine cation-type *N*-acyliminium ion exclusively by an *exo* pathway to yield **653** (eq 201).[223]



(201)

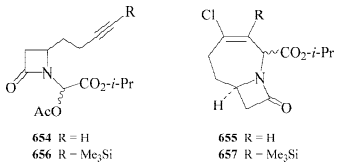
652 **653** (65%)



(202)

PNB = 4-nitrobenzyl
(61%; 5:1 mixture of alkene isomers)

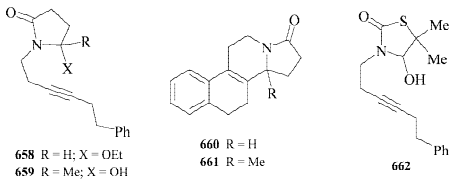
A more complex cyclization of this type served a central role in a formal enantiospecific synthesis of the carbacepham antibiotic loracarbef (eq 202).[223] The terminal alkyne analogue **654** cyclizes with tin(IV) chloride only by an *endo* pathway to give **655** as a single isomer in just 12% yield (which was not improved by addition of nucleophilic salts, such as NaI).[223] However, treatment of the internal alkyne **656**, possessing a terminal silyl group, with tin(IV) chloride produces only the *endo* cyclization product **657** in 71% yield.[223] In summary, internal aliphatic



654 R = H
656 R = Me_3Si
655 R = H
657 R = Me_3Si

alkynes are inclined to cyclize by an *exo* pathway in the absence of ring strain; phenylthio-, phenyl-, and bromo-substituted alkynes (e.g., **178** and **180**) evince a strong preference for the *exo* regiochemistry,[218,225,226,486,487] but a silyl-substituted alkyne favors the *endo* regiochemistry.

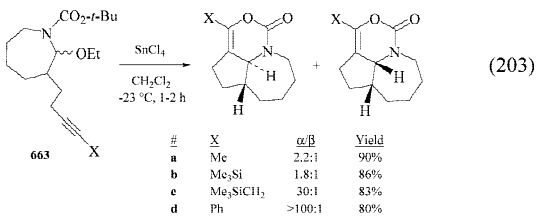
When a second carbon-based nucleophile is present, the intermediate vinyl cation can react further, in a tandem reaction, to yield tetracyclic products.[129,131,136] Lactams **658** and **659** in formic acid give azasteroids **660** (54% yield)[131] and **661** (38% yield),[136] which derive from the capture of an intermediate *endo* vinyl cation by the phenyl group. By contrast, thiazolidinone **662** fails to cyclize even under more strenuous conditions, probably due to steric hindrance.[429]



658 R = H; X = OEt
659 R = Me; X = OH
660 R = H
661 R = Me
662

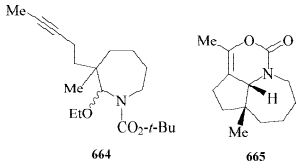
A carbamate group can participate in the Lewis acid-catalyzed alkyne cyclization to yield tricyclic products (eq 203).[224] The *N*-carbalkoxyiminium ion reacts with the alkyne via a formal intramolecular

[4 + 2] polar cycloaddition that results in an *exo* ring closure.[224] To arrive at a suitable geometry for



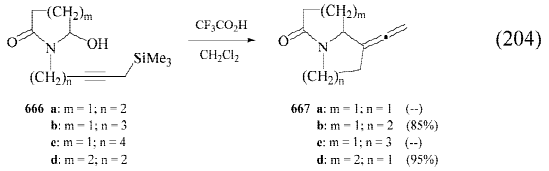
(203)

cyclization, an exocyclic *N*-acyl group is necessary. In eq 203, it is noteworthy that very high α (or *trans*) stereoselectivity is obtained with propargylsilane **663c** and phenylacetylene **663d**, and that **663c** does not lead to any allene-containing products, as might be expected from a conventional *N*-acyliminium ion cyclization of a propargylsilane (vide infra). Substitution of **663a** with a methyl group, as in **664**, results in the exclusive formation of the β (*cis*) product **665** in 69% yield.[224]



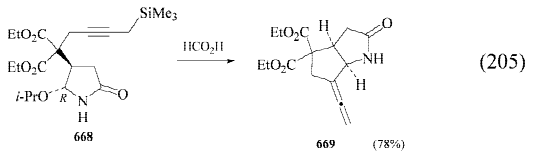
3.5.2. Propargylsilanes

There are numerous examples of cyclizations in which propargylsilanes are effective nucleophiles.[175,188,189,203−205,208,219,221,222,395,428,522,537,538] The ring closure is usually accompanied by elimination of the silicon moiety from the incipient, exocyclic vinyl cation to form an allene as the ultimate product. Treatment of **666a** with trifluoroacetic acid yields solely the air-unstable bicyclic allene **667a**, while



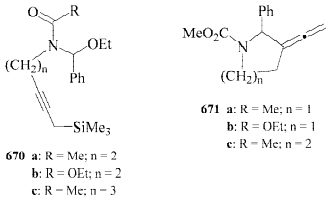
(204)

homologues **666b** and **666d** give **667b** and **667d**, and **666c** gives the seven-membered-ring product **667c** (eq 204).[188,204] It is significant that proto-desilylation does not occur in these reactions.[188,204] The synthetic utility of this method can be appreciated by the enantiospecific synthesis of pyrrolizidine **669** from **668** (eq 205).[395]

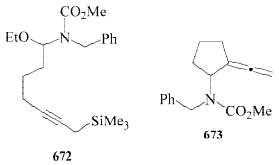


(205)

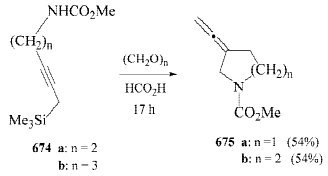
The propargylsilane approach is quite useful for the synthesis of monocyclic allenes.[189,537] Reaction of hemiaminal derivatives **670a** and **670c** with formic acid affords allenes **671a** and **671c** in yields of 68% and 74%,[537] with a minor amount of competing hydrolysis and proto-desilylation. However, proto-



desilylation prevails in the formic acid cyclization of **670b** to **671b**, although it can be suppressed by using a Lewis acid catalyst. Thus, the reaction of **670b** with diethylaluminum chloride gives **671b** in 55% yield. The formic acid cyclization of carbamate **672** proceeds readily to allene urethane **673** in a reasonable yield.[189] Carbamates **674a** and **674b** combine with

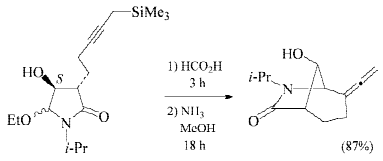


paraformaldehyde in formic acid to produce **675a** and **675b**, each in 54% yield (eq 206).[189] In a similar vein, the butyl α-acetoxyacetate of **674a** (from **674a** and butyl glyoxalate, followed by acetic anhydride/pyridine) is converted to the proline ester analogue of **675a** in ca. 50% yield with the aid of diethylaluminum chloride (CH_2Cl_2, 0 to 20 °C, 2 h).[189]



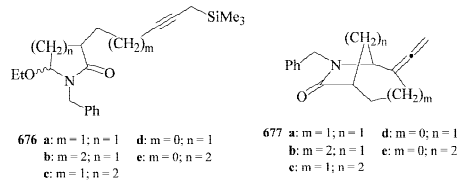
(206)

Bridged azabicyclic compounds with appended allene groups can be readily obtained.[202,203,208,219,221,222,538,539] A noteworthy enantiospecific conversion, involving a cyclic *N*-acyliminium ion with an alkyne chain attached α to the lactam carbonyl, is shown in eq 207.[219] While at-

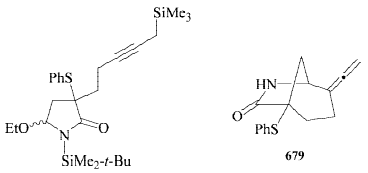


(207)

tempts to access this aza[3.2.1]bicyclic ring system by cyclization of a (*Z*)- or (*E*)-vinylsilane failed,[522,538] analogous cyclizations of various propargylsilanes (e.g., **676a**−**e**) worked well to provide azabicycles (e.g., **677a**−**e**) in 80−98% yields. A remarkable

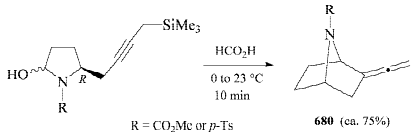


result, mentioned earlier, is the high-yield formation of a new eight-membered ring in a Lewis acid-induced cyclization (eq 185).[202,203,222,522] Although formic acid is not effective for this transformation (<10% yield of product), it has been useful in related cases of bridged bicycle formation.[202,222] In addition, **678** is converted to **679** with formic acid in excellent yield (87%) en route to gabaculine.[522,538] Good results



678 **679**

are obtained when the alkyne chain is tethered α to the acylated nitrogen.[208,221] By way of illustration, in a total synthesis of (−)-epibatidine, azabicyclo[2.2.1]-heptanes **680** are formed enantiospecifically in good yield (eq 208).[221] Also, the *N*-acylhydrazonium ion cyclization of **681** gives a diazabicyclo[2.2.1]heptane product in 62% yield (eq 209).[205]



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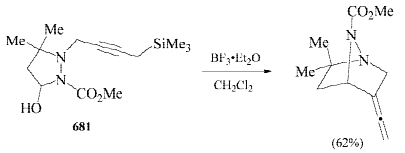


681

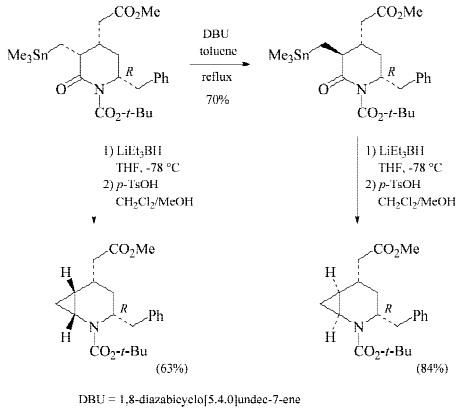
(209)

3.6. Reactions of σ-Nucleophiles (Carbocyclizations)

The vast majority of *N*-acyliminium ion cyclizations at carbon centers pertain to the reaction of π-nucleophiles, such as benzenoids, alkenes, and alkynes. Alternatively, cyclization could occur at saturated carbon centers, that is, σ-nucleophiles. Since there are only isolated examples of such reactions, this area holds considerable promise for future applications in organic synthesis.

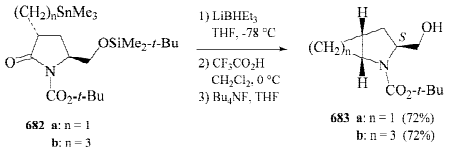
Organometallic species can serve as reactive σ-nucleophiles, although this poses certain constraints. The organometallic groups must be reactive enough to undergo the *N*-acyliminium cyclization but be robust enough to withstand the required acidic conditions. That is, the requisite functionality must not be otherwise destroyed prior to execution of the ring closure. Thus, it is not surprising that an alkylstannane can satisfy this purpose.[540,541]

A general route to compounds with a cyclopropane fused onto a lactam involves cyclization of α-stannylmethyl *N*-acyliminium ions (eq 210).[540,541] This approach was originally developed for destannylative



(210)

ring closure with a π-nucleophile, as in the conversion of **569** to **570** (eq 184),[212] and is quite useful for preparing enantiomerically pure 4,5-methanoproline via a key *N*-acyliminium carbocyclization in the three-step conversion of **682a** to **683a**.[541] This method is sufficiently versatile to construct a fused five-membered ring in the homologous conversion of **682b** to **683b** (eq 211).[541]

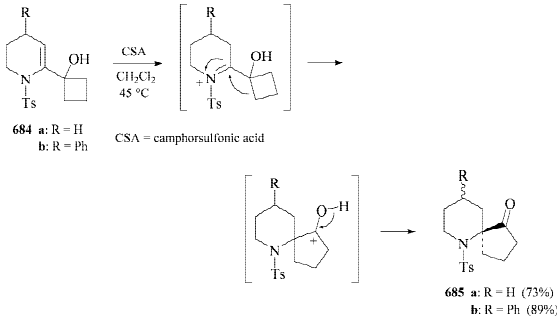


682 **a**: n = 1
b: n = 3

683 **a**: n = 1 (72%)
b: n = 3 (72%)

(211)

Another means to access a σ-nucleophile pathway (carbocyclization) is through carbocation rearrangements. A semipinacol-type rearrangement serves this purpose nicely in the context of an *N*-tosyliminium cyclization leading to azaspirocycles.[542] For example, cyclobutanols **684a** and **684b** rearrange on treatment with camphorsulfonic acid to **685a** (13 h) and **685b** (144 h), according to the process outlined in eq 212.

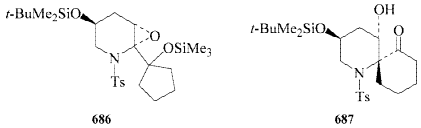


684 **a**: R = H
b: R = Ph

685 **a**: R = H (73%)
b: R = Ph (89%)

(212)

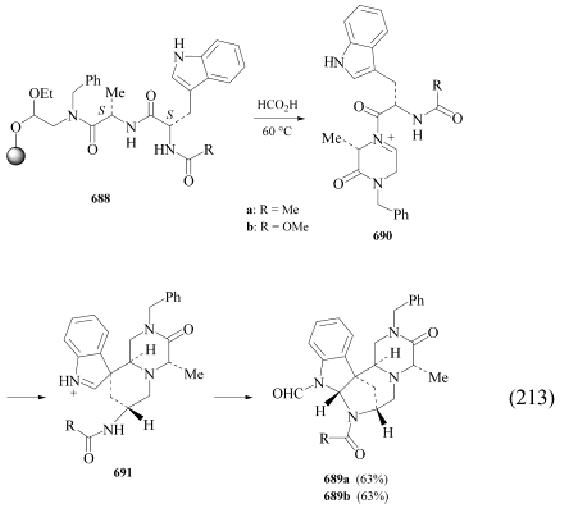
For **684b**, the use of HCl gives **685b** with a highly biased ratio of 14:1 (0 °C, 48 h). This type of reaction fails for a related cyclopentanol substrate but succeeds in a titanium(IV) chloride-promoted rearrangement of epoxide **686** to azaspirocycle **687** in an exceptional 96% yield (−78 °C, 30 min).[542]



686 **687**

3.7. Reactions on the Solid Phase

Given the popularity of solid-phase organic synthesis, it is not surprising to see some applications based on *N*-acyliminium ion chemistry.[543−546] One example is the synthesis of multifunctional heterocyclic scaffolds via tandem *N*-acyliminium ion cyclization−nucleophilic addition on a TentaGel-OH resin.[543] Although most of the routes involve trapping of the resin-bound *N*-acyliminium ion with heteroatom nucleophiles, carbon−carbon bond formation is exemplified by the reaction of indole π-nucleophiles with piperazinone-based ions. Treatment of **688a** or **688b** with formic acid at 60 °C produces complex polycycles **689a** or **689b**, each in 63% yield, via a cascade entailing (1) cleavage of the acetal from the resin to form an oxacarbenium ion, (2) cyclization to piperazinium ion **690**, (3) *N*-acyliminium cyclization onto the indole 3-position, (4) trapping of intermediate indolinium ion **691** by the pendant amide nitrogen, and (5) formylation of the indoline nitrogen (eq 213).

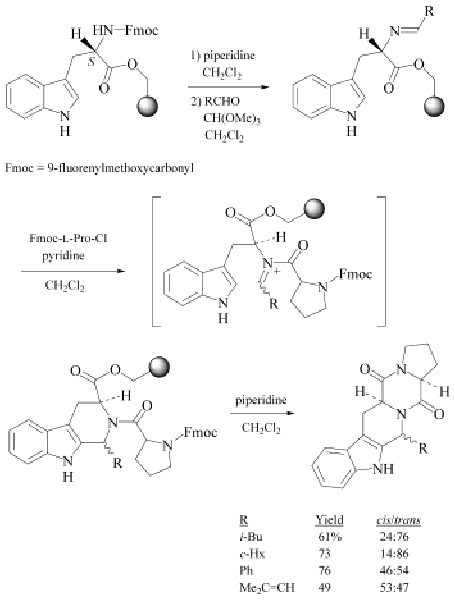


(213)

In another case, a Wang 4-benzyloxybenzyl alcohol resin[547] bearing L-tryptophan is subjected to an *N*-acyliminium cyclization by means of sequential addition of an aldehyde (to form an imine) and Fmoc-protected L-proline acid chloride (to activate the imine) (eq 214).[544] A cyclization-induced cleavage from the resin provides the final pentacyclic product in yields ranging from 50 to 75%. The yields and *cis*/*trans* isomer ratios are comparable to those obtained from the solution-phase synthesis, and the reaction is tolerant of a variety of aldehydes and amino acids. This *N*-acyliminium protocol is noteworthy in that it avoids acidic conditions, which should allow for a diversity of solid-phase linkers.

4. Comparison with Other Related Methods

Conventional iminium ions have been an integral part of organic synthesis for nearly 100 years in the



(214)

context of the Mannich reaction, wherein a new carbon−carbon bond is formed by addition of a carbon-based nucleophile to an electrophilic imine.[1−5] The intramolecular variant of the Mannich reaction (eq 215), generally referred to as the "Pictet−Spengler reaction", has been an important influence, especially in the synthesis of indole and isoquinoline alkaloids.[6−10] *N*-Acyliminium ions,[15−19] a subclass in the iminium ion family, usually possess higher reactivity, such that their intramolecular reactions are very versatile in synthetic applications. Structurally related iminium and *N*-acyliminium ions often cyclize to analogous products, with the former being an amine and the latter being an amide. As such, the workup procedure for iminium ion reactions may require neutralization of a large amount of acid to isolate the product, which can be rather inconvenient when dealing with a strong, nonvolatile acid (e.g., polyphosphoric acid). On the other hand, the workup of *N*-acyliminium ion reactions may just involve simple dilution with water or an aqueous salt solution. In this section, we present some comparisons between Mannich-type cyclizations and *N*-acyliminium ion cyclizations for structurally related systems, epecially to gain some understanding of their complementarity.

(215)

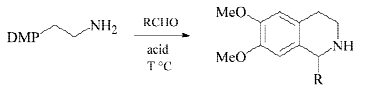
Second, we offer a comparison of some analogous cyclizations involving *N*-acyliminium ions and α-acylamino radicals, which are cognate species that exhibit a different pattern of reactivity. Their intramolecular reactions with alkene and alkyne π-nucleophiles, in particular, give rise to different types

of cyclic products. The *N*-acyliminium ion reactions complement the α-acylamino radical reactions, especially with respect to the preferred size of the nascent ring. As a consequence, these two approaches can be independently useful in synthetic applications.

4.1. Intramolecular Mannich Reactions

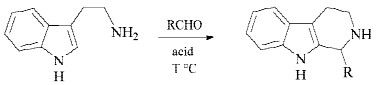
In general, iminium ions are comparatively weak electrophiles that often require fairly nucleophilic π bonds as reaction partners. Thus, *N*-acyliminum ion cyclizations can have a potential advantage over Mannich-type iminium ion cyclizations relative to the participation of less reactive π-nucleophiles, such as unactivated benzenoids and alkenes. Additionally, *N*-acyliminum ion cyclizations have an increased tendency for favorable stereochemical control, partly due to conformational and steric influences from the sp^2-hybridized amide carbonyl. One example of amide carbonyl-based control is the powerful stereochemical influence of A(1,3) strain (viz. eq 33 and **50** → **51**). Nevertheless, for the closure of six-membered rings onto more reactive π-nucleophiles, such as alkoxybenzenes and indoles, Mannich-type cyclizations can be quite competitive, if not superior.

First, it is instructive to examine some fundamental cyclizations of β-arylethylamines, which are classical substrates for the Pictet−Spengler reaction. Aldehyde-based iminium ion reactions of 3,4-dimethoxyphenethylamine[548−551] and tryptamine[552−555] proceed reasonably well (eqs 216 and 217); however, the cyclizations of phenethylamine[556−558] can be difficult, with variable results (eq 218). Fortunately, the



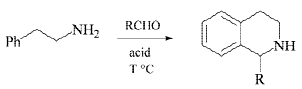
(216)

R	Acid	T	Yield	Ref
H	aq. HCl	100	52%	548
H	HCO_2H	40	87	549
Ph	H_3PO_4	37	71	550
Ph	CF_3CO_2H	73	86	551



(217)

R	Acid	T	Yield	Ref
H	aq. H_2SO_4	100	65%	552
Me	aq. H_2SO_4	110	86	553
Ph	pH 5.2 (3 wk)	25	48	554
Ph	CF_3CO_2H	23	64	555

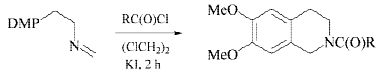


(218)

R	Acid	T	Yield	Ref
H	aq. HCl	100	36%	556
H	aq. HCl	140	trace	557
H	*a*	50	76	558
Ph	CF_3CO_2H	73	0	558
Ph	TfOH	120	90	558

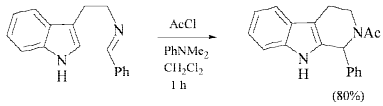
a. TfOH/CF_3CO_2H (9:1)

scope of the Pictet−Spengler process has been broadened by the use of trifluoroacetic and triflic acids.[558] In the case of related *N*-acyliminium ion cyclizations, 3,4-dimethoxyphenethylamine,[363] tryptamine,[340] and phenethylamine[293,340] furnish equivalent or better yields (eqs 219−222). Significantly, the *N*-acyliminium cyclization of an unactivated benzene proceeds effectively under milder reaction conditions.



(219)

R	Yield
Me	74%
Cl_2CH	80%



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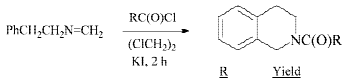
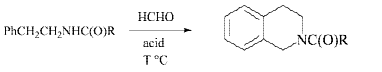


(221)

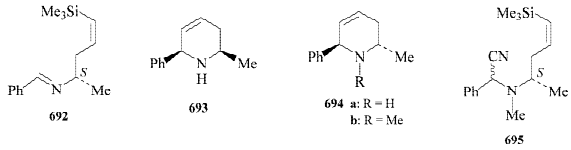
R	Yield
Me	50%
Cl_2CH	75%



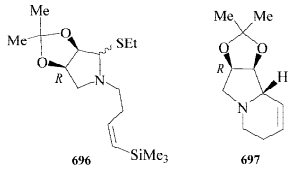
(222)

R	Acid	T	Yield
H	HCO_2H	101	74%
Ph	H_2SO_4/HOAc	23	88
OMe	H_2SO_4/HOAc	23	93

The relative merits of *N*-acyliminium ion and iminium ion cyclizations can be further appreciated from some examples in which the two methods can be compared directly,[168,172,475] or in which some notable synthetic issues arise.[228,229] Enantiopure (*Z*)-vinylsilane **543** reacts in an *N*-acyliminium ion cyclization to give tetrahydropyridines **544** and **555** (1:1 mixture) in 71% yield with boron trifluoride etherate at 0 °C.[168,174] In a corresponding Mannich reaction, (*Z*)-vinylsilane **692** affords tetrahydropyridines **693** and **694a** (1:1 ratio) in 85% yield with



trifluoroacetic acid at 60 °C, and (*Z*)-vinylsilane **695** affords tetrahydropyridine **694b** in 51% yield with $AgBF_4$ at 100 °C.[168] (*Z*)-Vinylsilane **533** cyclizes solely to indolizidine **534** with boron trifluoride etherate at 0 °C in 45−72% yield, depending on the reaction scale (eq 178),[172] while the corresponding Mannich conversion of (*Z*)-vinylsilane **696** to indolizidine **697** proceeds with copper(II) triflate in refluxing tetrahydrofuran in 73% yield. Thus, for (*Z*)-vinylsilane π-nucleo-



philes, cyclizations of *N*-acyliminium ions or regular iminium ions are competitive in terms of product yields, although the conditions employed vary, with somewhat milder conditions for the *N*-acyliminium cyclizations.[172,559]

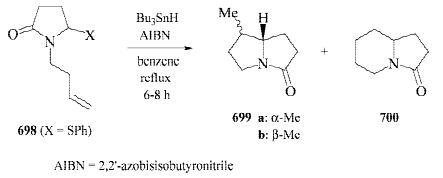
The cyclization of **197** to polycycle **198** occurs readily in 85% yield.[228] In this case, an *N*-acyliminium ion route was selected over an iminium ion route because of the difficult cyclization, owing to the strained polycyclic ring system in the product. To form the new carbon−carbon bond, the tetrahydropyridine ring must adopt a high-energy boat conformation for appropriate orbital overlap between the reactive centers (viz. **199**). The Mannich reaction would be less suitable because of the potential for retro-Mannich fragmentation of the target molecule.

In summary, the intramolecular Mannich reaction can provide a reasonable alternative to the *N*-acyliminium ion cyclization, particularly when more reactive nucleophiles are involved. *N*-Acyliminium ion cyclizations can offer advantages in terms of milder reaction conditions, decreased reaction times, good stereocontrol, and ease of reaction workup. Although intramolecular Mannich reactions are usually performed at higher temperatures, both methods can be conducted under reasonably convenient reaction conditions and frequently result in comparably respectable yields.

4.2. α-Acylamino Radical Cyclizations[560−594]

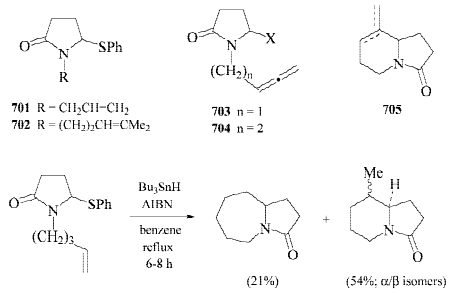
An α-acylamino radical cyclization can be perceived as a reaction that is parallel to the corresponding *N*-acyliminium ion cyclization. This single-electron process would be viable for ring closure onto receptive, radical-trapping groups, such as alkenes and alkynes, and would result in analogous products. The factors that stabilize radical species facilitate this type of reaction and enhance product yields by influencing the intermediate cyclic radicals. In standard practice, α-acylamino radicals are generated from α-phenylthio and α-phenylseleno lactams or tertiary amides thermally with the agency of a tin hydride reagent and 2,2′-azobisisobutyronitrile (AIBN). Radical cyclizations normally favor different size rings than those that emanate from the corresponding *N*-acyliminium ion cyclizations. Unfortunately, such a radical cyclization can be plagued by the formation of multiple cyclic products, due to assembly of different ring sizes, and reductive byproducts. These issues will be illustrated by some pertinent examples for which comparative *N*-acyliminium ion reactions have been reported.

The α-acylamino radical cyclization was introduced in 1982 by Hart as an alternative, or complement, to the *N*-acyliminium approach in alkaloid synthesis.[560] A prototypical reaction with **698** (X = SPh) produces a mixture of four compounds, **698** (X = H),



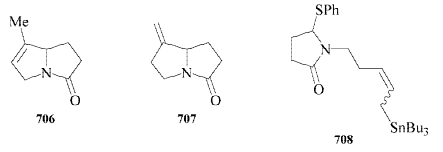
(223)

699a, **699b**, and **700**, in 84% yield and a ratio of 3:10:1:5 (eq 223).[560,561] Although pyrrolizidine **699a** predominates, it is contaminated by the other, related species. By contrast, the corresponding *N*-acyliminium reaction in eq 29 affords only indolizidine **65** in ca. 100% yield.[124,130] It is possible to guide the regiochemistry of the radical reaction toward *exo* or *endo* cyclization by positioning methyl groups on the alkene,[560,561] but mixtures of products are still commonly observed. Certain radical cyclizations fail because of reductive side reactions. For instance, *N*-allyl and *N*-(dimethylhomoallyl) derivatives **701** and **702** do not cyclize under tin hydride conditions because they are simply reduced. However, with a



(224)

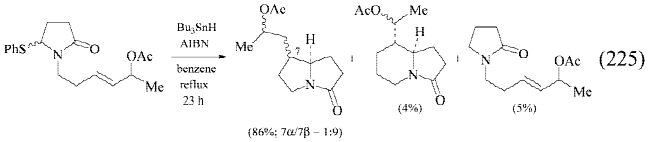
lengthier tether to the alkene, as in eq 224, the seven-membered-ring and six-membered-ring products are formed to a reasonable extent. Although the corresponding allenes **703** and **704** with X = SPh fail to cyclize, ring closure is successful when phenylselenide is the leaving group.[561] Indeed, the reaction of allene **704** (X = SePh) gives indolizidine **705** in 60% yield (*endo*/*exo* = 7:1), along with 26% of reduction product **704** (X = H).[561] By comparison, the cognate *N*-acyliminium cyclization of allene **600a** in formic acid gives a complex mixture of three indolizidines, **601**−**603**, and a 2-aza-Cope byproduct, **604** (2:1:1:2 ratio; 96% yield). A cleaner radical cyclization is realized with allene **703** (X = SePh), which cyclizes via a 5-*exo*-trig pathway to pyrrolizidines **706** and **707** in 52% and 14% yields.[561] The corresponding *N*-acyliminium ion cyclization proceeds via a 6-*endo*-trig pathway to give an indolizidine in excellent yield (eq 193).[527]



Pyrrolidinone **708**, bearing an allylstannane moiety, undergoes radical cyclization (450-W Hanovia

lamp, Pyrex filter) to 4-vinylpyrrolizidin-1-one **125** with good stereoselectivity (*endo*/*exo* = 11:1); however, the yield is only 45%.[211] In the corresponding *N*-acyliminium reaction, pyrrolidinone **133** cyclizes to **125** in 72% yield with an excellent 74:1 *endo*/*exo* isomer ratio (MsCl, Et_3N, 0 to 23 °C). The *N*-acyliminium ion approach is clearly superior here.

The regiochemistry of α-acylamino radical cyclizations can be improved by installing (1) polar heteroatom groups near the radical center of the cyclic intermediate or (2) radical-stabilizing substituents, such as heteroatom or conjugating groups (e.g., CO_2R, CN, SiR_3, SR, Ph), at the radical center (eqs 225−227[562]).[562,564,565,572,573,579] In comparative vinylsilane



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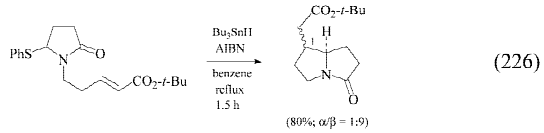

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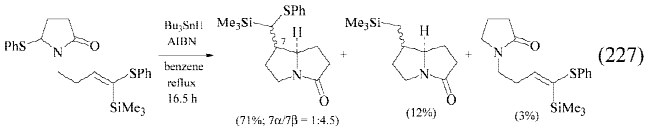
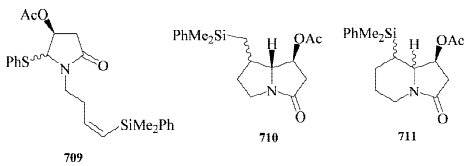
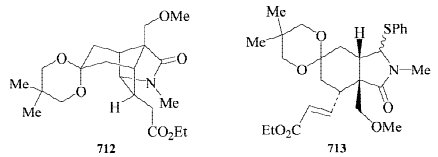


(227)

cyclizations, the radical cyclization is better than the *N*-acyliminium cyclization. Pyrrolidinone **112** cyclizes via an *N*-acyliminium process to yield solely an indolizidine by a 6-*endo*-trig pathway (eq 43). In contrast, the related radical reaction of **709** (*Z*/*E* = 18:1) proceeds mainly by a 5-*exo*-trig pathway to give pyrrolizidine **710** in 73% yield (ca. 6:1 α/*β* ratio), accompanied by a minor 6-*endo*-trig pathway to give indolizidine **711** in 18% yield (three isomers).[564] A radical-stabilizing carbethoxy group helps to effect a sterically demanding α-acylamino radical cyclization in the synthesis of gelsemine intermediate **712** from **713**,[565] whereas the related *N*-acyliminium ion cyclization of **512** to **513**/**514** necessitates a highly reactive silyloxyalkene nucleophile.[234]

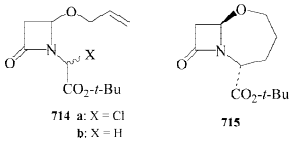


709 **710** **711**



712 **713**

α-Acylamino radicals may have an advantage over *N*-acyliminium ions for cyclizations of substrates with chemically labile groups. In this vein, α-acylamino radical cyclizations are useful in the synthesis of bicyclic *β*-lactams,[583−590] which are sensitive to nucleophiles and harsh reagents, often present in *N*-acyliminium ion cyclizations. For example, the radical derived from **714a** undergoes a 7-*endo*-trig cyclization to give **715** in 47% yield, along with 22%

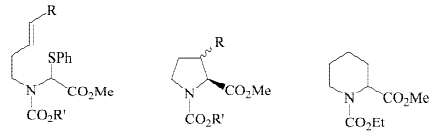


714 a: X = Cl
b: X = H

715

of reduced material **714b**.[583] *N*-Acyliminium ion cyclizations are feasible in the presence of *β*-lactams if highly reactive nucleophiles are used, as exemplified in eq 42, where the cyclization of a silyl enol ether leads to carbapenam **110**.[165]

Glycine-based radicals furnish monocyclic products in good yields as stereoisomeric mixtures.[567−570,578] Although glycine-cation *N*-acyliminium cyclizations tend to yield mixtures of stereoisomers,[161] these isomers result from the orientation of the quenching anion (e.g., formyloxy group), not the newly formed carbon−carbon bond. In eq 168, the tin(IV) chloride reaction gives a single isomer (*trans*) of 4-chloropipecolic acid ester in 77% yield, whereas the corresponding radical cyclization with **716** gives a mixture of five- and six-membered-ring products, **717** (60%) and **718** (30%), the former as a 35:65 *cis*/*trans* mixture.[567,580] Similarly, the radical cyclization of **719**

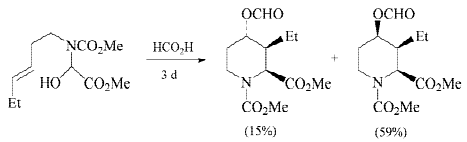


716 R = H; R' = Et
719 R = Et; R' = Me

717 R = Me; R' = Et
720 R = Pr; R' = Me

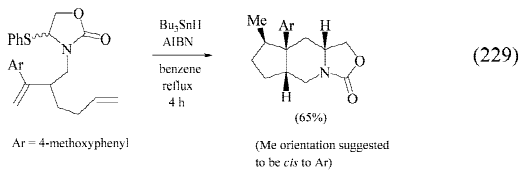
718

affords a 93% yield of proline ester **720** as a 35:65 *cis*/*trans* mixture, whereas the corresponding *N*-acyliminium reaction gives only the *cis*-3-ethylpipecolic acid ester, with two isomers arising from the orientation of the 4-formyloxy group (eq 228).[164]



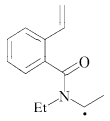
(228)

The α-acylamino radical cyclization is useful for tandem polyene reactions.[572,573] The example shown in eq 229,[572,573] which yields a single diastereomer, is analogous to the *N*-acyliminium ion tandem process shown in eq 37 (also cf. eq 36).[148] Although



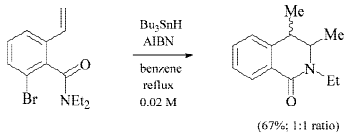
(229)

different ring systems (5,6,5 vs 6,6,5) are assembled, the yields and stereochemical control are comparable. A key distinction is that the radical process favors a 5-*exo*-trig pathway, whereas the cationic process favors a 6-*endo*-trig pathway, as expected.



721

1,5-Hydrogen atom translocation[595] initiates α-acylamino radical cyclizations with alkenes (eq 230[591] and reactive species **721**) and indoles (eq 231[592]).[591−594] It is noteworthy that this protocol can achieve a 5-*endo*-trig cyclization (eq 232),[594] whereas the related *N*-acyliminium ion cyclization generally cannot, since it does not favor generation of a new five-membered ring.



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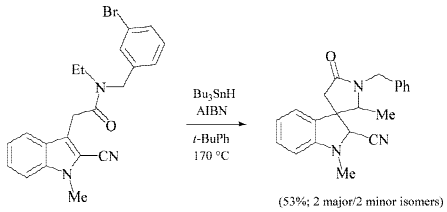

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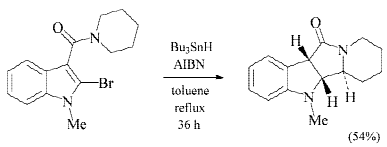


(232)

Alkynes are good traps for α-acylamino radicals.[563,564,567,571,575,580,581,588] Although there is not a solid basis for making direct comparisons between one-electron and two-electron processes for alkyne cyclizations, cyclization via an *exo* vinyl radical is strongly favored, regardless of the size of the ring being closed. However, with vinyl cations derived from *N*-acyliminium cyclizations, the *exo*/*endo* regiochemical preference can vary. The yields for α-acylamino radical cyclizations of internal alkynes are usually 70−90%.[563,564,567,571,575,580] A potential problem with the alkyne-based radical cyclization (besides reduction of the radical) is addition of tributyltin radical to the alkyne,[581,589] although this side reaction can be suppressed by using tricyclohexyltin hydride, as illustrated in Corey's synthesis of (+)-biotin.[581]

In summary, α-acylamino radical cyclizations can work reasonably well with alkenes as radical traps and less effectively, perhaps, with alkynes as radical traps. The alkene-based radical reaction usually proceeds more efficiently when radical-stabilizing substituents are present. Different products are likely to arise from an alkene-based α-acylamino radical cyclization vis-à-vis the corresponding *N*-acyliminium ion cyclization.

5. Comprehensive Tabular Survey of Reactions

The following tabular survey represents an effort to cover all of the published literature involving *N*-acyliminium ion cyclizations (intramolecular α-amidoalkylation reactions) through most of 2002. An emphasis has been placed on data from primary publications where there is some form of experimental support. Generally, we have discounted information from sources that lack experimental support, such as symposium lectures, unpublished results, and published results mentioned in passing (e.g., those in footnotes of papers or in review articles). Articles written in languages other the English, French, or German have not been included. No attempt has been made to address information from the patent literature or doctoral dissertations.

To hold this review to a manageable length, we applied some constraints on the scope of the coverage. Hence, certain classes of specialized *N*-acyliminium (or *N*-acyliminium-type) reactions are not contained in this comprehensive survey. We have excluded (1) cyclizations resulting from formation of new carbon−heteroatom bonds; (2) *β*-lactam synthesis from imines and activated derivatives of carboxylic acids; (3) intermolecular [4 + 2] polar cycloaddition of *N*-acyliminium ions; (4) intramolecular electrophile-induced [4 + 2] cycloaddition of *N*-acylimines; (5) Biginelli reactions; and (6) cyclizations of vinylogous *N*-acyliminium ions. Some examples of *N*-sulfonyliminium ion cyclizations are included for the purpose of comparison.

There are seven tables that are arranged as follows. Table 1 contains *bimolecular* reactions that involve a combination of "substrate" and "reactant", one bearing the electrophilic component and one bearing the nucleophilic component. This table is subdivided according to five classes of "substrates" and includes a wide range of nucleophiles. Tables 2−7 relate to *unimolecular* reactions, wherein the electrophilic and nucleophilic components are essentially present in the same reactant, and encompass the full range of nucleophiles. For the purpose of this tabular orga-

nization, we are not considering reactions of substrates with simple reagents, such as metal hydrides, organolithiums, halogens, or electrons, to generate *N*-acyliminium ion precursors as bimolecular-type reactions. Some examples of these "processed" unimolecular reactions would be the addition of metal hydrides or organometallic nucleophiles to imides, bromination of hydantoins, or electrochemical oxidation of lactams. Table 2, on benzenoid reactions, and Table 5, on alkene reactions, are subdivided into two parts (A and B), with section A containing only direct (i.e., "unprocessed") cyclizations of *N*-acyliminium ion precursors.

It is important to appreciate that certain reactions can be registered in bimolecular or unimolecular modes. For instance, reaction of 2,2-diphenylethylamine with α-angelicalactone to give an intermediate *N*-acyliminium ion precursor, followed by acid-catalyzed cyclization, would be a "bimolecular reaction" if the intermediate is not isolated and the yield is based on the amine substrate. In contrast, this case would be a "unimolecular reaction" if the key intermediate is isolated and the yield is based on it. In the latter situation, the intermediate *N*-acyliminium ion precursor would be the substrate of record. Similarly, an imide that is reduced to an intermediate *N*-acyliminium ion precursor and immediately cyclized, with the yield based on the imide substrate, would constitute a "bimolecular reaction", whereas the corresponding "unimolecular reaction" would entail cyclization of the isolated intermediate, with the yield based on it.

Percent yields are presented in parentheses. When no clear-cut percent yield was reported in the original paper, a dash ("−") is indicated. In published articles, information on yields and isomer ratios can sometimes differ between the body of the text and the experimental description. In case of a disparity, we opted to present the data contained in the Experimental Section of the paper. All temperatures are given in degrees Celsius (°C); "room temperature" is considered to be 23 °C throughout this review. In the tables, "rt" is used to indicate "room temperature" when no specific temperature was reported. The following abbreviations have been used in the tables:

Ac	acetyl
AIBN	2,2′-azobis(isobutyronitrile)
anhyd.	anhydrous
9-BBN	9-borabicyclo[3.3.1]non-9-yl
Bn	benzyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bz	benzoyl
cat.	catalytic amount
Cbz	benzyloxycarbonyl
conc.	concentrated
CSA	10-camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
de	diastereomeric excess
dr	diastereomeric ratio
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMD	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	3,4-dimethoxyphenyl
DMSO	dimethyl sulfoxide
DTBMP	2,6-di-(*tert*-butyl)-4-methylpyridine
ee	enantiomeric excess
eq	molar equivalent (mol equiv)
Fc	ferrocenyl
Fmoc	9-fluorenylmethoxy
Men	menthyl
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
NIS	*N*-iodosuccinimide
Phth	phthaloyl
PPA	polyphosphoric acid
PPE	polyphosphoric ester
Py	pyridine
quant.	quantitative
rt	room temperature
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tol	*p*-tolyl
Ts	*p*-toluenesulfonyl (*p*-tosyl)

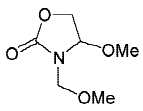
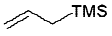
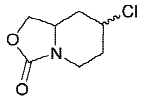
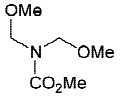
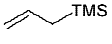
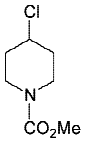
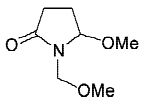
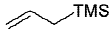
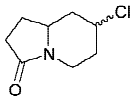
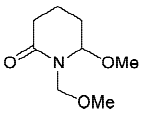
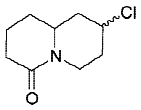
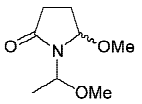
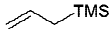
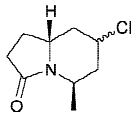
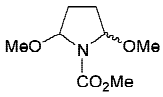
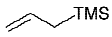
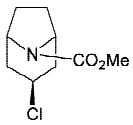
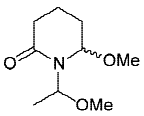
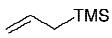
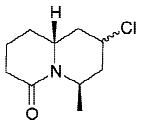
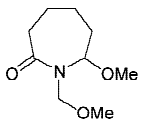
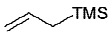
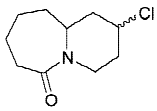
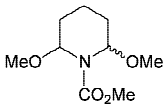
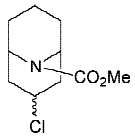
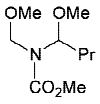
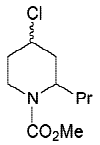
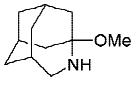
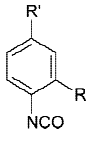
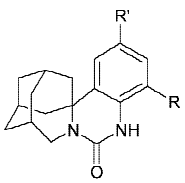
6. Acknowledgments and Dedication

We thank Robin Stanzione (Exton, Pennsylvania) for her invaluable contributions to the preparation of this article and the late Robert Joyce for his dedicated assistance with the assembly of the tables. We are grateful to Prof. Scott Denmark for his excellent advice and suggestions during his review of earlier versions of this article. We express our deep appreciation to Johnson & Johnson Pharmaceutical Research & Development, LLC (formerly The R. W. Johnson Pharmaceutical Research Institute) for supporting our efforts.

This chapter is dedicated to Prof. Robert O. Hutchins of Drexel University, who has illuminated the path to successful careers in chemistry for many students over the course of his academic career, and to the memory of Dr. Robert M. Joyce, deceased 19 January 2002.

Table 1. Bimolecular Reactions

Table 1A. Bimolecular Reactions: α-Alkoxy Amides and Amines

substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_6				
		$TiCl_4$, CH_2Cl_2, rt	 (77)	511
		$TiCl_4$, CH_2Cl_2, rt	 (65)	511
C_7				
		$TiCl_4$, CH_2Cl_2, rt	 (77)	511
C_8				
		$TiCl_4$, CH_2Cl_2, rt	 (83)	511
		$TiCl_4$, CH_2Cl_2, rt	 (70)	511
		$TiCl_4$, CH_2Cl_2, rt	 (41)	511
C_9				
		$TiCl_4$, CH_2Cl_2, rt	 (50)	511
		$TiCl_4$, CH_2Cl_2, rt	 (62)	511
		$TiCl_4$, CH_2Cl_2, rt	 (85)	511
		$TiCl_4$, CH_2Cl_2, rt	 (75)	511
C_{11}				
		1. CH_2Cl_2 or C_6H_6, rt 2. $AlCl_3$, CH_2Cl_2, rt, 14-36 h		51

R	R'	
H	H	(54)
Cl	H	(90)
H	Cl	(46)

Table 1. (Continued)

Table 1A (Continued)

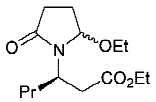
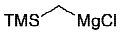
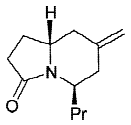
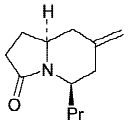
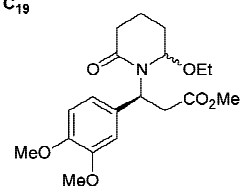
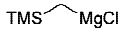
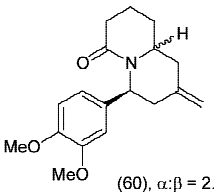
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_{14} 		$CeCl_3$, HCl	 (69) +  (17)	195
C_{19} 		1. $CeCl_3$, -78°C 2. HCl	 (60), α:β = 2.8:1	196

Table 1B. Bimolecular Reactions: Amides, Thioamides, and Carbamates

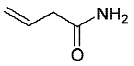
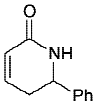
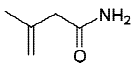
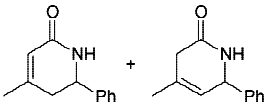
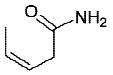
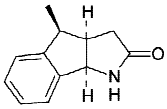
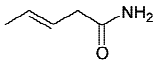
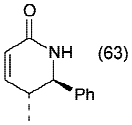
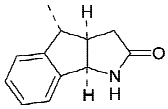
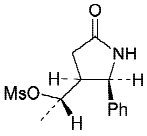
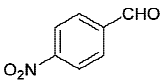
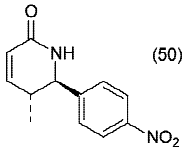
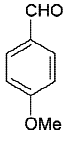
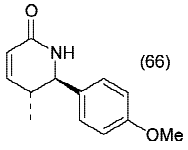
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_4 	PhCHO			301
		PPE, 60°, 16 h	(51)	
		PPA, 60°, 16 h	(30)	
C_5 	PhCHO			301
		PPE, 30°, 18 h	(30) (30)	
		TfOH, CH_2Cl_2	(36) (28)	
	PhCHO	PPA or PPE, 40°	 (0)	300
	PhCHO	PPE, 35°, 24 h	 (63)	301
	PhCHO	PPA, 35°, 48 h	 (74)	298
	PhCHO	MsOH, P_2O_5, 35°, 18 h	 (63)	298
		PPE, 45°, 18 h	 (50)	301
		PPE, 45°, 18 h	 (66)	301

Table 1. (Continued)

Table 1B (Continued)

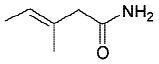
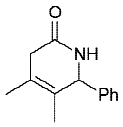
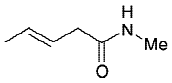
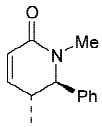
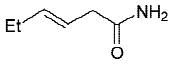
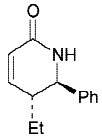
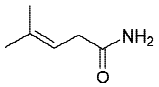
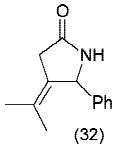
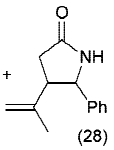
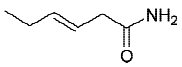
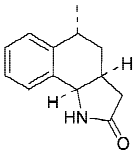
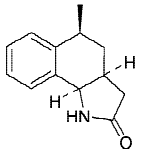
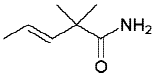
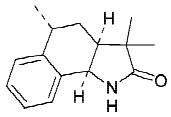
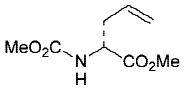
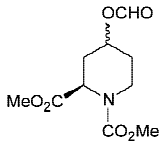
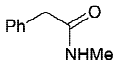
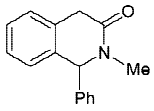
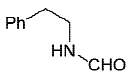
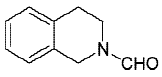
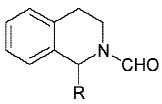
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_6 	PhCHO			301
		PPE, 40°, 19 h	(82)	
		PPA, 40°, 49 h	(65)	
	PhCHO	PPE, 40°, 16 h	 (30)	301
	PhCHO	PPE, 60°, 18 h	 (50)	301
	PhCHO	PPE, 35°, 24 h	 +  (32) (28)	300
	PhCHO		 + 	
		MsOH, P_2O_5, 35°, 18 h	(32) (28)	300
		PPA, 35°, 72 h	(45) (39)	298
C_7 	PhCHO	PPA, 35°, 48 h	 (32)	300
C_8 	$(CH_2O)_n$	HCO_2H, rt, 16 h	 (77), α:β = 1.1:1	164
C_9 	PhCHO	PPA, 150°, 5 h	 (21)	360
	HCHO			293
		AcOH:TFA (4:1) or TFA:MsOH (4:1), reflux, 3-10 h	(57)	
		HCO_2H, reflux, 3-8 h	(64)	
	RCHO	AcOH:TFA (4:1) or TFA:MsOH (4:1), reflux, 3-10 h		293
			R: Me (52); Ph (48); 4-$O_2NC_6H_4$ (57); 4-FC_6H_4 (52); 4-ClC_6H_4 (49); 4-MeC_6H_4 (41)	

Table 1. (Continued)

Table 1B (Continued)

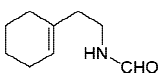
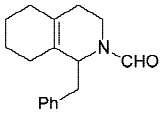
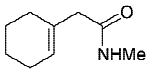
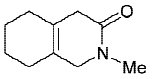
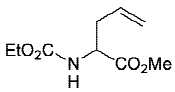
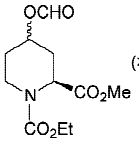
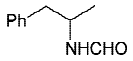
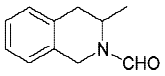
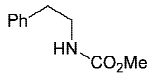
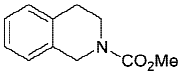
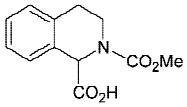
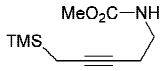
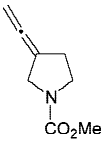
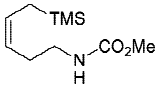
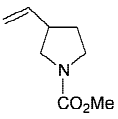
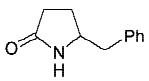
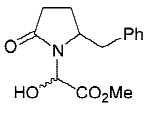
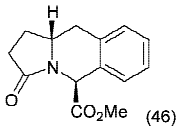
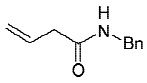
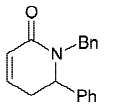
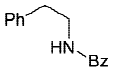
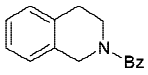
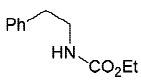
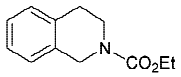
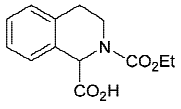
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
	$PhCH_2CHO$	TFA:AcOH (1:4), reflux, 3 h	 (34)	316
		TFA, 100°, 6 h	 (65)	25
	$(CH_2O)_n$	HCO_2H, rt, 24 h	 (>95), α:β = 1:1	161
C_{10}				
	HCHO	AcOH, TFA, reflux, 0.5-6 h	 (79)	295
	$(CH_2O)_n$	H_2SO_4:AcOH (1:3), rt, 24 h	 (93)	596
	HO_2CCHO	H_2SO_4:AcOH (1:3), rt, 48 h	 (80)	596
	$(CH_2O)_n$	HCO_2H, rt, 17 h	 (54)	189
	$(CH_2O)_n$	HCO_2H, rt, 17 h	 (58)	189
C_{11}				
	MeO_2CCHO	C_6H_6, reflux	 (39) +  (46)	215
	PhCHO	PPE, 60°, 56 h	 (95)	301
	$(CH_2O)_n$	H_2SO_4:AcOH (1:3), rt, 24 h	 (88)	596
	$(CH_2O)_n$	H_2SO_4:AcOH (1:3), rt, 24 h	 (95)	596
	HO_2CCHO	H_2SO_4:AcOH (1:3), rt, 48 h	 (84)	596

Table 1. (Continued)

Table 1B (Continued)

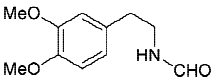
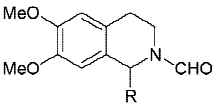
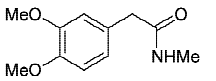
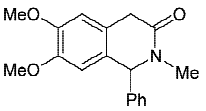
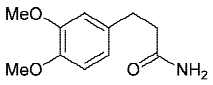
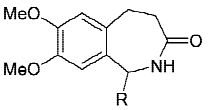
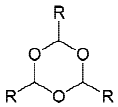
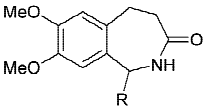
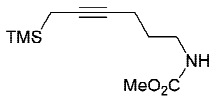
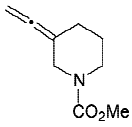
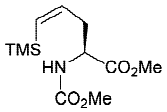
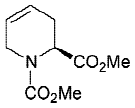
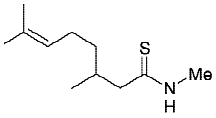
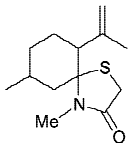
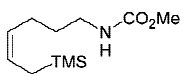
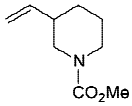
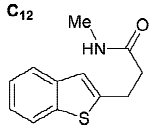
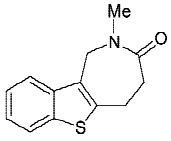
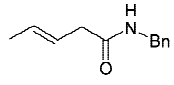
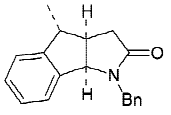
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
	RCHO	**A**: AcOH:TFA (4:1) or TFA:MsOH (4:1), reflux, 3-10 h **B**: HCO_2H, reflux, 3-8 h	 R / Method A / Method B H (73) (76) Me (66) (67) Ph (59) (62) 4-$NO_2C_6H_4$ (68) (72) 4-FC_6H_4 (64) (69) 4-ClC_6H_4 (65) (64) 4-MeC_6H_4 (56) (55)	293
	PhCHO	TFA, reflux, 2 h	 (54)	360
	RCHO	P_2O_5, H_3PO_4 (85%), AcOH, 2-3 days, rt	 R Ph (64) 3,4-$(MeO)_2C_6H_3$ (82)	388
	 R H H Me	PPA, AcOH, rt, 24 h TFA, rt, 48 h TFA, rt, 23 h	 (36) (8) (49)	388
	$(CH_2O)_n$	HCO_2H, rt, 17 h	 (54)	189
	$(CH_2O)_n$	HCO_2H, rt, 24 h	 (40)	164
	$BrCH_2COCl$	CH_2Cl_2, reflux, 2 h	 (63)	431
	$(CH_2O)_n$	HCO_2H, rt, 17 h	 (51)	189
C_{12} 	$(CH_2O)_n$	HCO_2H, 60°, 14 h	 (45)	441
	PhCHO	PPE, 35°, 24 h PPA, 45°, 24 h PPE, 60°, 24 h	 (52) (0); no rxn (0); polymer	300

Table 1. (Continued)

Table 1B (Continued)

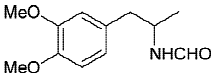
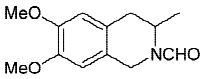
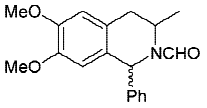
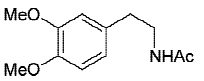
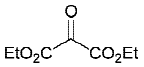
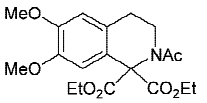
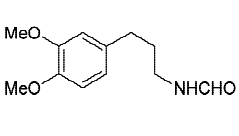
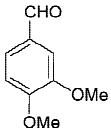
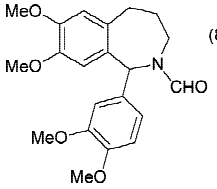
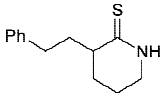
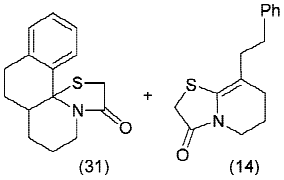
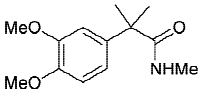
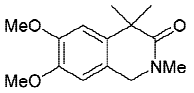
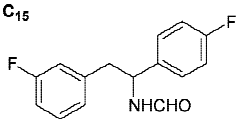
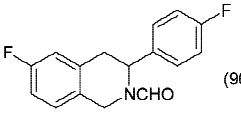
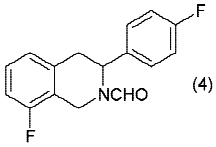
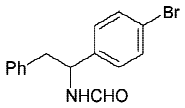
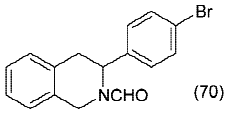
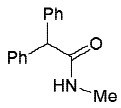
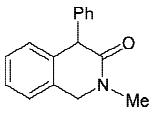
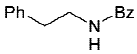
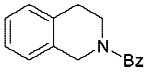
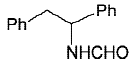
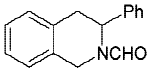
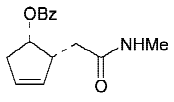
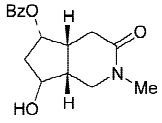
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
	HCHO	AcOH, TFA, reflux, 0.5-6 h	 (81)	295
	PhCHO	AcOH, TFA, reflux, 0.5-6 h	 (52)	295
		TFA, toluene, 85°, 3 h	 (96)	615
		P_2O_5, H_3PO_4, AcOH, rt, 24 h	 (84)	388
C_{13} 	$BrCH_2COCl$	CH_2Cl_2, $AlCl_3$, reflux, 2 h	 (31) + (14)	431
	$(CH_2O)_n$	HCO_2H, 60-70°, 6 h	 (80)	296
C_{15} 	$(CH_2O)_n$	TFA, reflux, 4.5 h	 (96) +  (4)	294
	$(CH_2O)_n$	TFA, reflux, 4.5 h	 (70)	294
	$(CH_2O)_n$	MsOH, 0°-rt, 24 h	 (81)	596
	$(CH_2O)_n$	H_2SO_4:AcOH (1:3), rt, 24 h	 (88)	596
	$(CH_2O)_n$	TFA, reflux, 4.5 h	 (71)	294
	HCHO	AcOH, TFA, reflux, 0.5-6 h	(74)	295
	$(CH_2O)_n$	$MeNO_2$, TFA, rt, 3 days	 (76)	518

Table 1. (Continued)

Table 1B (Continued)

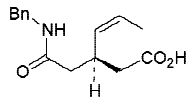
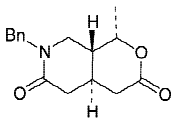
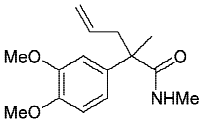
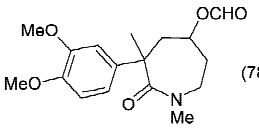
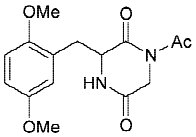
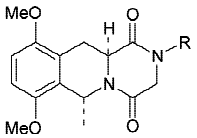
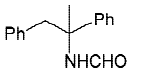
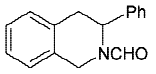
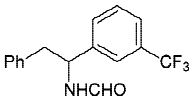
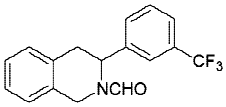
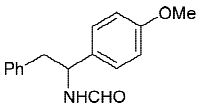
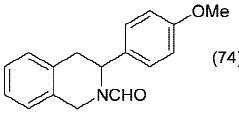
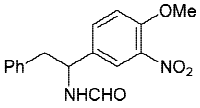
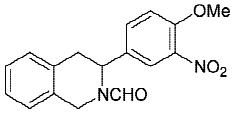
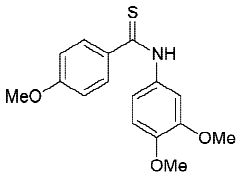
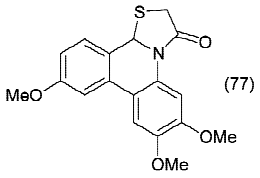
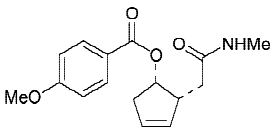
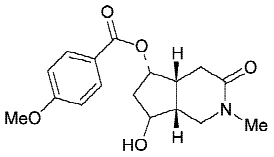
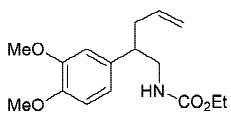
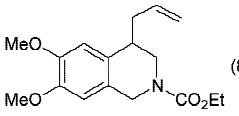
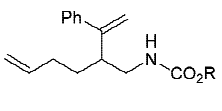
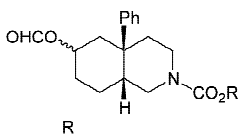
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
	$(CH_2O)_n$	TFA, $MeNO_2$, rt	 (85)	475
	$(CH_2O)_n$	HCO_2H, 60-70°, 6 h	 (78)	296
	MeCHO	AcOH, TFA, reflux, 5 h	 (—) + R = Ac and R = H	597
C_{16}				
	$(CH_2O)_n$	**A**: TFA/AcOH (1:4), reflux, 4.5 h **B**: TFA, reflux, 4.5 h	 (50) (0)	294
	$(CH_2O)_n$	TFA, reflux, 4.5 h	 (98)	294
	HCHO $(CH_2O)_n$	AcOH, TFA, reflux, 0.5-6 h TFA or TFA/AcOH (1:4) or AcOH, reflux, 4.5 h	 (74) (0)	295 294
	$(CH_2O)_n$	TFA, reflux, 4.5 h	 (70)	294
	$BrCH_2COCl$	CH_2Cl_2, reflux, 2 h	 (77)	431
	$(CH_2O)_n$	$MeNO_2$, TFA, rt, 3 days	 (57)	518
	$(CH_2O)_n$	HCO_2H, 60-70°, 6 h	 (84)	296
C_{16-17}				
 R = Me or Et	$(CH_2O)_n$	HCO_2H, rt, 1.5 h	 R: Me (75), Et (72)	146

Table 1. (Continued)

Table 1B (Continued)

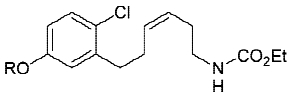
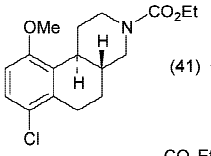
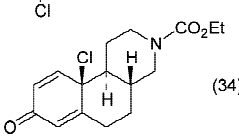
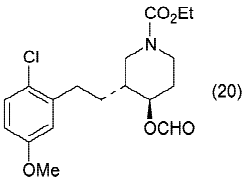
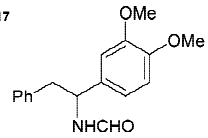
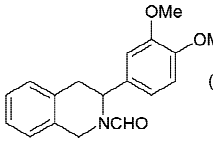
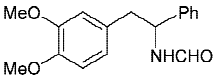
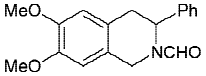
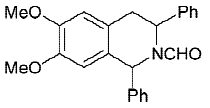
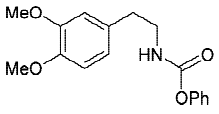
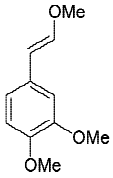
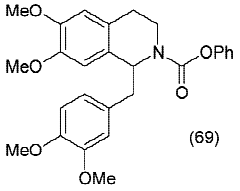
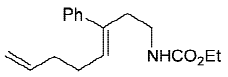
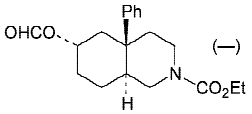
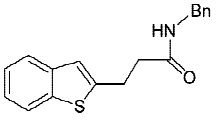
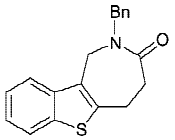
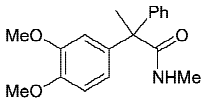
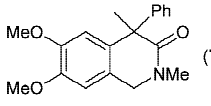
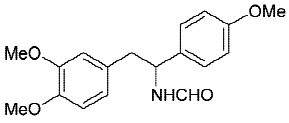
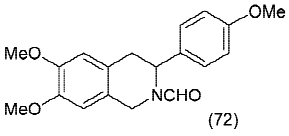
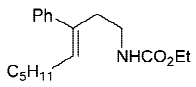
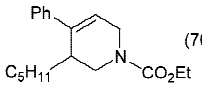
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
$C_{16\text{-}21}$  R = TBDMS, Me, or CH_2OMe	$(CH_2O)_n$	HCO_2H, 55°, 2 h	 (41) +  (34) +  (20)	513
C_{17} 	HCHO	AcOH, TFA, reflux, 0.5-6 h	 (83)	295
	HCHO	AcOH, TFA, reflux, 0.5-6 h	 (68)	295
	PhCHO	AcOH, TFA, reflux, 0.5-6 h	 (43)	295
		$POCl_3$, CH_2Cl_2, rt, 3 h	 (69)	598
	$(CH_2O)_n$	HCO_2H, rt, 1.5 h	 (—)	146
C_{18} 	$(CH_2O)_n$	HCO_2H, 60°, 14 h	 (47)	441
	$(CH_2O)_n$	HCO_2H, 60-70°, 6 h	 (74)	296
	HCHO	AcOH, TFA, reflux, 0.5-6 h	 (72)	295
	$(CH_2O)_n$	HCO_2H, 50°, 1.5 h	 (70)	144

Table 1. (Continued)

Table 1B (Continued)

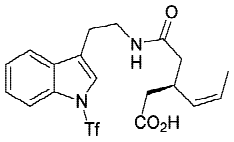
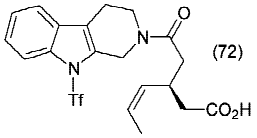
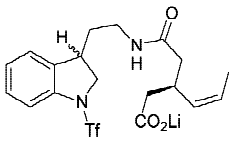
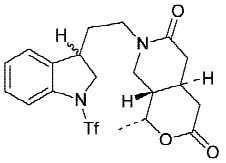
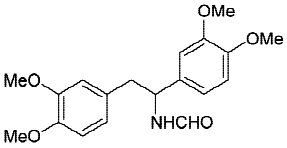
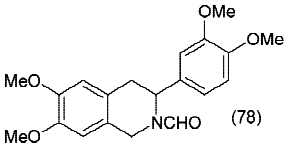
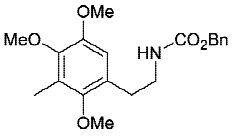
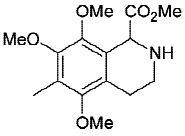
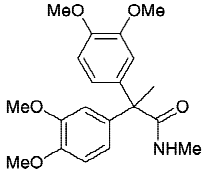
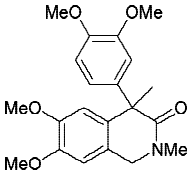
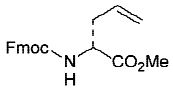
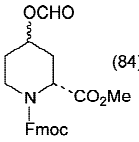
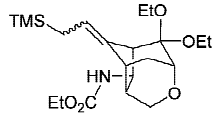
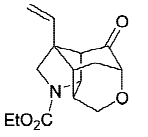
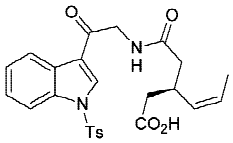
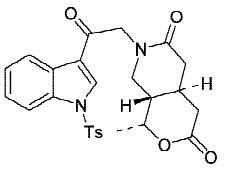
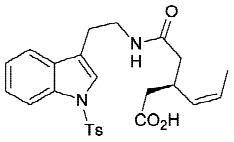
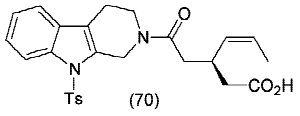
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_{19}				
	$(CH_2O)_n$	TFA, $MeNO_2$, rt or HCHO, HCO_2H, THF	 (72)	475
	$(CH_2O)_n$	TFA, CH_2Cl_2	 (—)	475
	HCHO	AcOH, TFA, reflux, 0.5-6 h	 (78)	295
C_{20}				
	Cl_2CHCO_2H	1. rt, 16 h 2. CH_2N_2 3. H_2, Pd/C, MeOH	 (80)	297
	$(CH_2O)_n$	HCO_2H, 60-70°, 6 h	 (82)	296
C_{21}				
	$(CH_2O)_n$	HCO_2H, rt, 16 h	 (84), α:β = 1.05:1	164
		HCO_2H, rt, 16 h	 (85)	190
C_{25}				
	$(CH_2O)_n$	TFA, $CHCl_3$	 (74)	475
	$(CH_2O)_n$	TFA, $MeNO_2$, rt or HCHO, HCO_2H, THF	 (70)	475

Table 1. (Continued)

Table 1B (Continued)

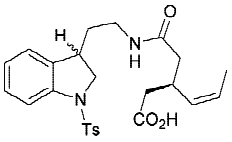
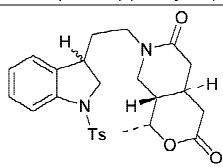
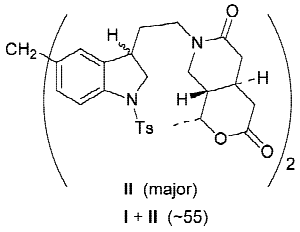
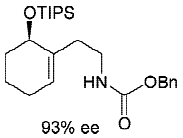
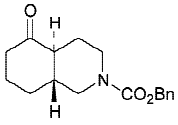
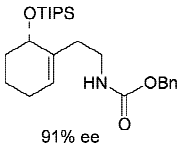
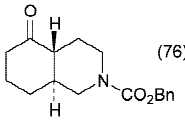
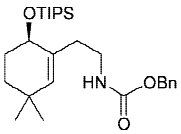
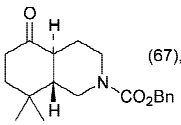
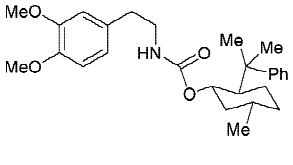
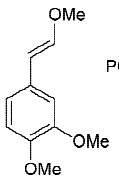
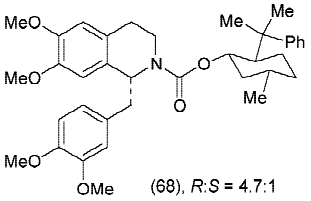
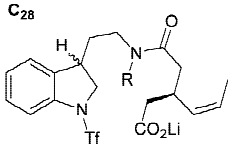
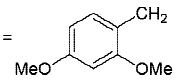
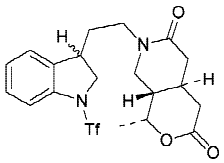
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
	$(CH_2O)_n$	TFA, $CHCl_3$	 **I** (minor) +  **II** (major) **I** + **II** (~55)	475
 93% ee	$(CH_2O)_n$	MsCl, Et_3N, CH_2Cl_2, rt TFA, toluene, rt	 (76), 86% ee (66), 66% ee	616
 91% ee	$(CH_2O)_n$	MsCl, Et_3N, CH_2Cl_2, rt	 (76), 87% ee	616
C_{27}				
 94% ee	$(CH_2O)_n$	MsCl, Et_3N, CH_2Cl_2, rt	 (67), 93% ee	616
		$POCl_3$, CH_2Cl_2 rt	 (68), *R*:*S* = 4.7:1	598
C_{28}				
 R = 	$(CH_2O)_n$	TFA, $CHCl_3$	 (85)	475

Table 1C. Bimolecular Reactions: Imines

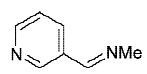
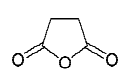
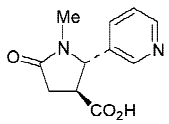
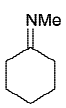
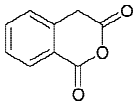
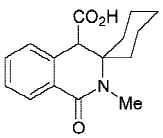
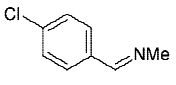
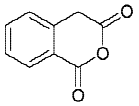
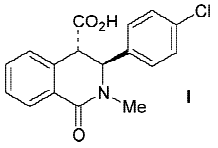
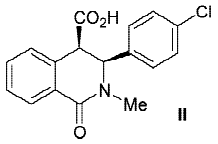
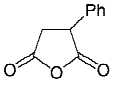
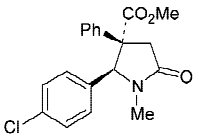
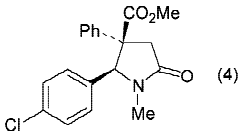
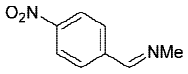
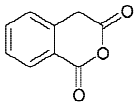
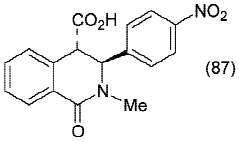
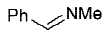
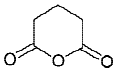
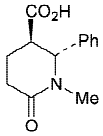
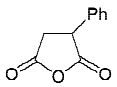
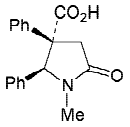
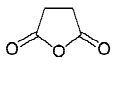
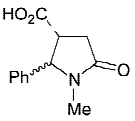
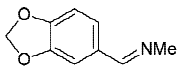
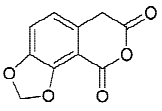
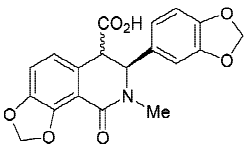
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_7				
		xylene, reflux, 24 h	 (55)	246
		xylene, 137°, 40 min	 (85)	249

Table 1. (Continued)

Table 1C (Continued)

substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_8				
			 + 	265
		$CHCl_3$, rt, overnight	I (33), II (0)	
		MeOH, 40°, 2 min	I (0), II (24)	
		$CHCl_3$, reflux, 1 h	 (39) +  (4)	265
		$CHCl_3$, rt, overnight	 (87)	265
		xylene, reflux, 24 h	 $(55)^a$	247, 248
		$CHCl_3$, rt, 18 h	 (50)	265
		C_6H_6, reflux, 36 h	 (83), α:β = 1:3.2	244
C_9				
				257

	β:α
MeCN, 82°, 1 h	67:33
MeCN:Et_3N (9:1), rt, 40 min	58:42
$MeNO_2$, rt, 30 min	38:62
t-BuOH, rt, 27 min	23:77
THF, rt, 65 min	20:80
neat, rt, 1 min	20:80
MeCN, –22°, 57 min	20:80
CH_2Cl_2, rt, 15 min	17:83
CH_2Cl_2, –78°, 72 min	11:89
DCE, 83°, 103 min	11:89
$PhCH_2CN$, 183°, 59 min	8:92

Table 1. (Continued)

Table 1C (Continued)

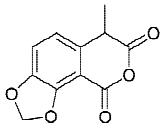
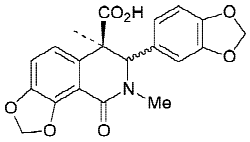
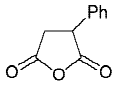
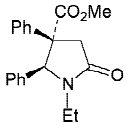
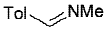
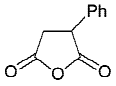
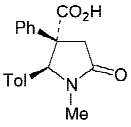
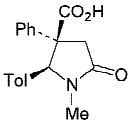
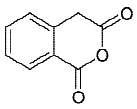
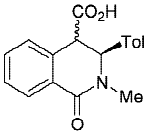
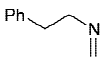
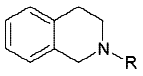
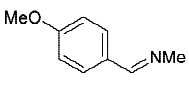
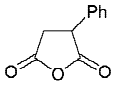
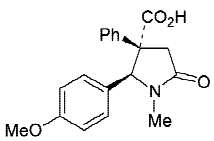
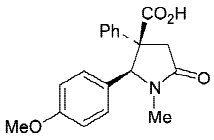
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
				259 260 262
			α β	
		C_6H_6, rt	(85) (0)	
		MeOH, rt, 1 h	(66) (29)	
		MeOH, 23°, 1 h	(55) (45)	
		MeOH, 65°, 1 h	(57) (43)	
		MeCN, 82°, 1 h	(58) (42)	
		TFA, 23°, 1 h	(60) (40)	
		MeCN, 23°, 1 h	(60) (40)	
		neat, 23°, 1 min	(60) (40)	
		DMF, 23°, 1 h	(61) (39)	
		MeOH, -65°, 1 h	(62) (38)	
		DMSO, 23°, 1 h	(68) (32)	
		AcOH, 118°, 1 h	(75) (25)	
		$CHCl_3$, 23°, 1 h	(77) (23)	
		$CHCl_3$, 61°, 1 h	(80) (20)	
		xylene, 23°, 1 h	(90) (10)	
		C_6H_6, 23°, 1 h	(92) (8)	
		$CHCl_3$, reflux, 5 h	 (36)	265
		$CHCl_3$, reflux, 2 h	 +  (27) (20)	265
				265
			α β	
		$CHCl_3$, rt, 1 h	(71) (0)	
		MeOH, 40°, 2 min	(0) (12)	
 (formed in situ)	RCl	Method A 1. DCE, rt, 0.5 h 2. $AlCl_3$, DCE, reflux, 3 h Method B DCE, KI, rt, 2 h Method C 1. No substrate, DCE, rt, 1 h 2. Add substrate, rt, 4 h		363
	R	Method A Method B Method C		
	Cl_2CHCO	(75) (75) (73)		
	$ClCH_2CO$	(45) (72) (70)		
	Ac	(25) (50) (46)		
	Bz	(36) (75) (70)		
	$PhOCH_2CO$	(40) (—) (70)		
	$2,4\text{-}Cl_2C_6H_3OCH_2CO$	(45) (—) (56)		
	$MeOCH_2CO$	(58) (—) (77)		
	$PhSO_2$	(56) (56) (—)		
		$CHCl_3$, reflux, 1 h	 (27) +  (9)	265

Table 1. (Continued)

Table 1C (Continued)

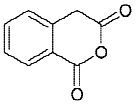
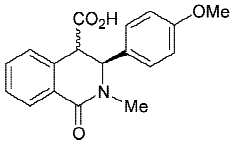
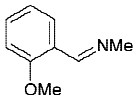
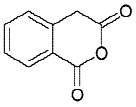
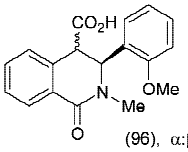
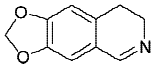
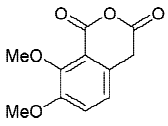
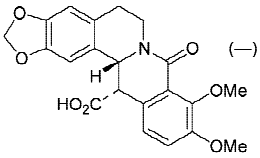
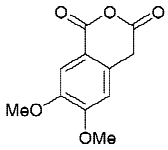
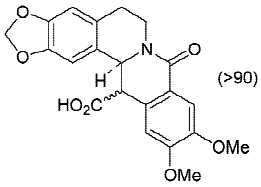
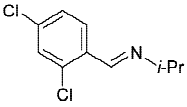
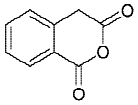
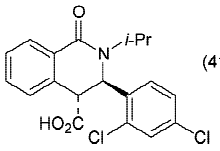
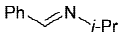
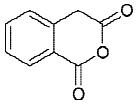
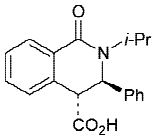
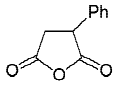
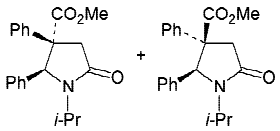
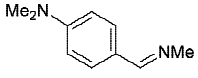
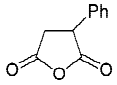
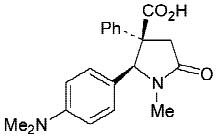
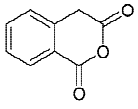
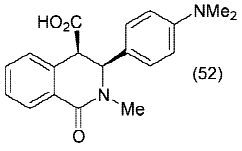
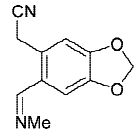
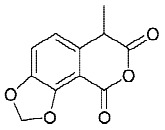
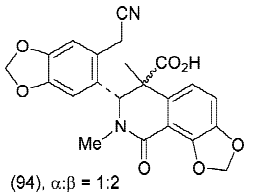
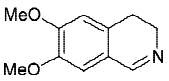
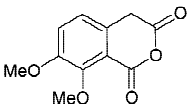
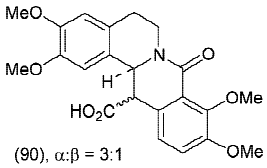
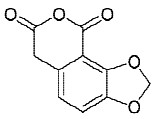
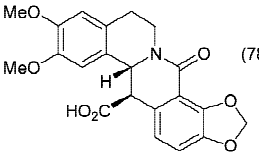
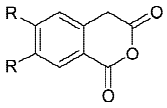
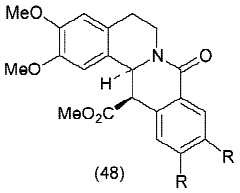
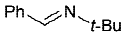
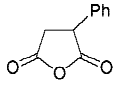
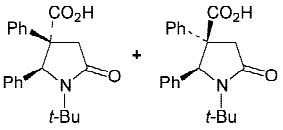
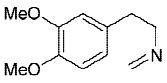
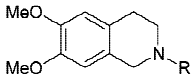
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
				265
		$CHCl_3$, rt, 1 h	α (55) β (0)	
		MeOH, 40°, 2 min	α (0) β (26)	
		$CHCl_3$, rt, 10 min	 (96), α:β = 1:2	249
C_{10}				
		1. $CHCl_3$, rt, 26 min 2. AcOH, reflux, 24 h	 (—)	276
		$CHCl_3$, rt, 0.5 h	 (>90)	249
		1. BF_3•Et_2O, 8-14 h 2. THF, MeCN, rt	 (41)	273
				
		A: 1. BF_3•Et_2O, 8-14 h 2. THF, MeCN, rt	(56)	273
		B: $CHCl_3$, rt, overnight	(54)	265
		$CHCl_3$, reflux, 1 h	 (36) (3)	265
		$CHCl_3$, reflux, 40 min	 (13)	265
		$CHCl_3$, rt, 1 h	 (52)	265

Table 1. (Continued)

Table 1C (Continued)

substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_{11}				
		MeCN, rt, 1.5 h	 (94), α:β = 1:2	263
		$CHCl_3$, rt, 0.5 h	 (90), α:β = 3:1	253
		$CHCl_3$, rt, 2.5 h	 (78)	276
	 R = H: MeO	1. DCE, Et_3N, rt, 18 h 2. CH_2N_2, Et_2O	 (48) (43)	250
				265
		$CHCl_3$, reflux, 1 h	(18) (0)	
		$CHCl_3$, rt, 48 h	(0) (23)	
 (formed in situ)	RCl			363

R	Method A	Method B	Method C
Cl_2CHCO	(65)	(80)	(76)
$ClCH_2CO$	(55)	(80)	(76)
Ac	(52)	(74)	(71)
Bz	(70)	(87)	(86)
$PhOCH_2CO$	(75)	(—)	(76)
$2,4\text{-}Cl_2C_6H_3OCH_2CO$	(60)	(—)	(69)
$MeOCH_2CO$	(60)	(—)	(82)
MeOCO	(80)	(—)	(77)
Cl_3CCO	(70)	(—)	(66)
CF_3CO	(—)	(—)	(70)
$PhSO_2$	(71)	(70)	(—)
Me_2NCO	(52)	(73)	(—)
$(EtO)_2PO$	(50)	(69)	(—)

Method A: 1. DCE, rt, 0.5 h; 2. $AlCl_3$, DCE, reflux, 3 h

Method B: DCE, KI, rt, 2 h

Method C: 1. No substrate, DCE, rt, 1 h; 2. Add substrate, rt, 4 h

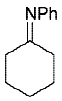
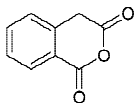
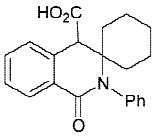
C_{12}				
		xylene, 137°, 0.5 h	 (91)	249

Table 1. (Continued)

Table 1C (Continued)

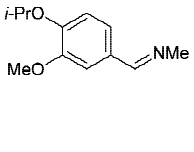
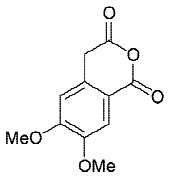
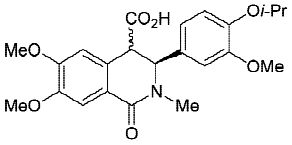
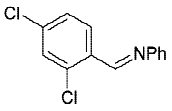
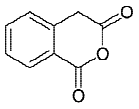
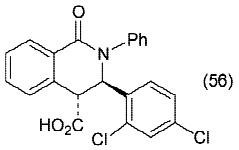
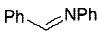
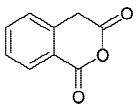
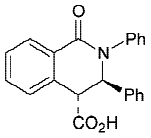
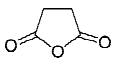
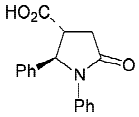
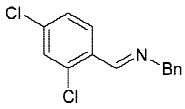
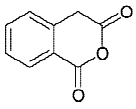
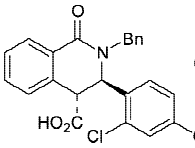
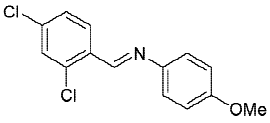
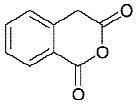
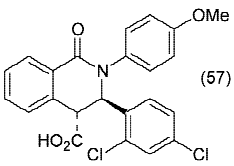
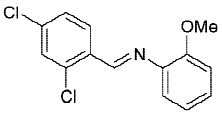
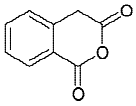
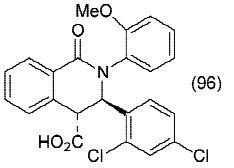
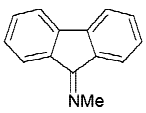
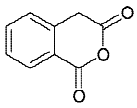
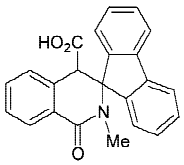
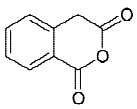
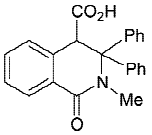
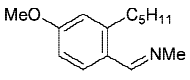
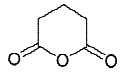
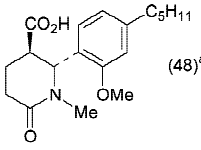
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		$CHCl_3$, rt, 0.5 h	 (100), α:β = 35:65	264
C_{13}				
		1. BF_3•Et_2O, 8-14 h 2. THF, MeCN, rt	 (56)	273
				
		A: 1. BF_3•Et_2O, 8-14 h 2. THF, MeCN, rt	(47)	273
		B: DCE, reflux, 15 min	(40)	265
		C_6H_6, reflux, 36 h	 (72)	244
C_{14}				
		1. BF_3•Et_2O, 8-14 h 2. THF, MeCN, rt	 (56)	273
		1. BF_3•Et_2O, 8-14 h 2. THF, MeCN, rt	 (57)	273
		1. BF_3•Et_2O, 8-14 h 2. THF, MeCN, rt	 (96)	273
		$CHCl_3$, 23°, 10 min	 (90)	249
		xylene, 137°, 0.5 h	 (50)	249
		xylene, reflux, 24 h	 (48)[a]	248

Table 1. (Continued)

Table 1C (Continued)

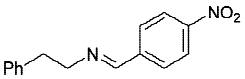
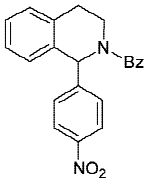
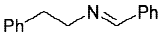
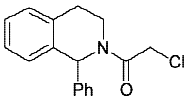
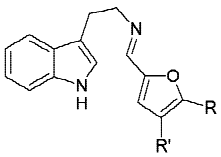
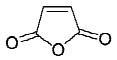
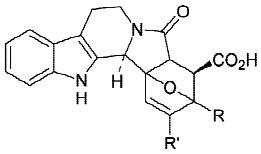
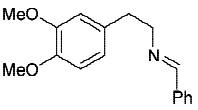
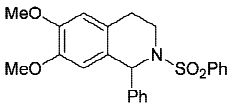
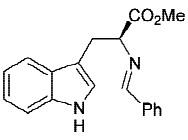
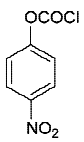
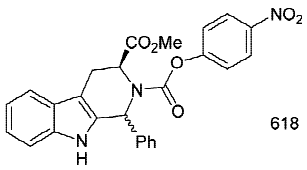
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_{15}				
	PhCOCl			363
		A: DCE, KI, rt, 2 h	(72)	
		B: 1. DCE, rt, 0.5 h 2. $AlCl_3$, DCE, reflux, 3 h	(75)	
		C: 1. No substrate, DCE, rt, 1 h 2. Add substrate, rt, 4 h	(67)	
	$ClCH_2COCl$			363
		A: DCE, KI, rt, 2 h	(65)	
		B: 1. DCE, rt, 0.5 h 2. $AlCl_3$, DCE, reflux, 3 h	(70)	
		C: 1. No substrate, DCE, rt, 1 h 2. Add substrate, rt, 4 h	(62)	
$C_{15\text{-}18}$				
		CH_2Cl_2, rt, 24 h		617
			R: H; R': H (80) R: Me; R': H (80) R: CH_2OAc; R': H (76) R: Me; R': Me (60)	
C_{17}				
	$PhSO_2Cl$			363
		A: 1. DCE, rt, 0.5 h 2. $AlCl_3$, DCE, reflux, 3 h	(51)	
		B: DCE, KI, rt, 2 h	(57)	
C_{19}				
		Py, CH_2Cl_2, DMAP, rt, 15 h		618

Table 1. (Continued)

Table 1C (Continued)

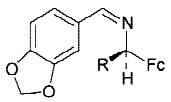
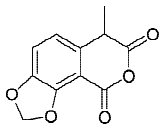
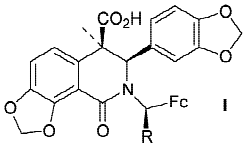
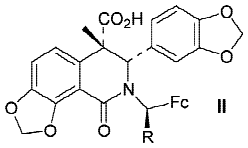
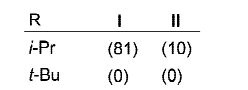
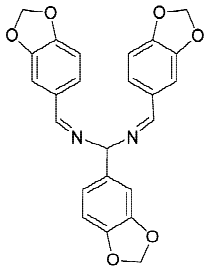
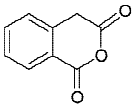
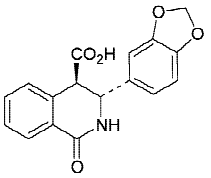
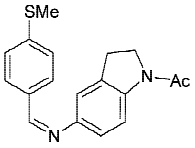
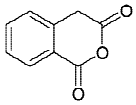
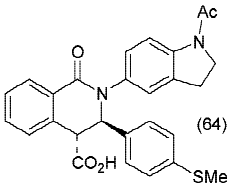
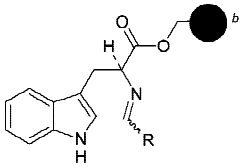
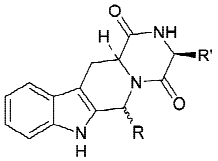
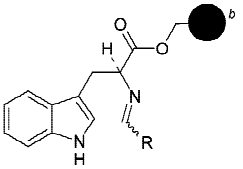
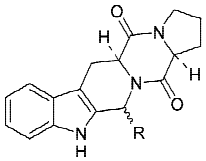
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_{22-23} 		C_6H_6, reflux, 84 h	 +  	266
			R I II *i*-Pr (81) (10) *t*-Bu (0) (0)	
C_{24} 		1. C_6H_6 or DCE, reflux, 10 min 2. rt, 1 h	 (92)	250
C_{27} 		1. BF_3•Et_2O, 8-14 h 2. THF, MeCN, rt	 (64)	273
	Fmoc-L-R'Cl	1. Py, CH_2Cl_2 2. 20% piperidine, CH_2Cl_2		544
R	R'			*cis*:*trans*
cyclohexyl	Bn		(39)	40:60
Me_2C=CH	*t*-Bu		(36)	64:36
PhCH=CH	*i*-Bu		(54)	59:41
Ph	Bn		(85)	58:42
Ph	*i*-Bu		(72)	57:43
4-$MeOC_6H_4$	Bn		(64)	57:43
4-$MeOC_6H_4$	*i*-Bu		(57)	49:51
4-$NO_2C_6H_4$	H		(74)	50:50
4-$NO_2C_6H_4$	Bn		(73)	50:50
4-$NO_2C_6H_4$	*i*-Bu		(88)	55:45
	Fmoc-L-ProCl,	1. Py, CH_2Cl_2 2. 20% piperidine, CH_2Cl_2		544
R				*cis*:*trans*
Me_2C=CH			(49)	53:47
Me_2CHCH_2			(61)	24:76
cyclohexyl			(73)	14:86
PhCH=CH			(61)	59:41
Ph			(76)	46:54
4-$MeOC_6H_4$			(75)	56:44
4-$NO_2C_6H_4$			(61)	44:56

Table 1. (Continued)

Table 1C (Continued)

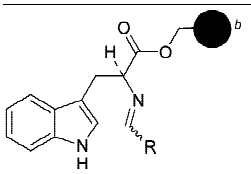
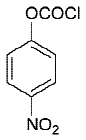
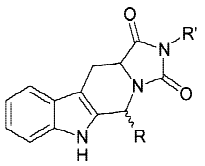
substrate	reactant	conditions	product(s) and yield(s) (%)		ref
		1. Py, CH_2Cl_2, DMAP rt, 18 h			618
R				R'	
Ph		2. $PhCH_2NH_2$	(31)	Bn	
Ph		2. *c*-$C_6H_{11}CH_2NH_2$	(38)	*c*-$C_6H_{11}CH_2$	
Ph		2. $Me_2CHCH_2NH_2$	(32)	Me_2CHCH_2	
3,4,5-$(MeO)_3C_6H_2$		2. $PhCH_2NH_2$	(20)	Bn	
3,4,5-$(MeO)_3C_6H_2$		2. *c*-$C_6H_{11}CH_2NH_2$	(33)	*c*-$C_6H_{11}CH_2$	
3,4,5-$(MeO)_3C_6H_2$		2. $Me_2CHCH_2NH_2$	(44)	Me_2CHCH_2	
4-$NO_2C_6H_4$		2. $PhCH_2NH_2$	(15)	Bn	
4-$NO_2C_6H_4$		2. *c*-$C_6H_{11}CH_2NH_2$	(35)	*c*-$C_6H_{11}CH_2$	
4-$NO_2C_6H_4$		2. $Me_2CHCH_2NH_2$	(30)	Me_2CHCH_2	
Me_2CHCH_2		2. $PhCH_2NH_2$	(17)	Bn	
Me_2CHCH_2		2. *c*-$C_6H_{11}CH_2NH_2$	(22)	*c*-$C_6H_{11}CH_2$	
Me_2CHCH_2		2. $Me_2CHCH_2NH_2$	(20)	Me_2CHCH_2	

Table 1D. Bimolecular Reactions: Amines

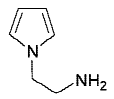
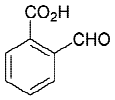
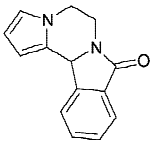
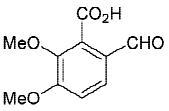
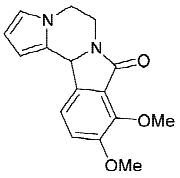
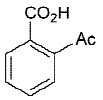
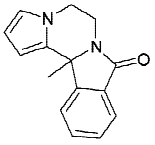
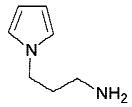
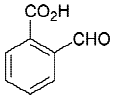
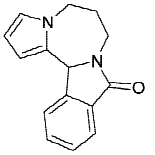
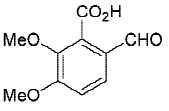
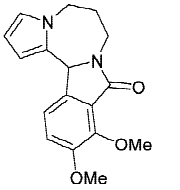
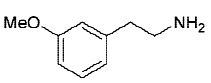
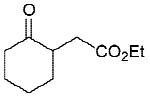
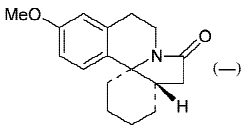
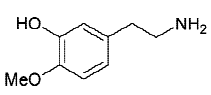
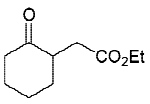
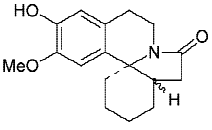
substrate	reactant	conditions	product(s) and yield(s) (%)		ref
C_6 		TsOH, benzene reflux		(76)	619
		TsOH, benzene reflux		(81)	619
		TsOH, benzene reflux		(79)	619
C_7 		TsOH, benzene reflux		(76)	619
		TsOH, benzene reflux		(66)	619
C_9 		1. Toluene, reflux, 8 h 2. 57% HI, rt, 30 min		(—)	77
		EtOH			62
			(—), α:β = 1:2.1		

Table 1. (Continued)

Table 1D (Continued)

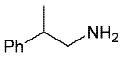
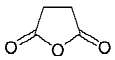
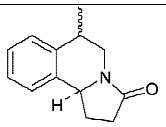
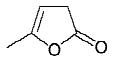
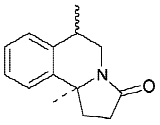
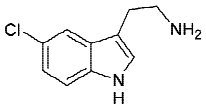
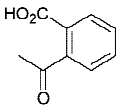
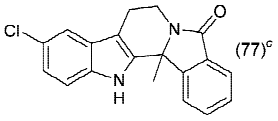
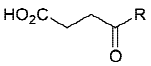
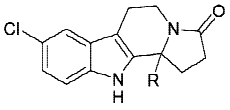
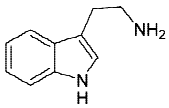
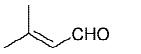
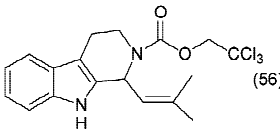
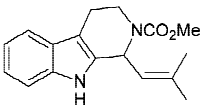
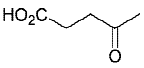
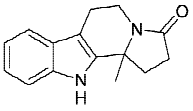
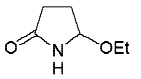
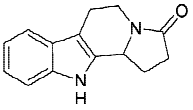
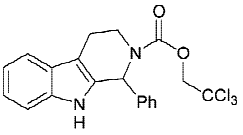
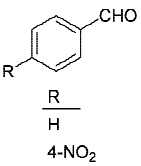
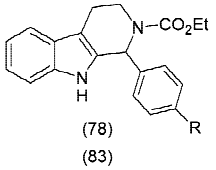
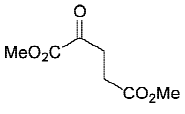
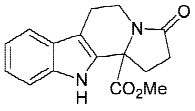
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		1. $NaBH_4$, MsOH, EtOH, -5 to 0° 2. PPA, 100°, 8 h	 (50), α:β = 72:28	45
		PPA, 100°, 8 h	 (80), α:β = 70:30	45
C_{10}				
		xylene, reflux, 7.5 h	 (77)[c]	312
	 R = Me	xylene, reflux, 70 h	 (41)[c]	312
	R = Ph	*p*-cymene, reflux, 72 h	(40)[c]	
		1. 4 Å MS, rt, overnight 2. $ClCO_2CH_2CCl_3$, Et_3N, 0-25°, 3-5 h	 (56)	473
		1. 4 Å MS, rt, overnight 2. $ClCO_2Me$, Py, 0-25°, 3-5 h	 (68)	473
		xylene, reflux, 4 h	 (70)[c]	312
		AcOH	 (67)	467
PhCHO		1. 4 Å MS, rt, overnight 2. $ClCO_2CH_2CCl_3$, Py, 0-25°, 3-5 h	 (67)	473
 R = H		EtO_2CCl, CH_2Cl_2, $PhNMe_2$, rt, 1 h	 (78)	340
4-NO_2			(83)	
		MeOH, reflux, 20 h	 (92)[c]	620

Table 1. (Continued)

Table 1D (Continued)

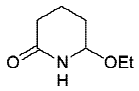
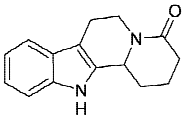
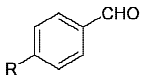
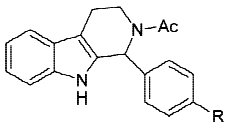
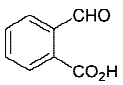
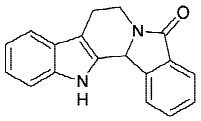
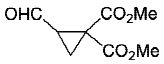
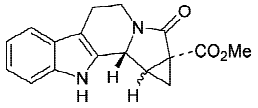
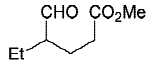
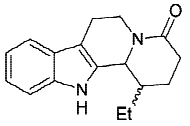
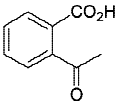
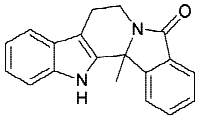
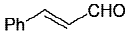
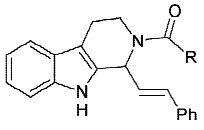
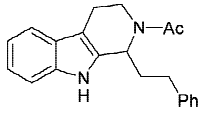
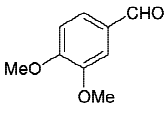
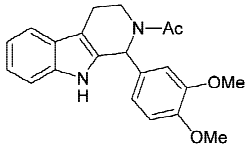
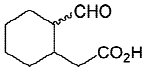
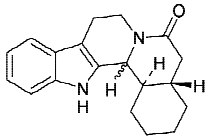
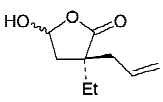
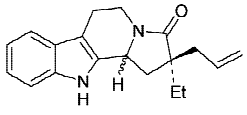
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		HOAc	 (81)	467
		AcCl, CH_2Cl_2, $PhNMe_2$, rt, 1 h		340
	R			
	H		(80)	
	Br		(65)	
	Cl		(85)	
	F		(50)	
	4-NO_2		(95)	
	Me		(75)	
		H_2SO_4 (2 N), EtOH, H_2O, reflux, 40 h	 (35)[c]	457
		— (probably: PhMe, rt, 2 h; AcOH, rt, 7 days)	 (—)[c], α:β > 100:1	453a
		AcOH, reflux, 12 h	 (88)[c]	93 94
		xylene, reflux, 6 h	 (63)[c]	312
		RCOCl, CH_2Cl_2, $PhNMe_2$, rt, 1 h		340
		R		
		Me	(80)	
		OEt	(85)	
		MeCOCl, CH_2Cl_2, $PhNMe_2$, rt, 1 h	 (35)	340
		MeCOCl, CH_2Cl_2, $PhNMe_2$, rt, 1 h	 (15)	340
		AcOH, reflux, 2 h	 α (—), β (61)[c]	452
		AcOH, reflux, 3 h	 (74)[c], α:β = 1:1	97

Table 1. (Continued)

Table 1D (Continued)

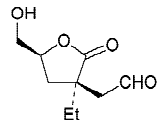
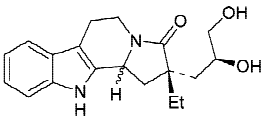
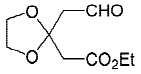
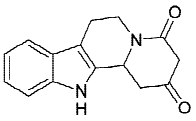
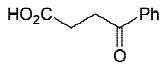
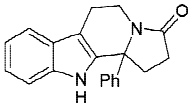
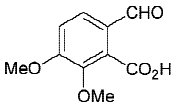
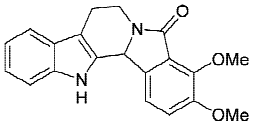
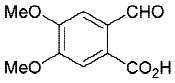
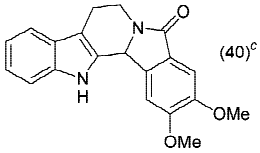
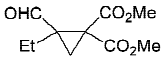
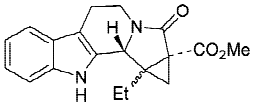
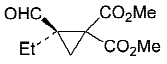
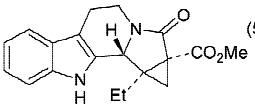
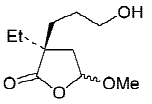
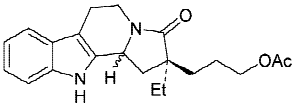
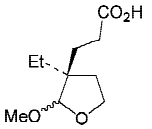
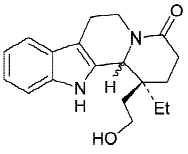
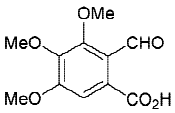
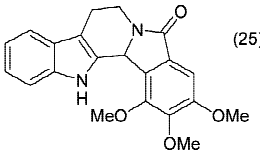
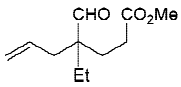
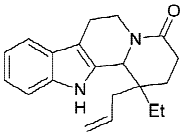
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		AcOH, reflux	 (47)[c], α:β = 1:1	98
		1. AcOH, reflux, 2 h 2. HCl/EtOH, rt, 24 h 3. H_2SO_4, reflux, 10 min	 (35)[c]	462
		butyl cellosolve, 20 h	 (46)[c]	312
		H_2SO_4 (2 N), EtOH, H_2O, reflux, 40 h	 (43)[c]	457
		H_2SO_4 (2 N), EtOH, H_2O, reflux, 40 h	 (40)[c]	457
				
		—	(—)[c], α:β = 85:15	453a
		1. Hot toluene; rt, 2 h 2. AcOH, rt, 7 days	(76)[c], α isomer	453b
		1. Toluene, rt, 2 h 2. AcOH, rt, 7 days	 (50)[c]	599
		AcOH, reflux, 18 h	 (84)[c], α:β = 1:1	54 99
		1. AcOH, reflux, 6 days 2. NaOH/MeOH	 (84)[c], α:β = 1:1	54 99
		H_2SO_4, EtOH, H_2O, reflux, 40 h	 (25)	457
		—	 (75)[c]	454

Table 1. (Continued)

Table 1D (Continued)

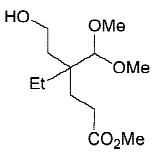
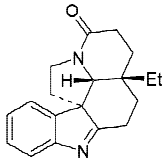
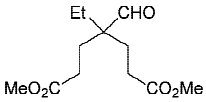
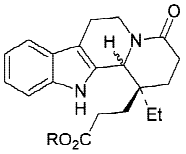
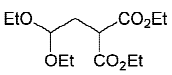
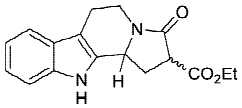
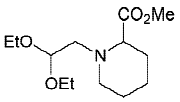
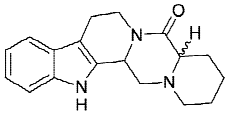
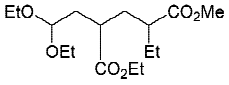
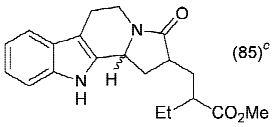
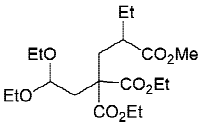
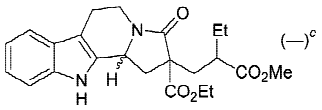
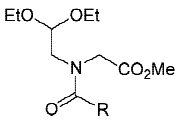
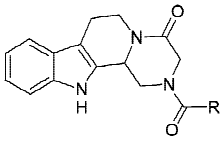
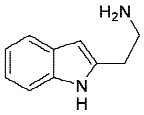
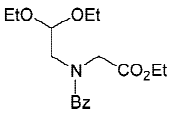
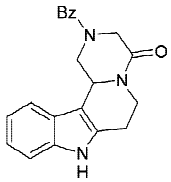
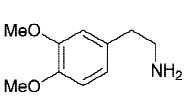
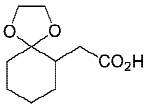
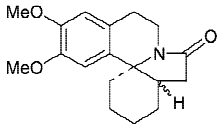
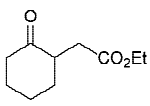
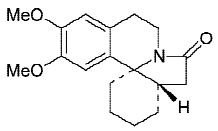
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		1. AcOH, reflux 2. BF_3•OEt_2 or H_2SO_4, 100°	 (—)[c]	54
		—	 R = Me (53)[c] R = H (37)[c]	92
		AcOH, H_2O, reflux	 (—)[c]	96
		AcOH, H_2O	 (<5)[c]	472
		AcOH, H_2O, reflux, 6 h	 (85)[c]	96
		AcOH, H_2O, reflux	 (—)[c]	96
		AcOH, H_2O, reflux, 2-3 h		621
	R Me Ph C_6H_{11} 4-pyridyl Bn		(59)[c] (81)[c] (77)[c] (68)[c] (71)[c]	
		AcOH, H_2O, reflux, 3 h	 (73)[c]	476
		EtOH	 (—), α:β = 3.2:1	62
		1. Toluene, reflux, 8 h 2. 57% HI, rt, 0.5 h	 (85)	77

Table 1. (Continued)

Table 1D (Continued)

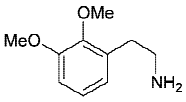
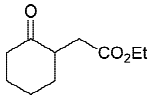
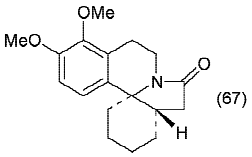
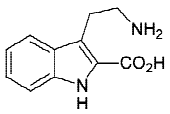
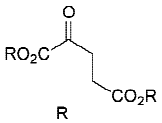
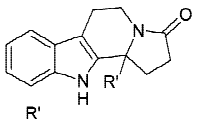
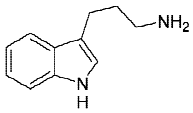
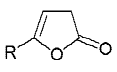
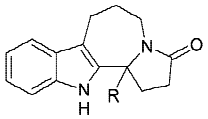
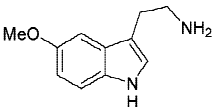
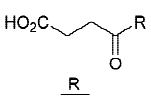
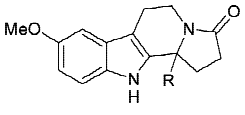
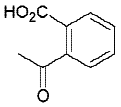
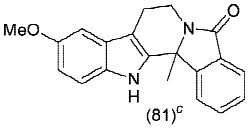
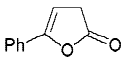
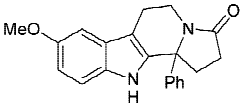
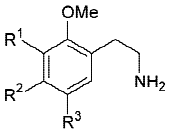
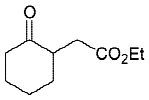
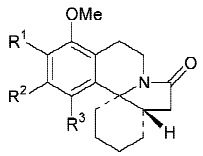
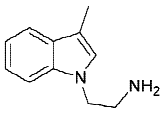
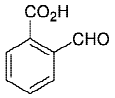
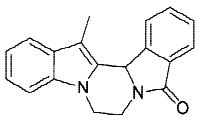
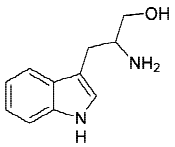
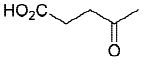
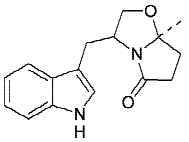
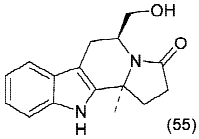
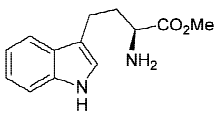
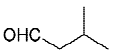
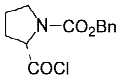
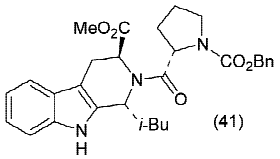
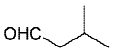
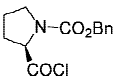
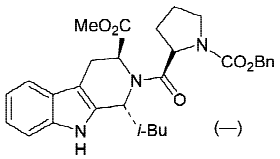
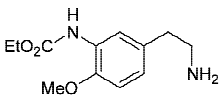
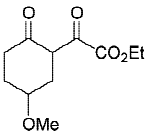
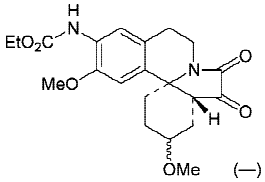
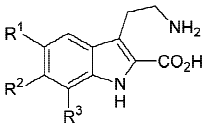
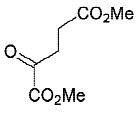
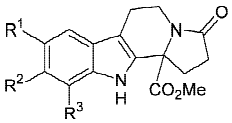
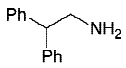
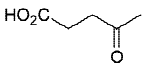
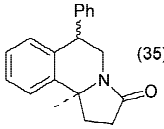
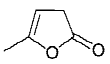
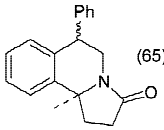
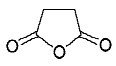
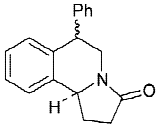
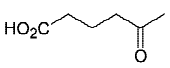
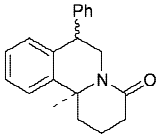
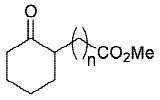
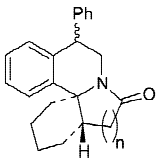
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		1. Toluene, reflux, 8 h 2. 57% HI, rt, 0.5 h	 (67)	77
C_{11} 	 R: H; Me	TFA, C_6H_6, dioxane, reflux	 R': H (58); CO_2Me (55)	456
	 R: Ph; Me	HCl, EtOH, rt, 20 h	 (41) (33)	463
	 R: Me; Ph	xylene, reflux, 22 h *p*-cymene, reflux, 22 h	 (61)[c] (50)[c]	312
		*p*-cymene, reflux, 4 h	 (81)[c]	312
		HCl, EtOH, rt, 20 h	 (—)	463
 R^1 R^2 R^3 OMe H OMe H OMe OMe OMe OMe H		1. Toluene, reflux, 8 h 2. 57% HI, rt, 0.5 h 2. PPA, 80°, 8 h 2. 57% HI, rt, 0.5 h	 (57) (51) (80)	77 75, 77 76, 77
		TsOH, benzene, reflux	 (82)	619
		TsOH, reflux, 48 h	 (3) +  (55)	622

Table 1. (Continued)

Table 1D (Continued)

substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_{12}				
		1. CH_2Cl_2, 4 Å MS, rt, 12 h 2. 	 (41)	474
		1. CH_2Cl_2, 4 Å MS, rt, 12 h 2. 	 (—)	474
		1. C_6H_6, reflux, 10 h 2. H_3PO_4 (85%), MeOH, reflux, 20 h	 (—)	71
C_{12-13}				
		TFA, C_6H_6, dioxane, reflux		456

R^1	R^2	R^3	
OMe	H	H	(60)
H	OMe	H	(80)
OMe	H	OMe	(65)

C_{14}				
		PPA, 100°, 20 h	 (35), α:β = 94:6	45 67
		PPA, 100°, 4 h	 (65), α:β = 94:6	45 67
		1. $NaBH_4$, MsOH, EtOH, -5 to 0° 2. PPA, 100°, 6 h	 (60), α:β = 93:7	45 67
		PPA, 100°, 20 h	 (74), α:β = 96:4	45 67
		PPA, 100°, 24 h		45

n	
1	(60), α:β = 95:5
2	(50), α:β ≥ 95:5

Table 1. (Continued)

Table 1D (Continued)

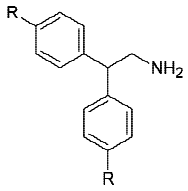
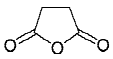
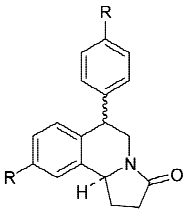
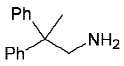
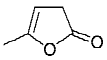
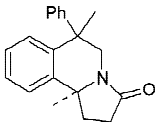
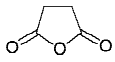
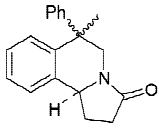
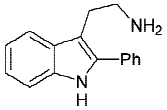
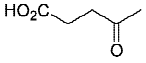
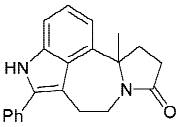
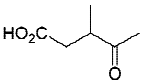
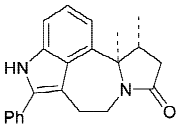
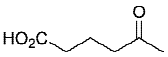
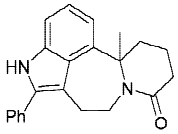
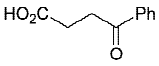
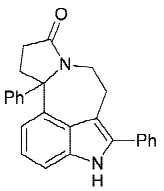
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		1. $NaBH_4$, MsOH, EtOH, -5 to 0° 2. PPA, 100°, 6 h	 R = F (55), α:β = 93:7 R = Cl (50), α:β = 93:7	45 115
C_{15}				
		PPA, 100°, 4 h	 (65), α:β = 60:40	45
		1. $NaBH_4$, MsOH, EtOH, -5 to 0° 2. PPA, 100°, 6 h	 (55), α:β = 55:45	45
C_{16}				
		**A**: xylene, reflux, 12 h **B**: DCC, DMAP, THF, rt, 12 h	 (61) (71)	382
		**A**: xylene, reflux, 12 h **B**: DCC, DMAP, THF, rt, 12 h	 (45) (64)	382
		**A**: xylene, reflux, 12 h **B**: DCC, DMAP, THF, rt, 12 h	 (23) (58)	382
		**A**: xylene, reflux, 12 h **B**: DCC, DMAP, THF, rt, 12 h	 (16) (26)	382

Table 1. (Continued)

Table 1D (Continued)

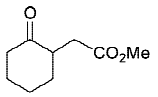
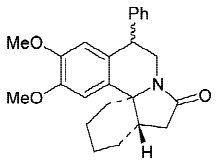
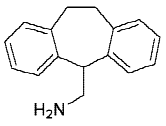
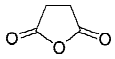
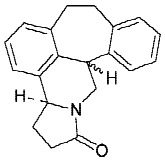
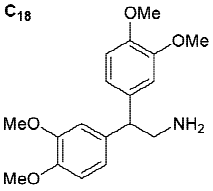
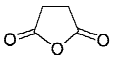
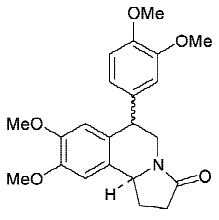
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		HCl, EtOH, reflux, 10 min	 (80), α:β ≥ 95:5	45
		1. $NaBH_4$, MsOH, EtOH, -5 to 0° 2. PPA, 100°, 6 h	 (45), α:β = 95:5	45
C_{18} 		1. $NaBH_4$, MsOH, EtOH, -5 to 0° 2. HCl, EtOH, reflux, 30 min	 (60), α:β = 90:10	45 67

Table 1E. Bimolecular Reactions: Sulfonamides and Related Derivatives

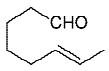
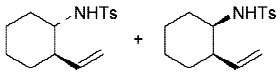
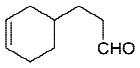
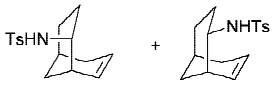
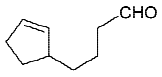
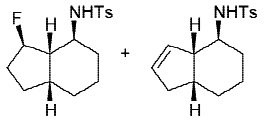
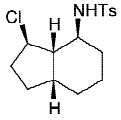
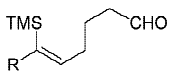
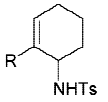
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
C_7 TsNSO		BF_3•Et_2O, 0°, CH_2Cl_2	 (38) (12)	519
		BF_3•Et_2O, C_6H_6, 0°	 (40) (39)	519
				519
		BF_3•Et_2O (1 eq)	(50-60)	
		BF_3•Et_2O (0.2 eq)	(25) (25)	
		$FeCl_3$, CH_2Cl_2	 (50)	519
				176
	R			
	Br	BF_3•Et_2O	(0)	
	Ph	BF_3•Et_2O	(0)	
	H	BF_3•Et_2O, CH_2Cl_2, 5°	(50)	
	H	BF_3•Et_2O, CH_2Cl_2, 0°	(61)	
	H	BF_3•Et_2O, C_6H_6, 5°	(59)	
	H	BF_3•Et_2O, toluene, −15°	(50)	
	H	$SnCl_4$, CH_2Cl_2, 0°	(55)	
	H	$SnCl_4$, CH_2Cl_2, −78° to rt	(47)	

Table 1. (Continued)

Table 1E (Continued)

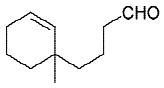
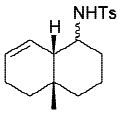
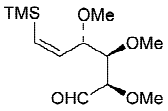
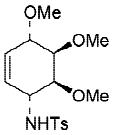
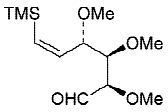
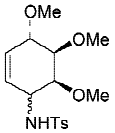
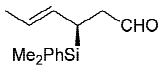
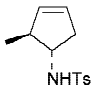
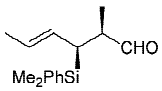
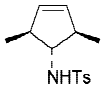
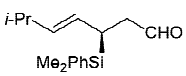
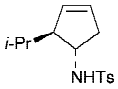
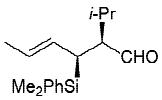
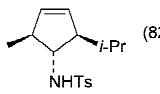
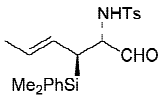
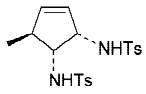
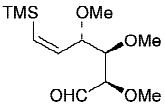
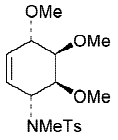
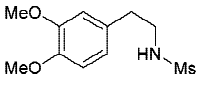
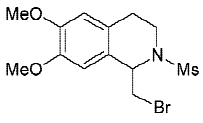
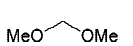
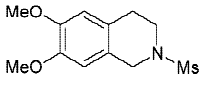
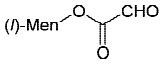
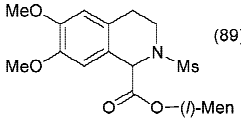
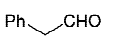
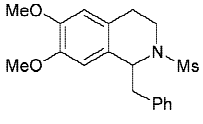
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		BF_3•Et_2O (0.5 eq), CH_2Cl_2, 0°	 (52), α:β = 1:3	519
		1. DCE, 80°, 24 h 2. BF_3•OEt_2, 0°-rt	 (36)	176
$TsNH_2$		BF_3•OEt_2, –78° to rt	 (73) , a:b = 9.4:1	176
		BF_3•Et_2O, CH_2Cl_2, –78 to –35°	 (80)	306
		BF_3•Et_2O, CH_2Cl_2, –78 to –35°	 (85)	306
		BF_3•Et_2O, CH_2Cl_2, –78 to –35°	 (82)	306
		BF_3•Et_2O, CH_2Cl_2, –78 to –35°	 (82)	306
		BF_3•Et_2O, CH_2Cl_2, –78 to –35°	 (80)	306
C_8				
$TsNHMe$		BF_3•Et_2O, –78° to rt	 (68)	176
C_{11}				
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (95)	623
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (83)	623
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (89)	623
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (67)	623

Table 1. (Continued)

Table 1E (Continued)

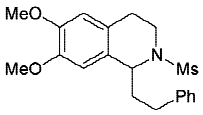
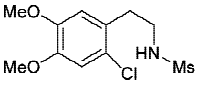
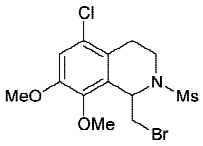
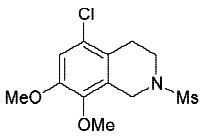
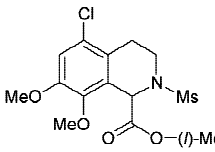
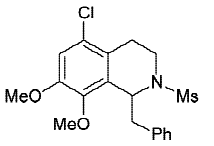
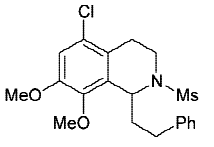
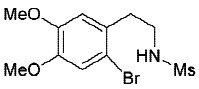
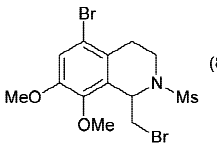
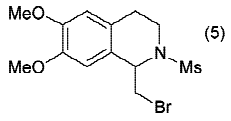
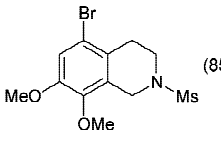
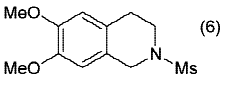
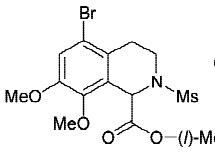
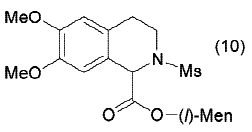
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (58)	623
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (90)	623
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (88)	623
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (81)	623
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (58)	623
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (55)	623
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (87) +	623
			 (5)	
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (85) +	623
			 (6)	
		BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (66) +	623
			 (10)	

Table 1. (Continued)

Table 1E (Continued)

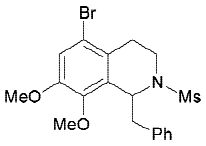
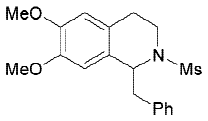
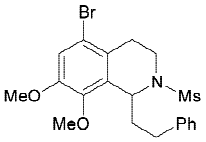
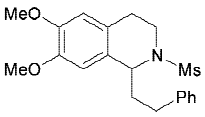
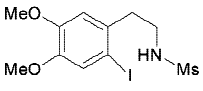
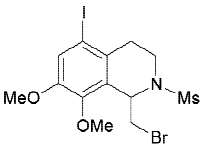
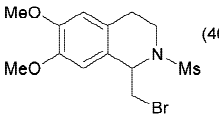
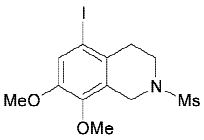
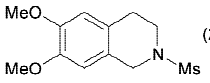
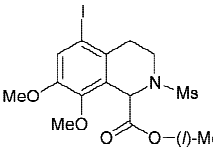
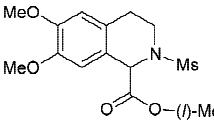
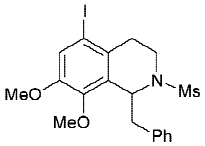
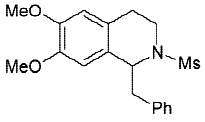
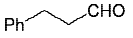
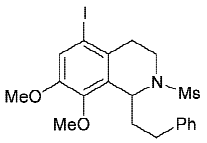
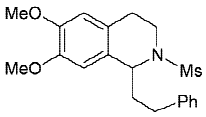
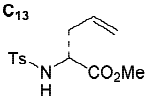
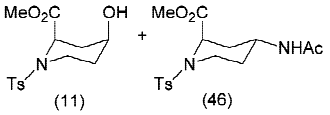
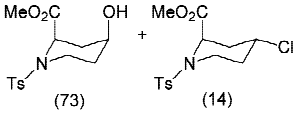
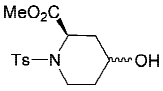
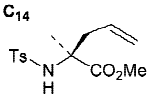
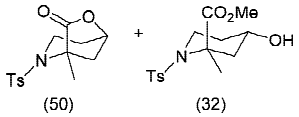
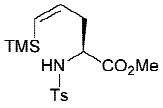
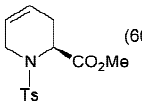
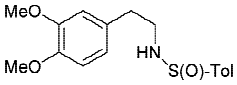
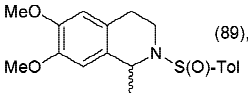
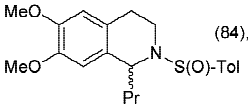
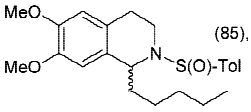
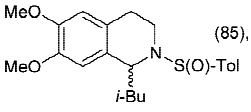
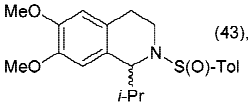
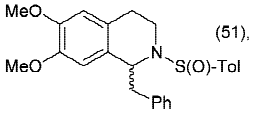
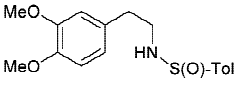
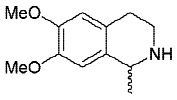
substrate	reactant	conditions	product(s) and yield(s) (%)	ref
	Ph⌒CHO	BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (47) +  (18)	623
	Ph⌒CHO	BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (41) +  (29)	623
	Br⌒OEt OEt	BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (53) +  (46)	623
	MeO⌒OMe	BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (68) +  (21)	623
	(*l*)-Men⌒O⌒CHO O	BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (32) +  (51)	623
	Ph⌒CHO	BF_3•Et_2O, CH_2Cl_2, rt, 1 h	 (37) +  (38)	623

Table 1. (Continued)

Table 1E (Continued)

substrate	reactant	conditions	product(s) and yield(s) (%)	ref
		$BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 1 h	 (2) +  (60)	623
C_{13} 		$SnCl_4$, MeCN, 50°, 18 h	 (11) (46)	164
		$SnCl_4$, CH_2Cl_2, rt, 20 h	 (73) (14)	164
	$(CH_2O)_n$	HCO_2H, 50°, 18 h	 (90), α:β = 1:1.5	164
C_{14} 	$(CH_2O)_n$	HCO_2H, 50°, 22 h	 (50) (32)	164
	$(CH_2O)_n$	HCO_2H, rt, 60 h	 (60)	164
C_{17}  *R* enantiomer	MeCHO	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°, 1 h	 (89), dr = 93:7[d]	624
	PrCHO	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°, 1 h	 (84), dr = 96:4[d]	624
	$CH_3(CH_2)_4CHO$	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°, 1 h	 (85), dr = 91:9[d]	624
	i-BuCHO	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°, 1 h	 (85), dr = 92:8[d]	624
	i-PrCHO	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°, 1 h	 (43), dr = 96:4[d]	624
	$PhCH_2CHO$	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°, 1 h	 (51), dr = 77:23[d]	624
 *S* enantiomer	MeCHO	1. $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°, 1 h 2. HCl, EtOH	 (70), ee > 98% mainly *S*	624

[a] Other isomers were detected by NMR. [b] Fmoc-L-Trp-Wang resin was used for these solid-phase reactions. [c] This reaction might proceed via a Pictet−Spengler reaction instead of an *N*-acyliminium ion cyclization. [d] *R*,*R*/*S*,*S* ratio.

Table 2. Unimolecular Reactions with Benzenoids

Table 2A. Unimolecular Reactions with Benzenoids: α-Hydroxy/Alkoxy/Thioalkoxy/Acyloxy/Halo Amides and Enamides

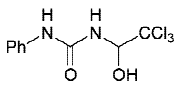
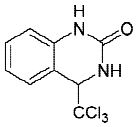
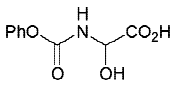
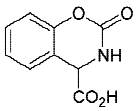
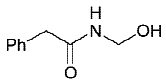
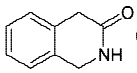
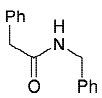
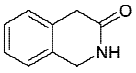
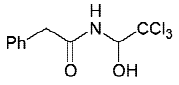
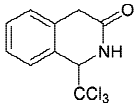
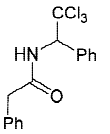
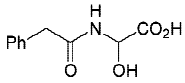
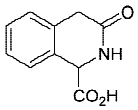
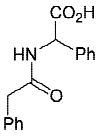
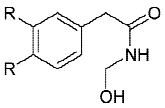
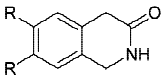
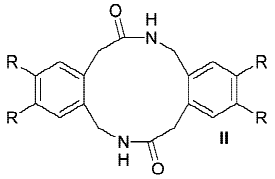
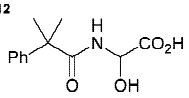
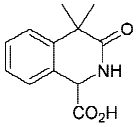
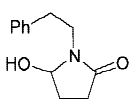
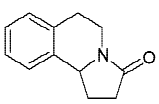
substrate	conditions	product(s) and yield(s) (%)	ref
C_9 	$MsOH, C_6H_6$, rt	 (—)	386
	$MsOH, C_6H_6$, rt	 (—)	386
	$MsOH, C_6H_6$, rt	 (—) +  (73)	386
			359
	$H_4P_2O_7$, 140-160°, 1 h	(77)	
	PPA, 140-160°, 1 h	(57)	
	H_3PO_4, 140-160°, 1 h	(28)	
	P_2O_5, $CHCl_3$, reflux, 1 h	(3)	
	P_2O_5, DCE, reflux, 1 h	(14)	
C_{10} 	MsOH, C_6H_6, rt	 (—) +  (82)	386
	MsOH, C_6H_6, rt	 (—) +  (92)	386
$C_{10\text{-}11}$ 		 I +  II	359
R		I II	
-OCH_2O-	$H_4P_2O_7$, rt, 14 h	(trace) (93)	
-OCH_2O-	$H_4P_2O_7$, 60°, 1 h	(trace) (60)	
OMe	$H_4P_2O_7$, rt, 14 h	(4) (93)	
OMe	$H_4P_2O_7$, 60°, 1 h	(17) (68)	
C_{12} 	$MsOH, C_6H_6$, rt	 (35)	386
	TsOH, C_6H_6, 80°	 (—)	467

Table 2. (Continued)

Table 2A (Continued)

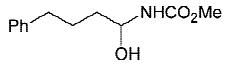
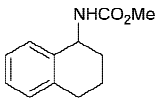
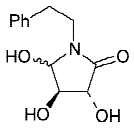
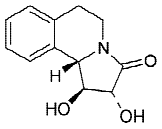
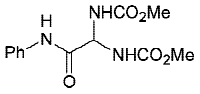
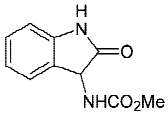
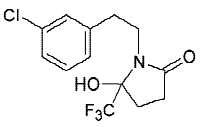
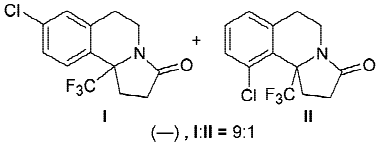
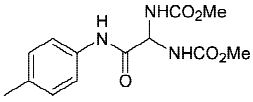
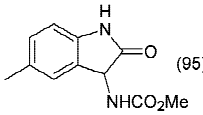
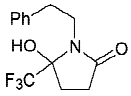
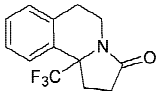
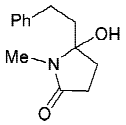
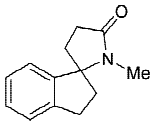
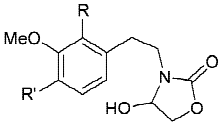
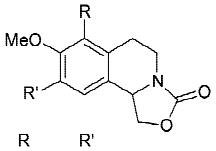
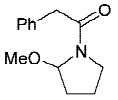
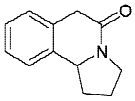
substrate	conditions	product(s) and yield(s) (%)	ref
			625
	Tf_2O, CH_2Cl_2, 0-25°	(<5)	
	CSA, CH_2Cl_2, rt	(<5)	
	TFA, CH_2Cl_2, rt	(<5)	
	$(i\text{-PrO})_2TiCl_2$, CH_2Cl_2, 0-25°	(<5)	
	TFA, CH_2Cl_2, -78-0°	(12)	
	$BF_3{\cdot}Et_2O$, CH_2Cl_2, -60°	(55)	
	$TiCl_4$ (0.5 eq), CH_2Cl_2, -78°	(15)	
	$TiCl_4$ (1.0 eq), CH_2Cl_2, -78°	(25)	
	$TiCl_4$ (1.5 eq), CH_2Cl_2, -78°	(80)	
			
	$BF_3{\cdot}Et_2O$, rt, 14 h	(36)	392
	HCl, reflux 12 h	(22)	392
	$BF_3{\cdot}Et_2O$, 0°-rt, 2 days	(66)	391
	TFA, rt	 (67)	386
C_{13}			
	TfOH, CH_2Cl_2, 7 days	 (—), I:II = 9:1	358
	TFA, rt	 (95)	386
			358
	TFA, 2 days	(85)	
	TfOH, CH_2Cl_2, 1 day	(100)	
	TFA, reflux	 (69)	374
	HCO_2H, rt, 14 h	 R = OMe, R' = H (73); R = H, R' = OMe (70)	120
			
	H_2SO_4	(86)	325
	H_2SO_4, rt, 4 h	(85)	323

Table 2. (Continued)

Table 2A (Continued)

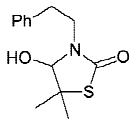
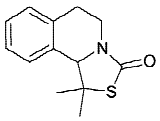
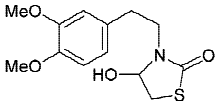
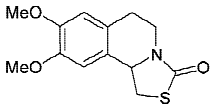
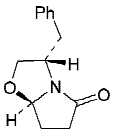
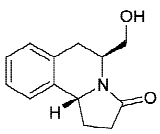
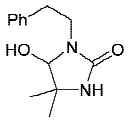
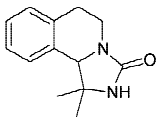
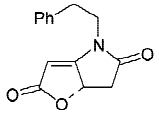
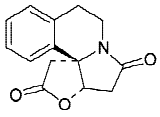
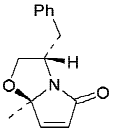
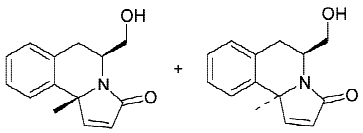
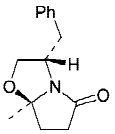
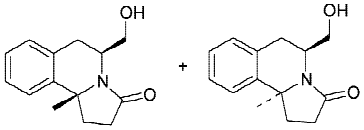
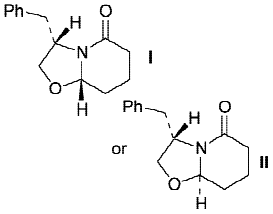
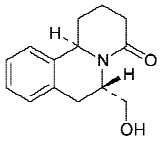
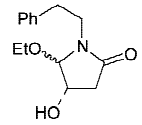
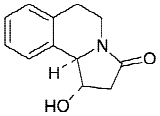
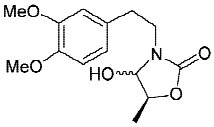
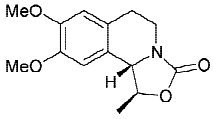
substrate	conditions	product(s) and yield(s) (%)	ref
			429
	$TsOH$, CH_2Cl_2, reflux, 112 h	(74)	
	HCO_2H, reflux	(—)	
	HCO_2H, rt, 112 h	 (84)	429
			
	$TiCl_4$, CH_2Cl_2, -10°, 20 h	(80)	626, 627
	$SnCl_4$, CH_2Cl_2, -10°, 20 h	(60)	627
	TMSOTf, CH_2Cl_2, -10°, 20 h	(78)	627
	BF_3•Et_2O, CH_2Cl_2, -10°, 20 h	(0)	627
	TFA:TFAA (12:1), CH_2Cl_2, reflux, 2 days	 (40)	386
C_{14} 			320
	TsOH, toluene, reflux	(50)	
	PPA, toluene, reflux	(43)	
	$TiCl_4$, CH_2Cl_2, -78°, 20 h	 (23) (68)	627
	$TiCl_4$, CH_2Cl_2, -10°, 20 h	 (29) (58)	626 627
	$TiCl_4$, CH_2Cl_2, -10°, 20 h	 I: (65) II: (34)	628
	HCO_2H, reflux	 (<20)	629
	HCO_2H, rt, 14 h	 (72) (73) (75)	398 119 120

Table 2. (Continued)

Table 2A (Continued)

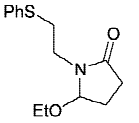
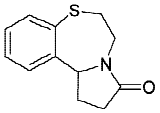
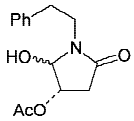
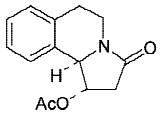
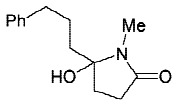
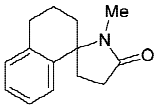
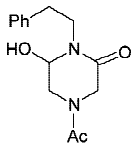
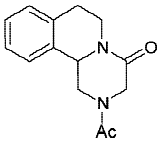
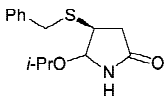
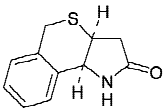
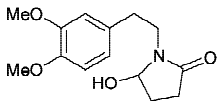
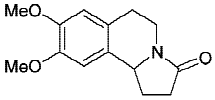
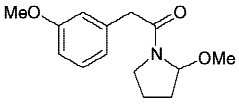
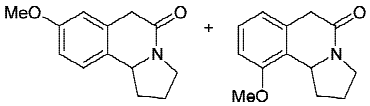
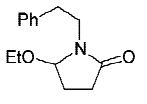
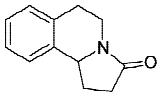
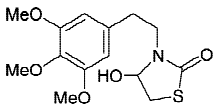
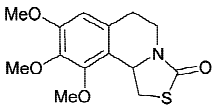
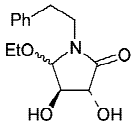
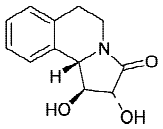
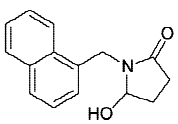
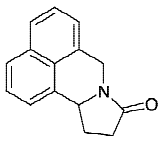
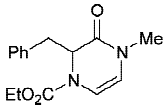
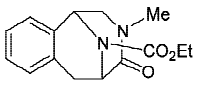
substrate	conditions	product(s) and yield(s) (%)	ref
	$SnCl_4$, CH_2Cl_2, rt, 24 h	 (26)	384
	BF_3•Et_2O, CH_2Cl_2, rt, 48 h	 (74)	391 629
	TFA, reflux	 (—)	374
	HCl, 0°, overnight	 (94)	407
	$TiCl_4$, CH_2Cl_2, −78° to rt, 2 h	 (99)	394
	TsOH, C_6H_6, 80°	 (high)	467
	1. $TiCl_4$, CH_2Cl_2, −78°, 1 h 2. −78° to rt	 (54) (19)	429
	TsOH, C_6H_6, 80°	 (—)	467
	TsOH, CH_2Cl_2, reflux, 114 h	 (66)	429
			392
	BF_3•Et_2O, rt, 14 h	(46)	
	HCl (10%), reflux, 12 h	(49)	
	HCO_2H, reflux, 17 h	(55)	
C_{15}			
	TFA, reflux, 5 h	 (65)	373
	TFA, reflux	 (100)	49

Table 2. (Continued)

Table 2A (Continued)

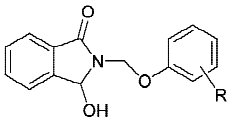
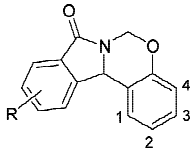
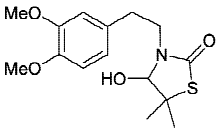
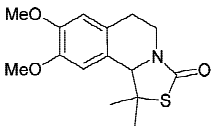
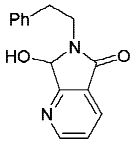
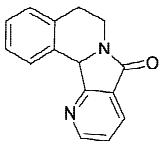
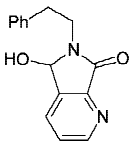
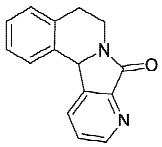
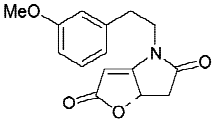
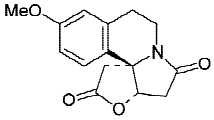
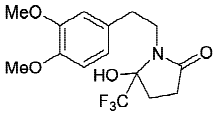
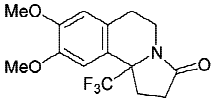
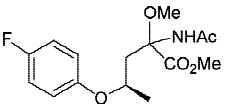
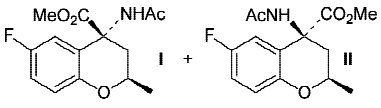
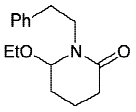
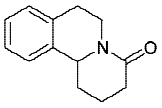
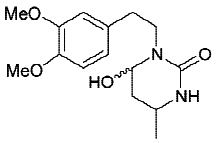
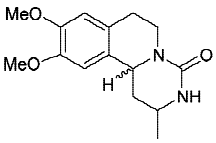
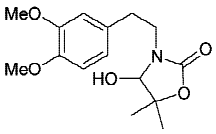
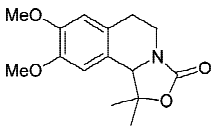
substrate	conditions	product(s) and yield(s) (%)	ref
	TFA, rt, 24 h	 R: H (86); 2-Br (84); 4-Br (82); 4-Cl (68); 1-Cl (46); 3-Cl (42); 4-F (91); 4-Br-2-Cl (78)	600
	HCO_2H, rt, 113 h	 (quant.)	429
	TFA, reflux, 3 h	 (93)	355
	TFA, reflux, 3.5 h	 (55)	355
	TsOH, CH_2Cl_2, reflux	 (53)	320
	TFA, 24 h TfOH, CH_2Cl_2, 24 h	 (97) (97)	358
	MsOH, 0° TMSOTf, CH_2Cl_2, –78°	 I + II I+II: (85) (85); I:II: 2:1 2:1	362
	PPA, 100°, 1.5 h	 (62)	116
	HCO_2H, rt, 14 h	 (27)	406
	HCO_2H, rt, 14 h	 (60)	119

Table 2. (Continued)

Table 2A (Continued)

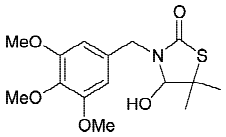
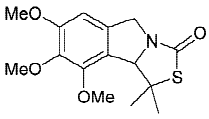
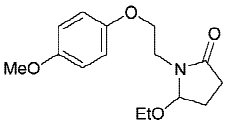
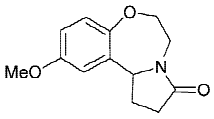
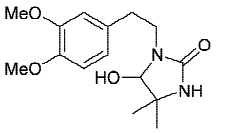
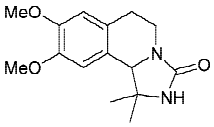
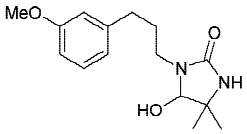
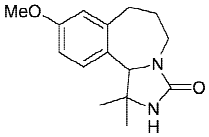
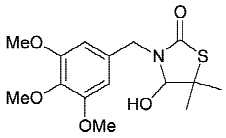
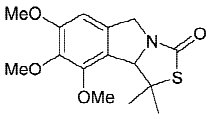
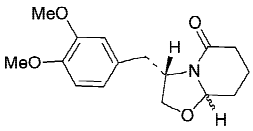
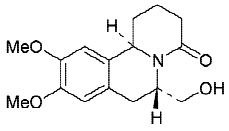
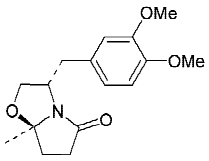
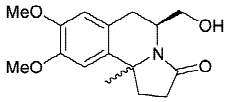
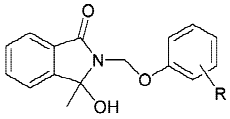
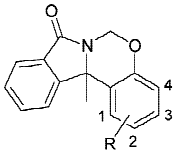
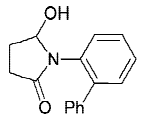
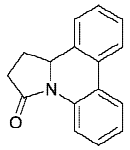
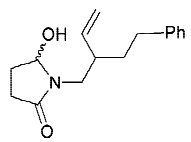
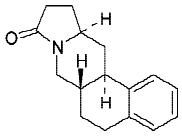
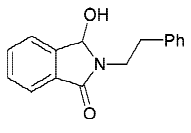
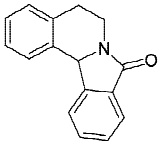
substrate	conditions	product(s) and yield(s) (%)	ref
	TsOH, C_6H_{12}, reflux, 24 h	 (84)	156
	$SnCl_4$, CH_2Cl_2, rt, 24 h	 (26)	384
	TFA:TFAA (12:1), CH_2Cl_2, reflux, 2 days	 (72)	320
	TFA:TFAA (12:1), CH_2Cl_2, reflux, 2 days	 (68)	402
	TsOH, C_6H_{12}, reflux, 24 h	 (84)	156
C_{16}			
	$TiCl_4$, CH_2Cl_2, –10°, 20 h	 (68)	628
	$TiCl_4$, CH_2Cl_2, –78° to rt, 20 h	 (91), α:β = 1.9:1	627
	TsOH, toluene, reflux, 3 h	 R: H (70); 2-F (20); 2-F,4-Cl (25)	600
	PPA, 150-170°, 1.25 h	 (84)	373
	HCO_2H, rt, 18 h	 (> 90), *trans*	124
	H_2SO_4, 25°, 2 h	 (84)	354

Table 2. (Continued)

Table 2A (Continued)

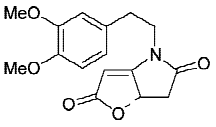
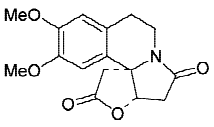
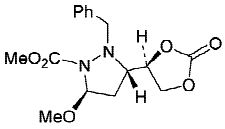
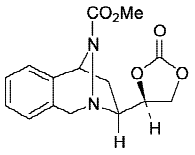
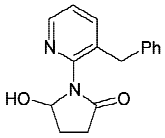
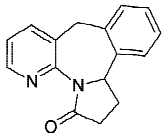
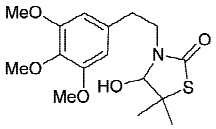
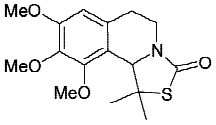
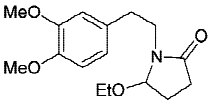
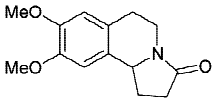
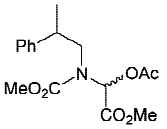
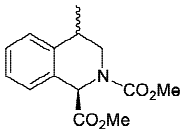
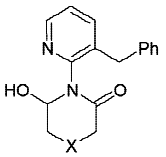
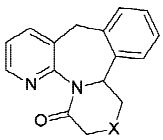
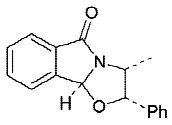
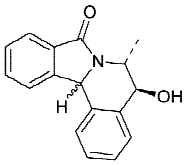
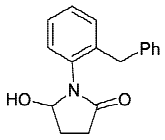
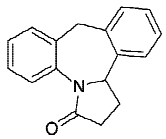
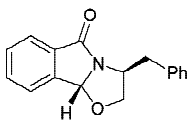
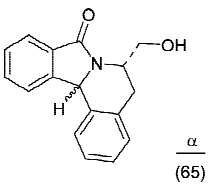
substrate	conditions	product(s) and yield(s) (%)	ref
	TsOH, toluene, reflux, 1 h	 (85)	321
	$TiCl_4$, CH_2Cl_2, −78° to rt, 5 h	 (87)	427
	H_2SO_4, rt, 2 h	 (45)	630
	HCO_2H, rt, 113 h	 (58)	429
	TsOH, C_6H_6, 80°	 (high)	467
	$SnCl_4$, CH_2Cl_2, −78° to rt, 3 h	 α (21)[a] β (62)	166
C_{16-17}			
	H_2SO_4, rt, 2 h	 X: CH_2 (60); O (63); S (70)	630
C_{17}			
	TMSOTf, CH_2Cl_2, −10°	 (99), α:β = 24:1	117
			631
	HCO_2H, reflux	(88)	
	MsOH, CH_2Cl_2, reflux	(91)	
	CH_2Cl_2, −10°		117
		α: $SnCl_4$ (65); $TiCl_4$ (62); BF_3•Et_2O (74); H_2SO_4 (69); TMSOTf (95)	
		β: $SnCl_4$ (33); $TiCl_4$ (31); BF_3•Et_2O (25); H_2SO_4 (11); TMSOTf (2)	

Table 2. (Continued)

Table 2A (Continued)

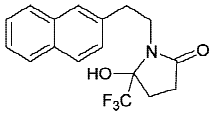
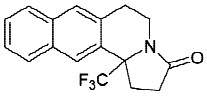
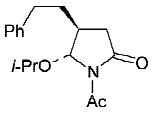
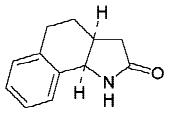
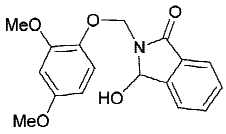
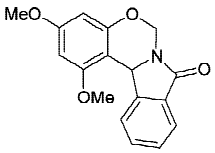
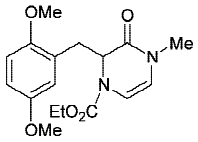
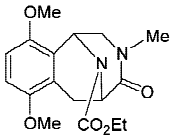
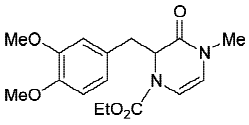
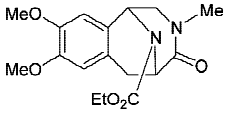
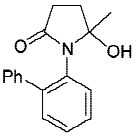
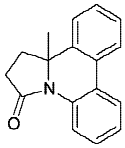
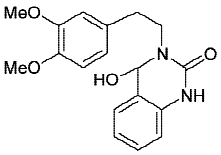
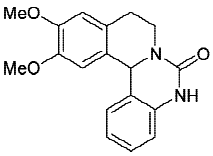
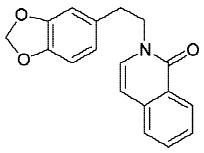
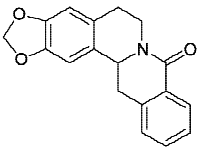
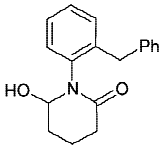
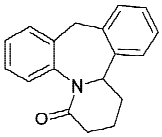
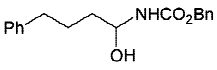
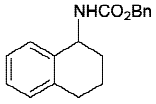
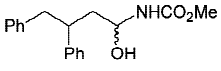
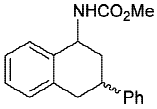
substrate	conditions	product(s) and yield(s) (%)	ref
	TFA, 1.5 days	 (52)	358
	1. Me_2NH, DMF, 18 h, rt 2. $TiCl_4$, CH_2Cl_2, –78° to rt	 (95)	236
	TFA, rt, 24 h	 (20)	600
	TFA, reflux	 (100)	49
	TFA, reflux	 (100)	49
	PPA, 150-170°, 1.25 h	 (75)	373
C_{18}			
	HCO_2H, rt, 14 h	 (63)	406
	—	 (55)	343
	MsOH, CH_2Cl_2, reflux	 (85)	631
	$TiCl_4$, CH_2Cl_2, -78°, 1 h	 (78)	625
	$TiCl_4$, CH_2Cl_2, -78°, 1 h	 (76)	625

Table 2. (Continued)

Table 2A (Continued)

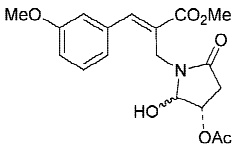
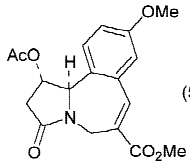
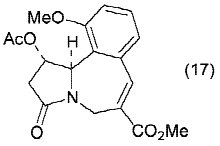
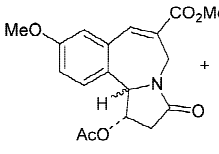
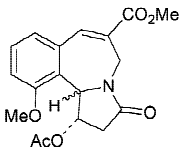
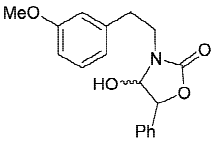
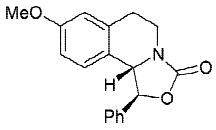
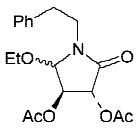
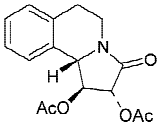
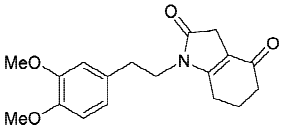
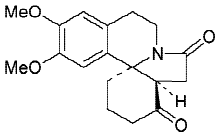
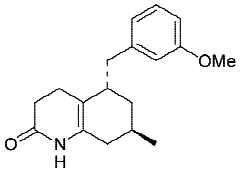
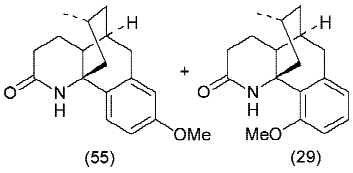
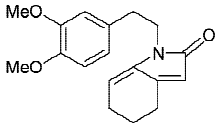
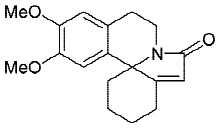
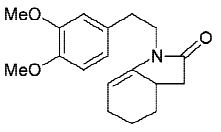
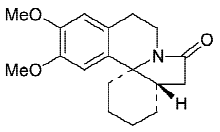
substrate	conditions	product(s) and yield(s) (%)	ref
	TfOH, CH_2Cl_2, 20°, 75 min	 (53) +  (17)	632
	TfOH, CH_2Cl_2, 20°, 75 min	 (63), α:β = 7:1 +  (17), α:β = 7.5:1	389
	HCO_2H, rt, 14 h	 (65)	119
	**A**: 1. HCO_2H, reflux, 17 h 2. AcCl, EtOH	 (90)	392
	B: 1. MsOH, rt, 1 h 2. AcCl, EtOH	(82)	
	C: 1. BF_3•Et_2O, rt, 1.5 h 2. AcCl, EtOH	(84)	
	H_3PO_4, reflux, 3 h	 (78)	349
	H_3PO_4, HCO_2H, rt	 (55) (29)	350 351
	TsOH, C_6H_6, reflux	 (90)	317
	H_3PO_4 (85%)	 (—)	601

Table 2. (Continued)

Table 2A (Continued)

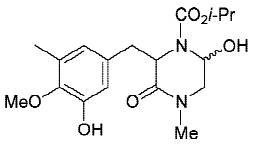
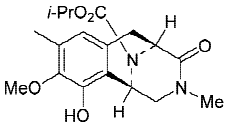
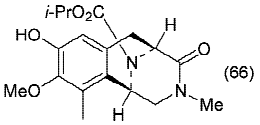
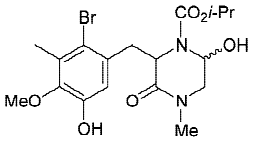
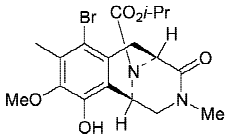
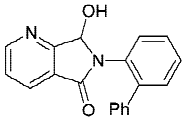
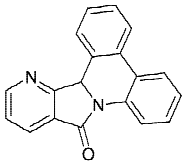
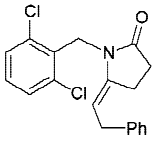
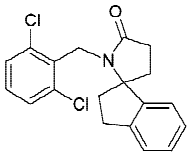
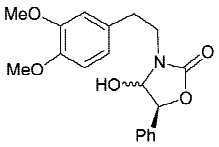
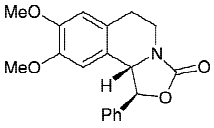
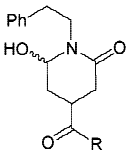
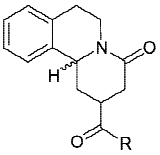
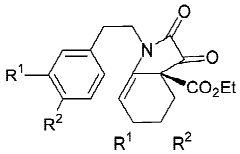
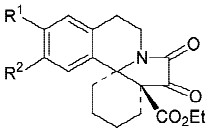
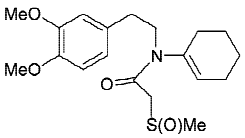
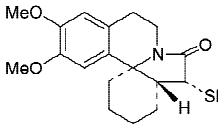
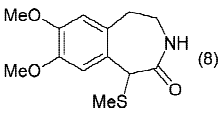
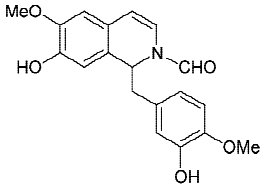
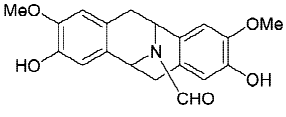
substrate	conditions	product(s) and yield(s) (%)	ref
	TFA, rt, 1 h	 (22) +  (66)	419 423
	TFA, rt, 13 h	 (97)	419
C_{19}			
	TFA, reflux, 4.5 h	 (88)	355
	TFA, reflux	 (—)	374
	HCO_2H, rt, 14 h	 (70)	398 119
	HCl, 0°, overnight	 R: Ph (95); C_6H_{11} (95)	407
			68 80
R^1 = H, R^2 = H	PPA, 80°, 0.5 h	(96)	
R^1 = H, R^2 = OH	H_3PO_4, 80°, 0.5 h	(31)	
R^1 = OH, R^2 = OH	BF_3•Et_2O, reflux, 2 h	(56)	
	TsOH, DCE, reflux, 10 min	 (60) +  (8)	72 73
	MsOH, MeCN, rt, 6.5 h	 (75)	305

Table 2. (Continued)

Table 2A (Continued)

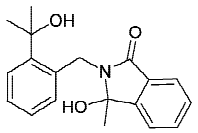
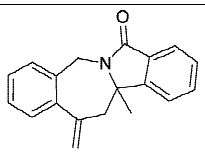
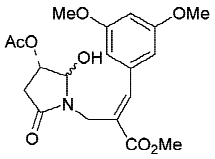
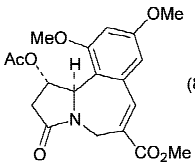
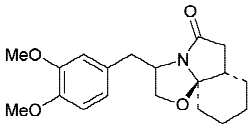
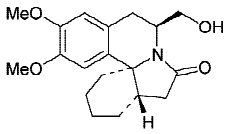
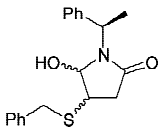
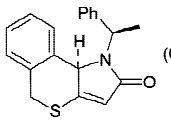
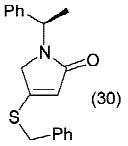
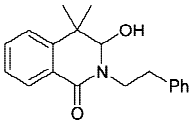
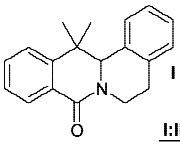
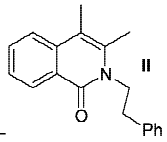
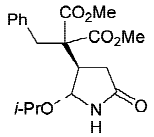
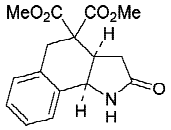
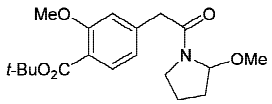
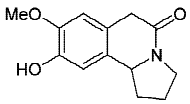
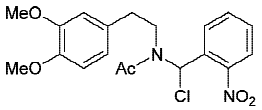
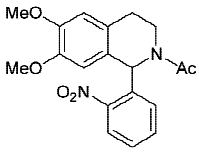
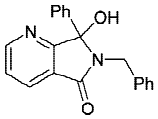
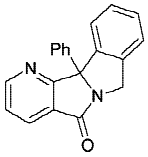
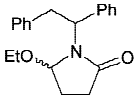
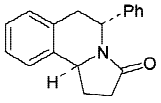
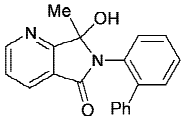
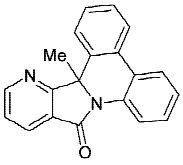
substrate	conditions	product(s) and yield(s) (%)	ref
	TsOH, toluene, reflux	 (70)	500
	TfOH, CH_2Cl_2, 2 h	 (80)	632
	$TiCl_4$, CH_2Cl_2, −78° to rt, 20 h	 (98)[b]	633
	TFA, CH_2Cl_2, rt, 3 days	 (63) +  (30)	634
		 I +  II	635
	$AlBr_3$, *o*-diClC_6H_4, −5°	I:II[c] 7:3	
	$AlBr_3$, CH_2Cl_2, −5°	9.5:0.5	
	$AlBr_3$, *o*-diClC_6H_4, rt	1:1	
	$AlBr_3$, *o*-diClC_6H_4, 180°	0.6:9.4	
	$TiCl_4$	 (79)	395
	1. $TiCl_4$, CH_2Cl_2, −78°, 1 h 2. −78° to rt	 (59)	325
	$AlCl_3$, DCE, rt, 3 h	 (86)	364
C_{20}			
	PPA, 150°, 1.25 h	 (72)	355
	PPA, rt, 1 h	 (83)	45
	PPA, 150°, 2 h	 (62)	355

Table 2. (Continued)

Table 2A (Continued)

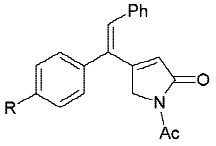
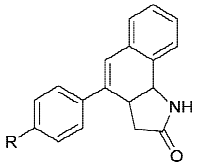
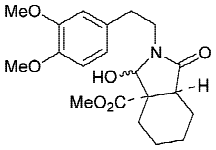
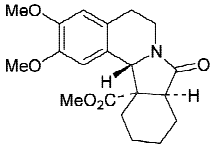
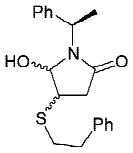
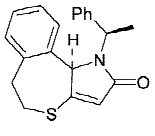
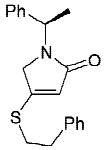
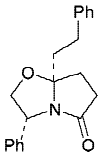
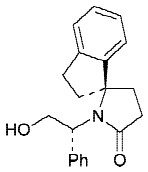
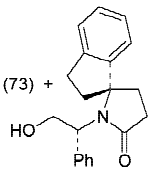
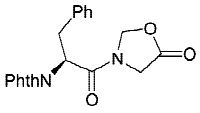
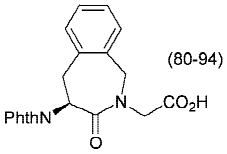
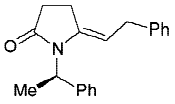
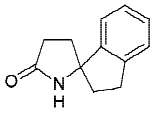
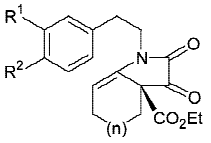
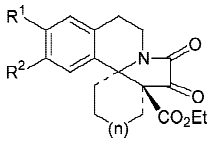
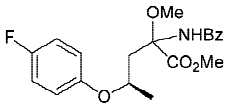
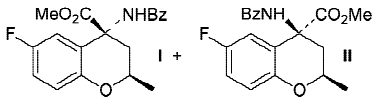
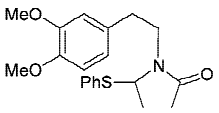
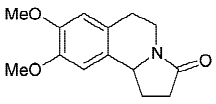
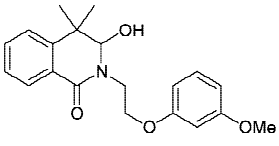
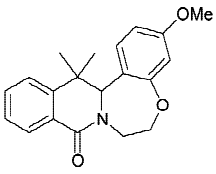
substrate	conditions	product(s) and yield(s) (%)	ref
	AcOH, HCl, H_2O, reflux, 8 h	 R: Br (57), H (71)	602
	CSA, toluene, 80°	 (69)	307a
	TFA, CH_2Cl_2, rt, 3 days	 (64) +  (22)	634
	$AlCl_3$, DCE, –5°	 (73) +  (20)	375
	PPA, 100°, or MsOH or TfOH or TMSOTf	 (80-94)	378
	TFA, reflux	 (69)	374
			68 80
n: 1, R^1: H, R^2: OMe	PPA, 80°, 3 h	(82)	
n: 0, R^1: OMe, R^2: OMe	H_3PO_4, rt, 50 min	(62)	
		 I + II	376
	MsOH, 0°	I+II: (85), I:II: 72:28	
	$SnCl_4$, CH_2Cl_2, –78°	(85), 60:40	
	TMSOTf, CH_2Cl_2, –78°	(85), 60:40	
	BF_3•2AcOH, CH_2Cl_2, rt	 (98)	343 346
	$TiCl_4$, CH_2Cl_2, –78° to rt	 (32)	635

Table 2. (Continued)

Table 2A (Continued)

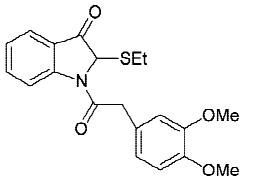
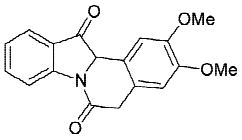
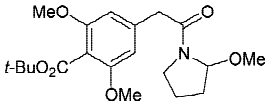
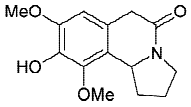
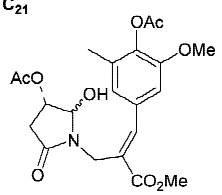
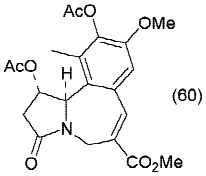
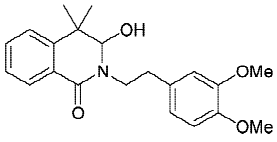
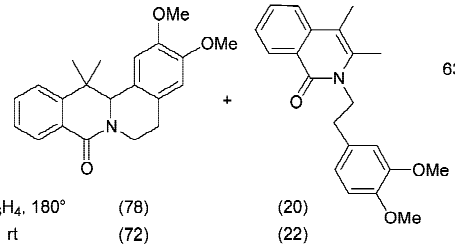
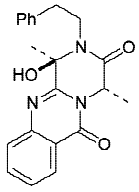
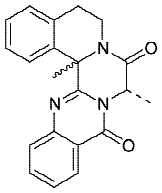
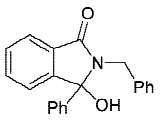
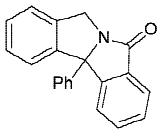
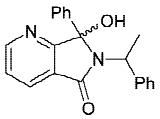
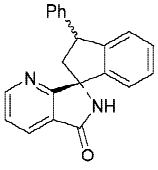
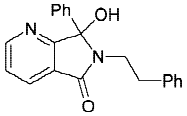
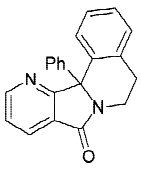
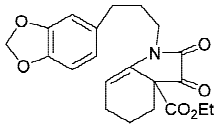
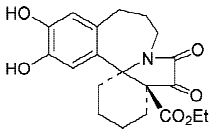
substrate	conditions	product(s) and yield(s) (%)	ref
	$TiCl_3$, H_2O_2, MeCN, MeOH, rt, 15 h	 (50)	346
	1. $TiCl_4$, CH_2Cl_2, −78°, 1 h 2. −78° to rt	 (90)	325
C_{21} 	TfOH, CH_2Cl_2, 20°, 75 min	 (60)	632
			635
	$AlBr_3$ (1 eq), *o*-diClC_6H_4, 180°	(78) (20)	
	$AlBr_3$ (1 eq), CH_2Cl_2, rt	(72) (22)	
	$AlBr_3$ (3 eq), −5°, 2 h	(—) (42)	
	$AlBr_3$ (3 eq), rt, 2 h	(—) (100)	
	H_2SO_4, rt, overnight	 (94), α:β = 1:4	636
	PPA, 135°, 4 h	 (75)	354
	PPA, 100-125°, 1 h	 (56), α:β = 1:3.3	603
	TFA, reflux, 3 h	 (72)	355
	H_3PO_4 (anhyd.), rt, 2 h	 (3)	84

Table 2. (Continued)

Table 2A (Continued)

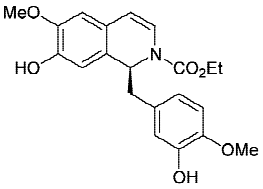
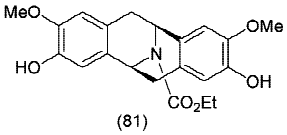
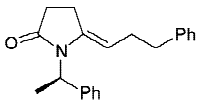
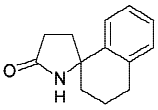
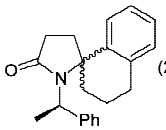
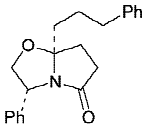
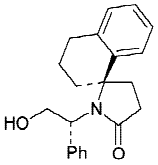
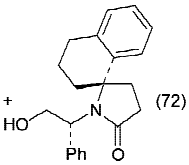
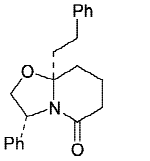
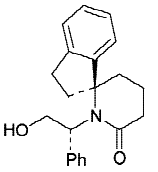
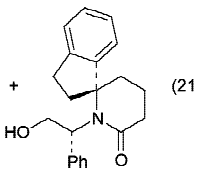
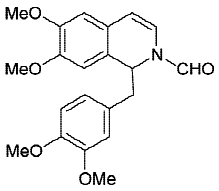
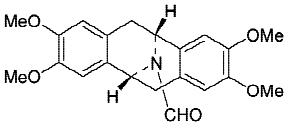
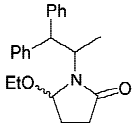
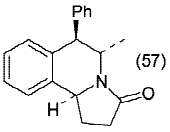
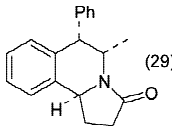
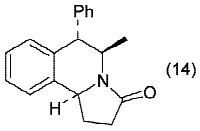
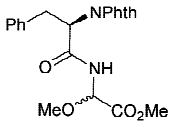
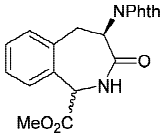
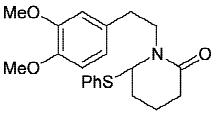
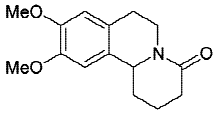
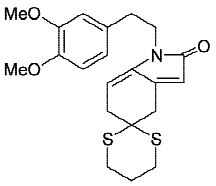
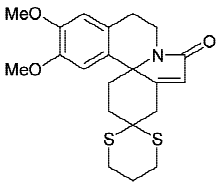
substrate	conditions	product(s) and yield(s) (%)	ref
	MsOH, MeCN, rt, 1.5 h	 (81)	305
	TFA, reflux	 (58) +  (25)[d]	374
	$AlCl_3$, DCE, –5°	 (18) +  (72)	375
	$AlCl_3$, DCE, –5°	 (67) +  (21)	375
	MsOH, MeCN, rt, 4 h	 (68)	604
	PPA, 100°, 6 h	 (57) +  (29) +  (14)	116
	TfOH, CH_2Cl_2, rt, 17 h	 (82), α:β = 1:11	378
	BF_3•2AcOH, CH_2Cl_2, rt	 (98)	343 346
	TsOH, C_6H_6, reflux	 (84)	317

Table 2. (Continued)

Table 2A (Continued)

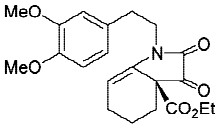
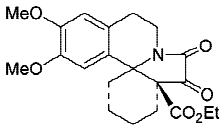
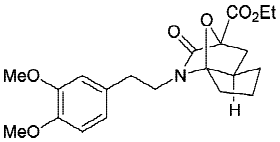
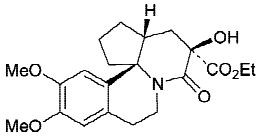
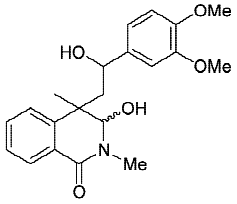
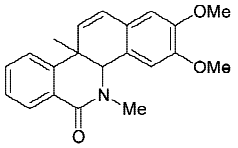
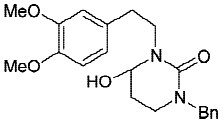
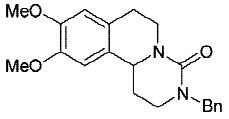
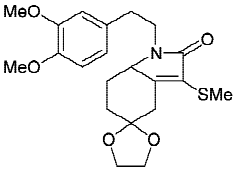
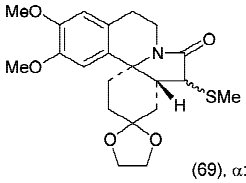
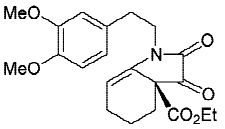
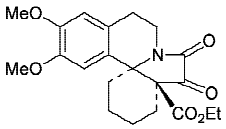
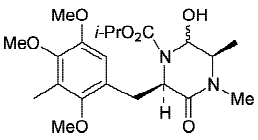
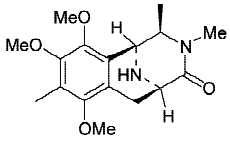
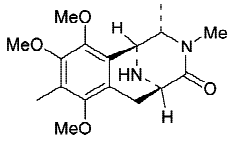
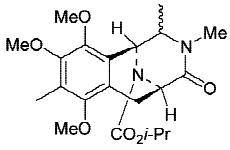
substrate	conditions	product(s) and yield(s) (%)	ref
			68 80
	H_3PO_4, rt, 1.5 h	(90)	
	PPE, 90°, 1.5 h	(100)	
	BF_3•Et_2O, CH_2Cl_2, rt, 3 h	(100)	
	$AgClO_4$, C_6H_6, 80°, 0.5 h	(100)	
	$POCl_3$, toluene, 100°, 2.5 h	(61)	
	H_3PO_4, MeOH, H_2O, reflux, 7.5 h	(35)	
	$AgBF_4$, C_6H_6, reflux, 11 h	(40)	
	$AlCl_3$, Me_2S, rt, 20 min	(41)	
	HCl-MeOH (10%), reflux, 2.5 h	(0)	
	BF_3•Et_2O, CH_2Cl_2, rt, 3 h	 (90)	86
	TsOH or HCl, C_6H_6, reflux	 (90), *cis*	605
	HCO_2H, rt, 14 h	 (72)	406
	TsOH, $HO(CH_2)_2OH$, reflux, 5 h	 (69), α:β = 1:1.4	79
	BF_3•Et_2O, CH_2Cl_2, rt, 20 min	 (100)	68 80
	H_2SO_4, TFA, rt, 2 h	 (50) +	421
		 (42)	
	TFA, reflux, 24 h	 (51)	421

Table 2. (Continued)

Table 2A (Continued)

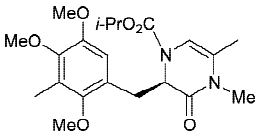
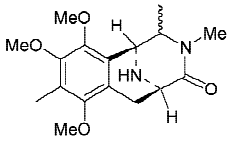
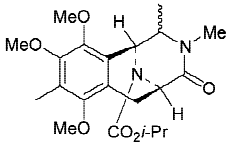
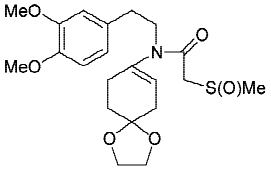
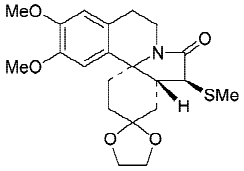
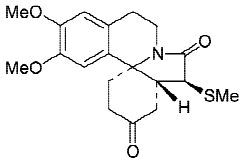
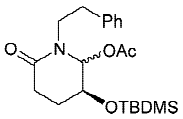
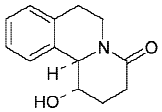
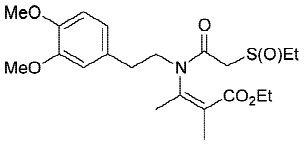
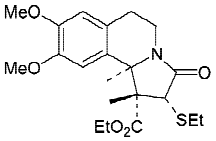
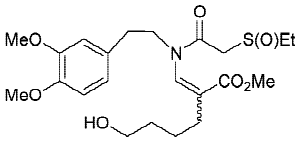
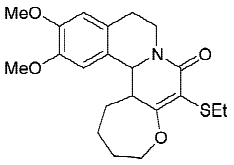
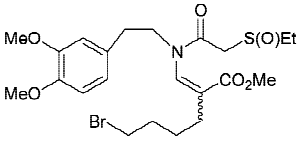
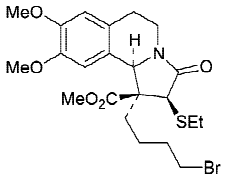
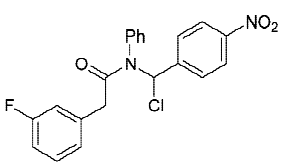
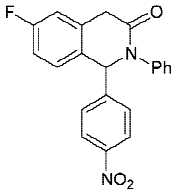
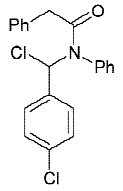
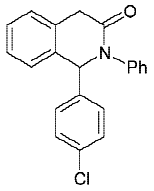
substrate	conditions	product(s) and yield(s) (%)	ref
	H_2SO_4, TFA, rt, 2 h	 (93), α:β = 1:1.1	421
	TFA, reflux, 24 h	 (98)	421
	TsOH, C_6H_6, reflux, 1 h	 (19) +  (53)	78
	1. HCO_2H, reflux, 22 h 2. AcCl, EtOH, rt, 5 h	 (20)	393
	TsOH, C_6H_6, reflux	 (78)	344
	1. MsCl, Et_3N 2. CSA, benzene, reflux 3. NaI, acetone 4. NaH, THF, reflux	 (34)	637
	CSA, toluene, reflux	 (88)[e]	637
	neat, 130°, 24 h	 (55)	371
	neat, 130°, 24 h	 (66)	371

Table 2. (Continued)

Table 2A (Continued)

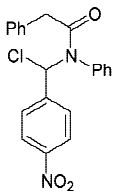
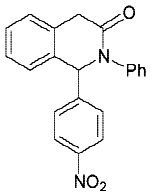
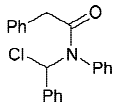
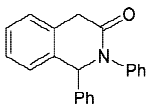
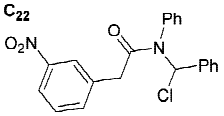
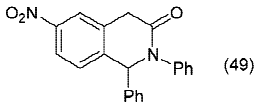
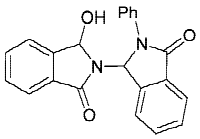
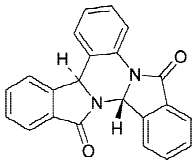
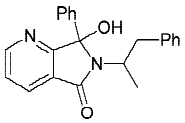
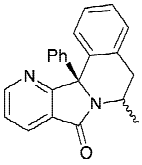
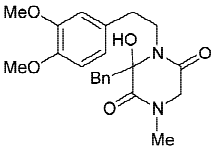
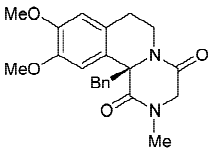
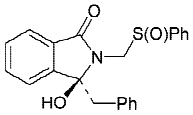
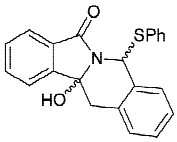
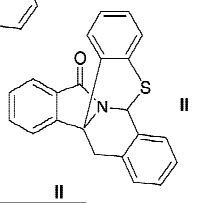
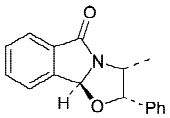
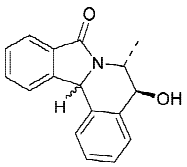
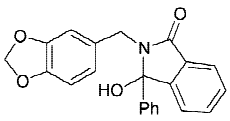
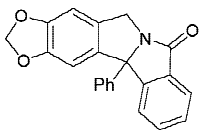
substrate	conditions	product(s) and yield(s) (%)	ref
	neat, 130°, 24 h	 (68)	371
	neat, 130°, 24 h	 (40)	371
	neat, 130°, 24 h	 (49)	371
	TFA, reflux	 (93)	439
	PPA, 100-110°, 1 h TFA, reflux, 2 h	 β: (65), (67); α: (22), (22)	638
	HCl, MeOH	 (100)	639
	**A**: TFAA, CH_2Cl_2, rt, 12 h **B**: TFAA, Py, rt, 5 h **C**: 1. TFAA, CH_2Cl_2, rt, 8-12 h 2. TFA, rt, 12 h	 +  II I: (minor)[f] (56)[g] (0); II: (major) (0) (42)	640
	$TiCl_4$, CH_2Cl_2, –10°	 (94), α:β = 46:1	117
	PPA, H_3PO_4, 30°, 3.5 h	 (37)	354

Table 2. (Continued)

Table 2A (Continued)

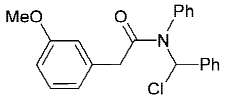
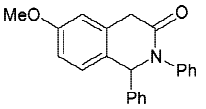
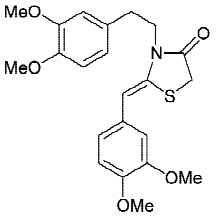
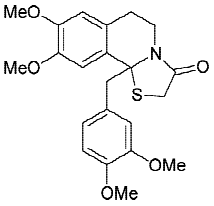
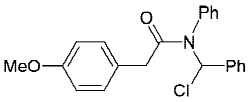
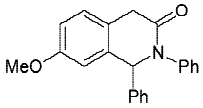
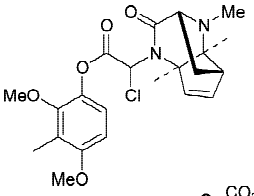
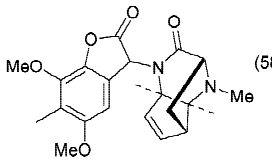
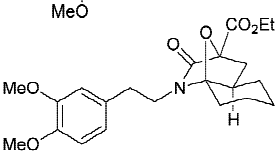
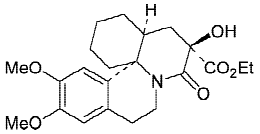
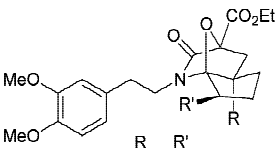
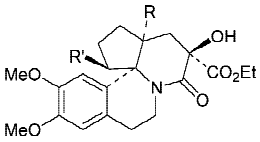
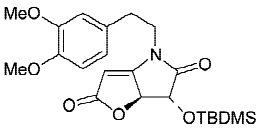
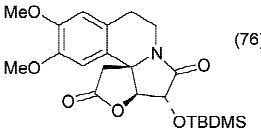
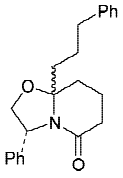
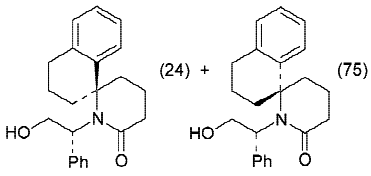
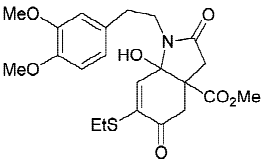
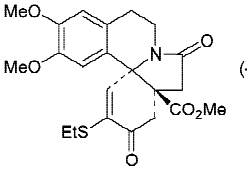
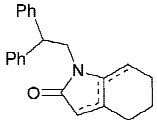
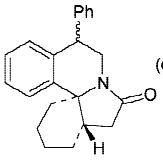
substrate	conditions	product(s) and yield(s) (%)	ref
	neat, 130°, 24 h	 (45)	371
	TFA, CH_2Cl_2, rt, 48 h	 (93)	431
	neat, 130°, 24 h	 (66)	371
	AgOTf, CH_2Cl_2, rt	 (58)	361
	BF_3•Et_2O, CH_2Cl_2, rt, 3 h	 (91)	86
	BF_3•Et_2O, CH_2Cl_2		86
R R' Me H H Me	reflux, 24 h rt, 3 h	(95) (90)	
	TsOH, CH_2Cl_2, reflux, 1 h	 (76)	321
	$AlCl_3$, DCE, –5°	 (24) + (75)	375
	BF_3•Et_2O	 (—)	78
	PPA, 100°, 24 h	 (quant.), α:β = 95:5 (41%); purified α isomer	45 67

Table 2. (Continued)

Table 2A (Continued)

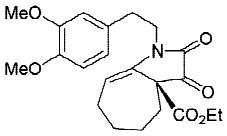
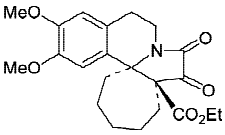
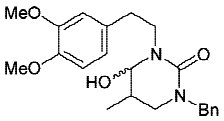
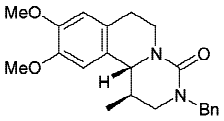
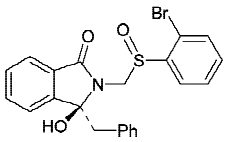
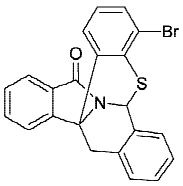
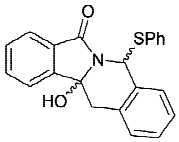
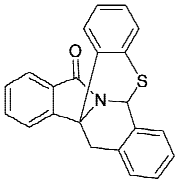
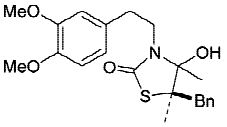
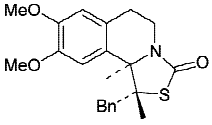
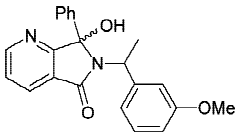
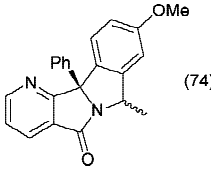
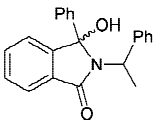
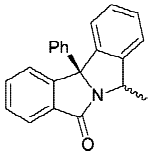
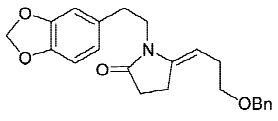
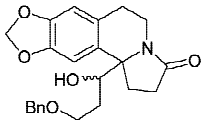
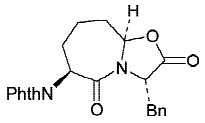
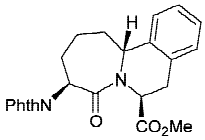
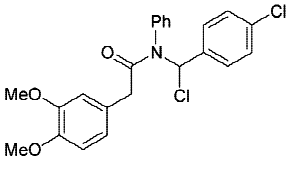
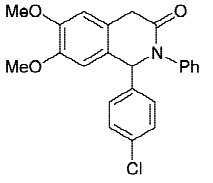
substrate	conditions	product(s) and yield(s) (%)	ref
	H_3PO_4, 50°, 2 h	 (63)	68 80
	HCO_2H, rt, 14 h	 (53)	405
	1. TFAA, CH_2Cl_2, rt, 8-12 h 2. TFA, rt, 12 h	 (62)	640
	TFA, rt, 12 h	 (58)	640
	TFA, CH_2Cl_2, reflux	 (98)	433
	PPA, 100-110°, 1 h or TFA, reflux, 3 days	 (74), α:β = 1:3.9	638
	$AlCl_3$, DCE, -7°, 4 h	 (20), α:β = 1:4	638
C_{23} 	1. DMD, MeOH, −78 to 30° 2. BF_3•Et_2O, CH_2Cl_2, −45 to 0°	 (80)[h]	641
	1. TfOH, Tf_2O, CH_2Cl_2, rt, 21 h 2. CH_2N_2, MeOH, CH_2Cl_2	 (72)	399
	neat, 130°, 24 h	 (76)	371

Table 2. (Continued)

Table 2A (Continued)

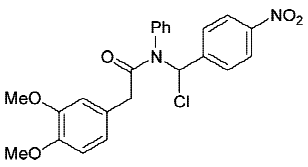
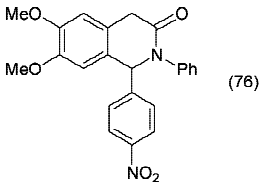
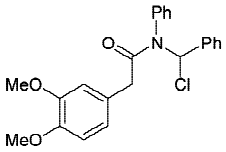
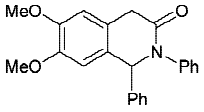
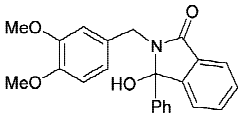
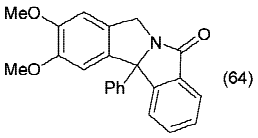
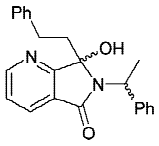
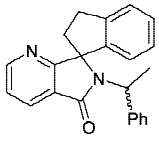
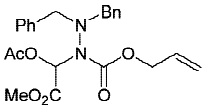
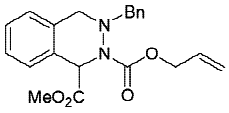
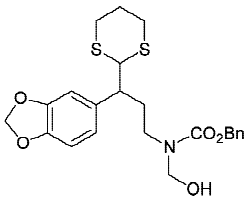
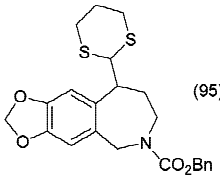
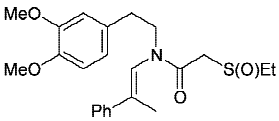
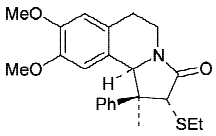
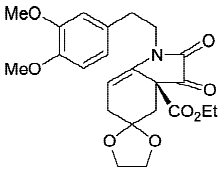
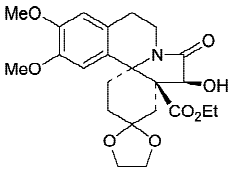
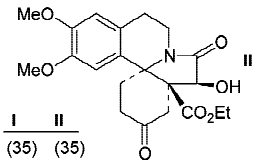
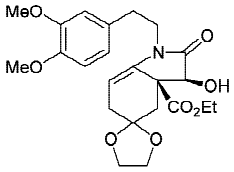
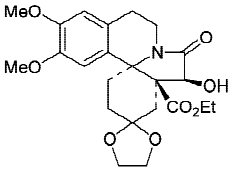
substrate	conditions	product(s) and yield(s) (%)	ref
	neat, 130°, 24 h	 (76)	371
	neat, 130°, 24 h	 (55)	371
	PPA, H_3PO_4, 30°, 4 h	 (64)	354
	PPA, 100-125°, 1 h	 (9)	376
	$SnCl_4$, CH_2Cl_2	 (91)	428
	TsOH, C_6H_6, reflux, 20 min	 (95)	385
	TsOH, C_6H_6, reflux	 (69)	344
		 I +	69
		 I II	
	BF_3•Et_2O, CH_2Cl_2, reflux, 40 min	(35) (35)	
	$AgClO_4$, C_6H_6, 90°, 1 h	(25) (32)	
	BF_3•Et_2O, CH_2Cl_2, rt, 2 h	 (100)	70

Table 2. (Continued)

Table 2A (Continued)

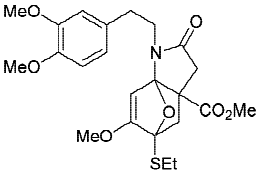
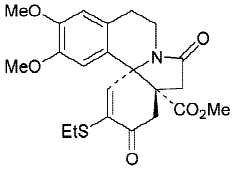
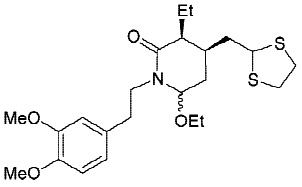
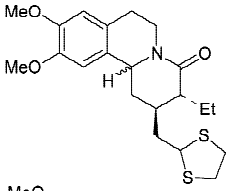
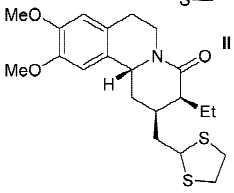
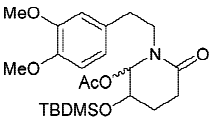
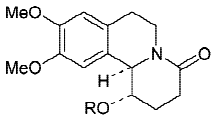
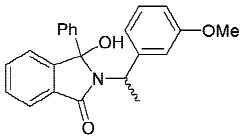
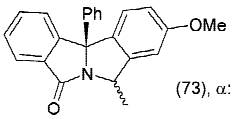
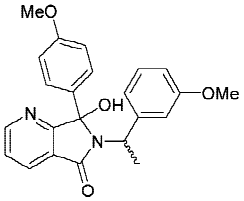
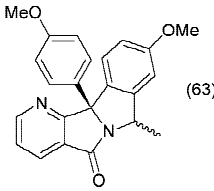
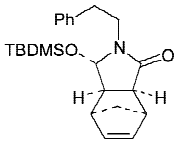
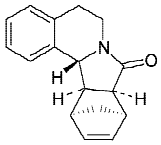
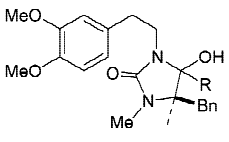
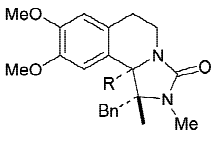
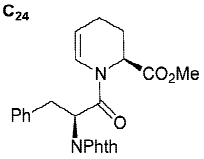
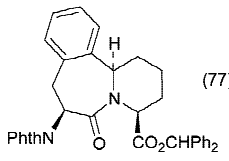
substrate	conditions	product(s) and yield(s) (%)	ref
	BF_3•Et_2O	 (—)	88
	TsOH, C_6H_6, reflux	 I +  II	606
		Iα (24) Iβ (24) II (20)	
			393
		R H (83) TBDMS (86)	
	BF_3•Et_2O, rt, 36 h BF_3•Et_2O , -78 to -30°, 4 h		
	PPA, 100-110°, 1 h	 (73), α:β = 1:3.9	638
	PPA, 100-110°, 1 h	 (63), α:β = 1:6	638
			629
	BF_3•Et_2O $TiCl_4$, CH_2Cl_2, –78°, 2 h	(10) (77)	
C_{23-26}			
 R = Me or Bu	TFA or SiO_2	 (0)	433
C_{24}			
	1. TFA, CH_2Cl_2, 25° 2. $Ph_2C{=}N_2$, CH_2Cl_2	 (77)	118

Table 2. (Continued)

Table 2A (Continued)

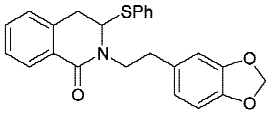
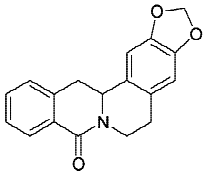
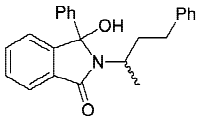
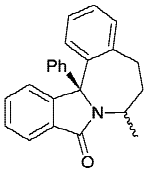
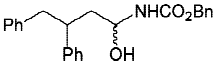
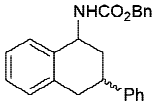
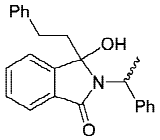
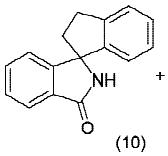
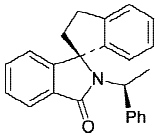
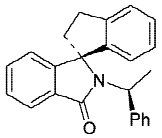
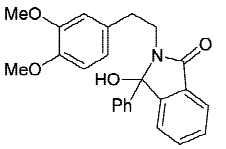
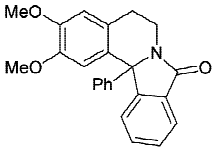
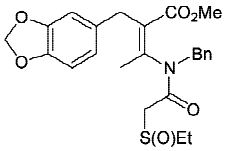
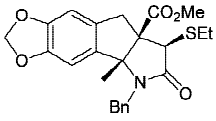
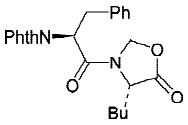
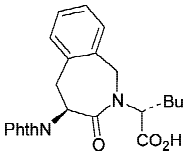
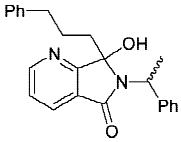
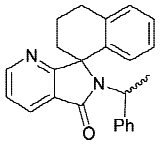
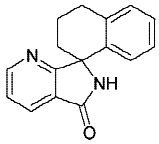
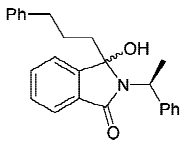
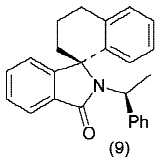
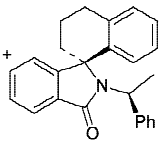
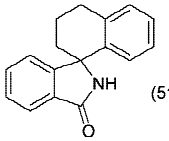
substrate	conditions	product(s) and yield(s) (%)	ref
	HCl, rt, 48 h	 (55)	346
	PPA, 120-125°, 1 h	 (19), α:β = 1:1.4	638
	$TiCl_4$, CH_2Cl_2, -78°, 1 h	 (80)	625
	TFA, reflux, 60 h	 (10) +  (42) +  (20)	385
	$POCl_3$, 50°, 2 h	 (91)	354
	TsOH, C_6H_6, reflux	 (79)	344
	TfOH, CH_2Cl_2, rt, overnight	 (96)	380
	PPA, 100-125°, 1 h	 (4) +  (73)	376
C_{25} 	TFA, reflux, 50 h	 (9) +  (26) +  (51)	376

Table 2. (Continued)

Table 2A (Continued)

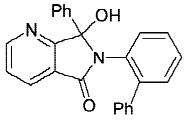
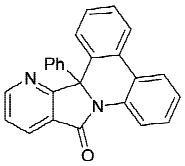
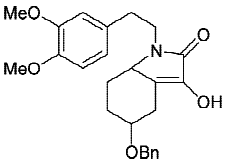
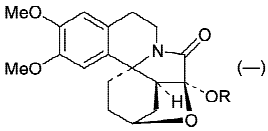
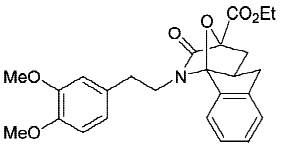
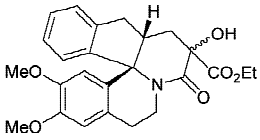
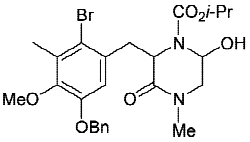
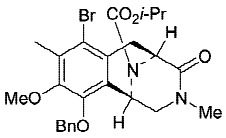
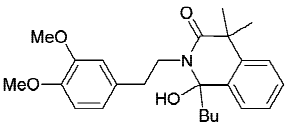
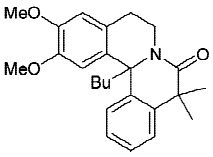
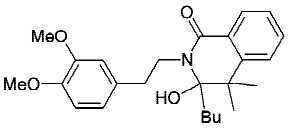
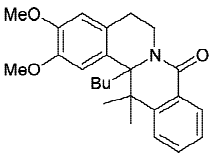
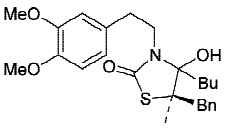
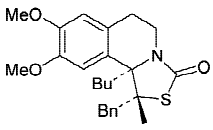
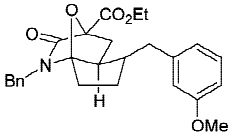
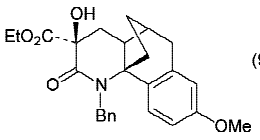
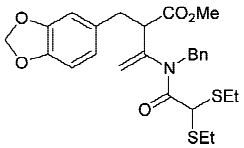
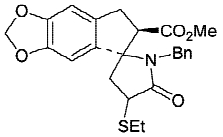
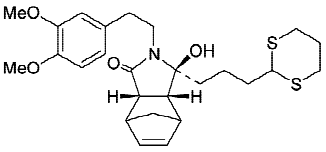
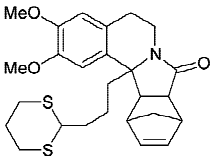
substrate	conditions	product(s) and yield(s) (%)	ref
	TFA, reflux, 3 h	 (63)	355
	H_3PO_4:MeOH (1:1), 90°, 18 h	 (—) R = H and R = Me	60
	BF_3•Et_2O, CH_2Cl_2, rt, 4 h	 (80)	86
			
	H_2SO_4, TFA, rt, 21 h	(65)	419
	HCO_2H, 70°, 1 h	(11)	423
	TFA, $CHCl_3$, reflux	 (95)	607
	TFA, $CHCl_3$, reflux	 (75)	607
	TFA, CH_2Cl_2, reflux	 (89)	433
C_{26} 	BF_3•2AcOH, CH_2Cl_2, 24 h , rt	 (93)	350
	$(Me_2SSMe)^+BF_4^-$	 (53)	344
	TFA, CH_2Cl_2, rt, 12 h	 (85)	206

Table 2. (Continued)

Table 2A (Continued)

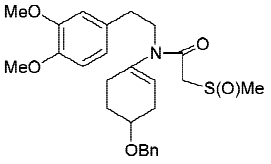
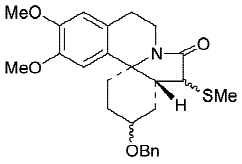
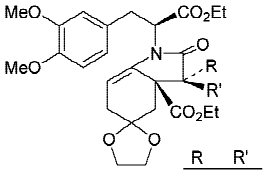
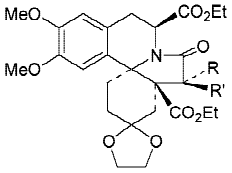
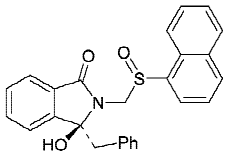
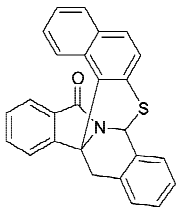
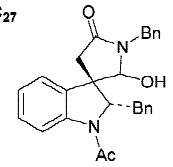
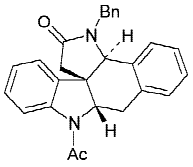
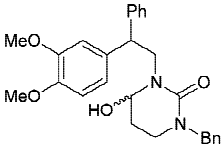
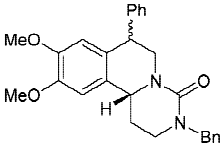
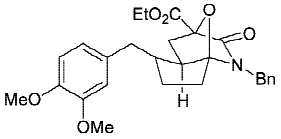
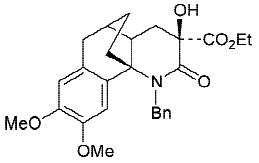
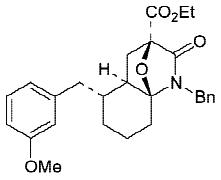
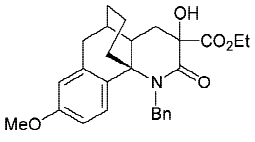
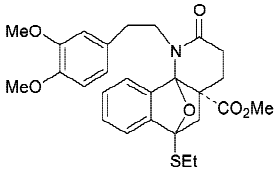
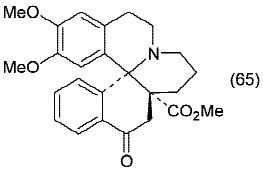
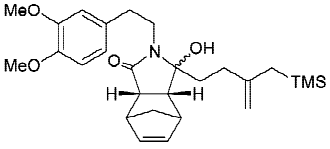
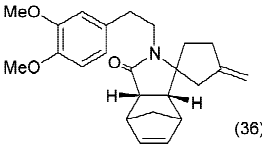
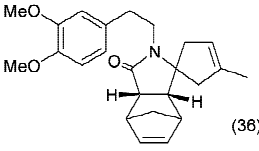
substrate	conditions	product(s) and yield(s) (%)	ref
	TsOH, C_6H_6, reflux, 10 min	 (51)	73
 R = H, R' = OH; R = OH, R' = H	BF_3•Et_2O, CH_2Cl_2; reflux, 1.5 h; reflux, 3.5 h	 (87); (—)	81 82
	1. TFAA, CH_2Cl_2, rt, 8-12 h 2. TFA, rt, 12 h	 (41)	640
C_{27} 	HCO_2H, 18 h, rt	 (quant.)	230
	HCO_2H, rt, 14 h	 (48)	405
	BF_3•Et_2O, CH_2Cl_2, 5 h, rt	 (80)	350
	BF_3•2AcOH, CH_2Cl_2, 24 h, rt	 (88)	350
	TsOH, toluene, reflux	 (65)	87
	MsCl, Et_3N, CH_2Cl_2, rt, 12 h	 + (36);  (36)	206

Table 2. (Continued)

Table 2A (Continued)

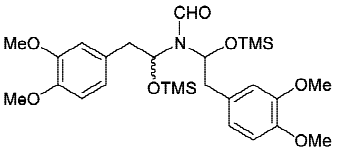
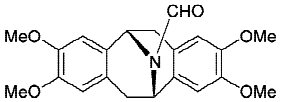
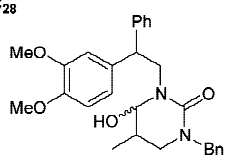
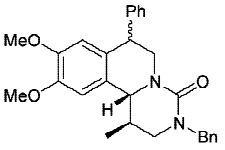
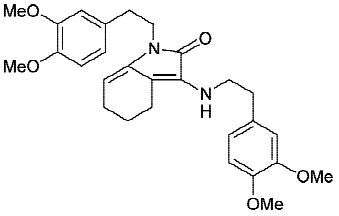
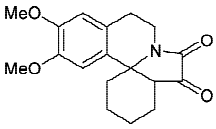
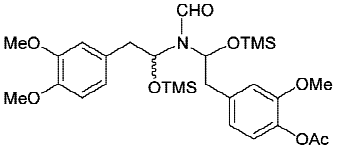
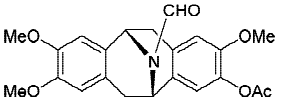
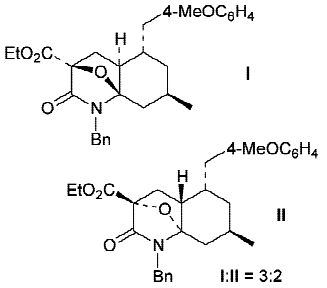
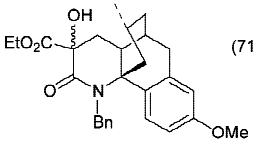
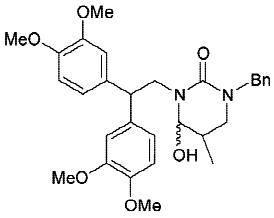
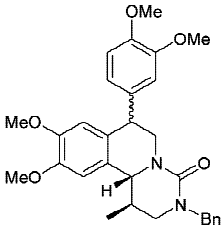
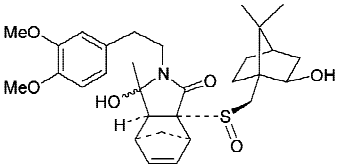
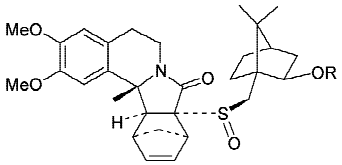
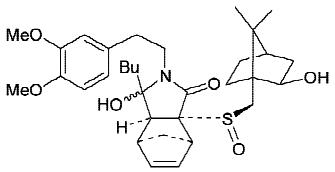
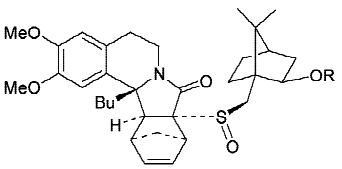
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 5 h	 (82)	304
C_{28} 	HCO_2H, rt, 14 h	 (28)[i]	405
	H_3PO_4 (85%), MeOH, reflux	 (90)	347 348
	HCO_2H, rt, 3h	 (70)	304
 I:II = 3:2	BF_3•2AcOH, CH_2Cl_2, 30 h, rt	 (71)[j]	350
C_{30} 	HCO_2H, rt, 14 h	 (24)[a] (+ 30% st. mat.)	405
	TFA, CH_2Cl_2, rt, 3 days	 R = H (51) R = OC(O)CF_3 (16)	642
C_{32} 	TFA, CH_2Cl_2, rt, 3 days	 R = H (23) R = OC(O)CF_3 (63)	642

Table 2. (Continued)

Table 2A (Continued)

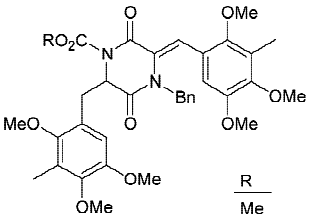
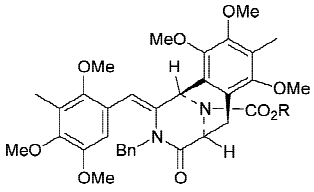
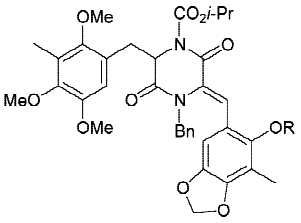
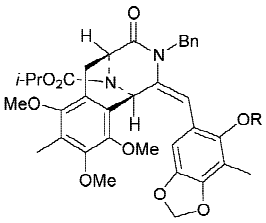
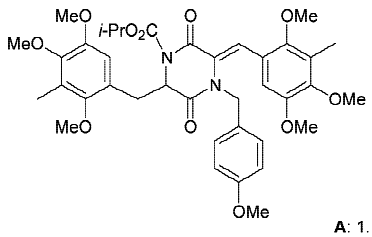
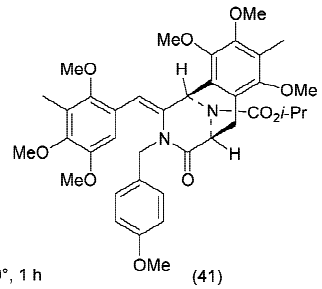
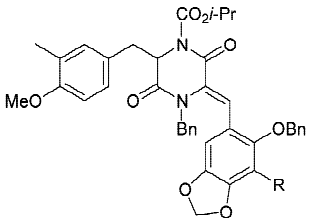
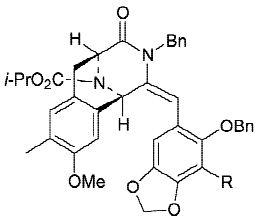
substrate	conditions	product(s) and yield(s) (%)	ref
$C_{35\text{-}41}$  R: Me, *i*-Pr, *i*-Bu, Bn	1. LiAlH(OBu-*t*)$_3$, THF, 0°, 1 h, 2. HCO_2H, 60°, 1 h	 (64), (60), (60), (58)	415, 416
$C_{36\text{-}42}$ 			424
R: $MeOCH_2$	1. LiAlH(OBu-*t*)$_3$, THF, 0°, 1 h 2. HCO_2H, 60°, 1 h or HCl, *i*-PrOH, reflux, 1 h	(0)	
Me	1. LiAlH(OBu-*t*)$_3$, THF, 0°, 1 h **A**: 2. HCO_2H, 70°, 16 h	(16)	
	B: 2. Ms_2O, CH_2Cl_2, rt, 48 h	(71)	
Bn	1. LiAlH(OBu-*t*)$_3$, THF, 0°, 1 h 2. MsCl, Et_3N, CH_2Cl_2, reflux, 17 h	(58)	
C_{38} 			424
	A: 1. LiAlH(OBu-*t*)$_3$, THF, 0°, 1 h 2. HCO_2H, 60°, 1 h	(41)	
	B: 1. LiAlH(OBu-*t*)$_3$, THF, 0°, 1 h 2. MsCl, Et_3N, CH_2Cl_2, reflux, 20 h	(70)	
$C_{39\text{-}40}$  R: H, Me			424
H	1. LiAlH(OBu-*t*)$_3$, THF, 0°, 1 h 2. HCO_2H, 70°, 2 h	(63)	
Me	1. LiAlH(OBu-*t*)$_3$, THF, 0°, 1 h **A**: 2. HCO_2H, 70°, 2 h	(14)	
	B: 2. Ms_2O, CH_2Cl_2, rt, 72 h	(36)	
	C: 2. MsCl, Et_3N, CH_2Cl_2, reflux, 38 h	(7)	

Table 2. (Continued)

Table 2B. Unimolecular Reactions with Benzenoids: Amides, Imides, Carbamates, and Ureas

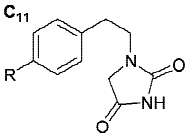
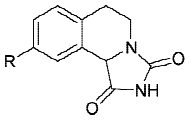
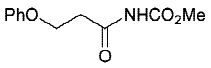
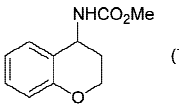
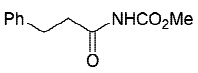
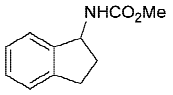
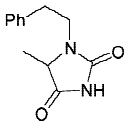
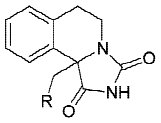
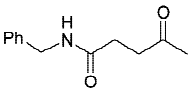
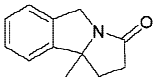
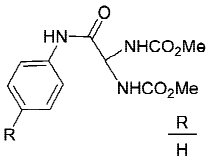
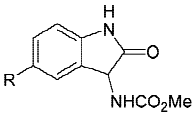
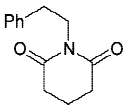
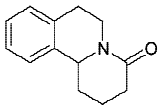
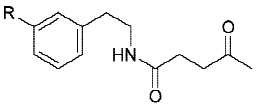
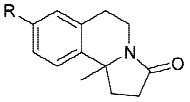
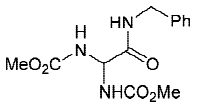
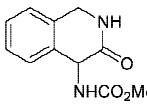
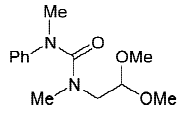
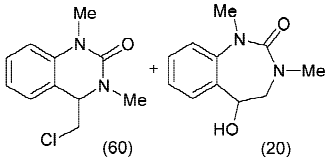
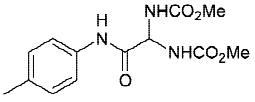
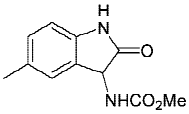
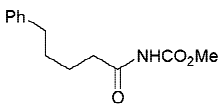
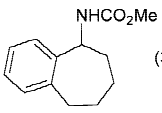
substrate	conditions	product(s) and yield(s) (%)	ref
C_{11} 	1. Br_2, HOAc, 55-95° 2. $SnCl_4$, 0°, 2 h	 R: H (30), Cl (66)	400
	1. DIBAL-H, CH_2Cl_2, –78°, 2 h 2. BF_3•Et_2O, CH_2Cl_2, –78°, 40 min	 (76)	625
	1. DIBAL-H, CH_2Cl_2, –78°, 2h 2. $TiCl_4$, CH_2Cl_2, –78°, 4 h	 (0)	625
C_{12} 	**A**: Br_2, HBr, AcOH, Ac_2O, 60-70°, 84 h **B**: HBr, AcOH, Ac_2O, 55°, 24 h; 70°, 24 h	 R: H (83), Br (56)	403
	PPA, 135°, 2 h	 (0)	354
 R: H; Cl	**A**: TFA, rt, 72 h **B**: MsOH, toluene, 0°-rt, 24 h MsOH, 0°-rt, 24 h	 (67) (59) (98)	377 386
C_{13} 	1. $NaBH_4$, EtOH, H^+ 2. PPA, 100°, 6 h	 (38)	116
	PPA, 135°, 2 h	 R: H (71), Cl (84)	354
	MsOH, 0°-rt, 24 h	 (84)	377 386
	HCl, reflux, 10 min	 (60) + (20)	387
	TFA, rt, 24 h	 (95)	377 386
	1. DIBAL-H, CH_2Cl_2, –78°, 2 h 2. $TiCl_4$, CH_2Cl_2, –78°, 2 h	 (38)	625

Table 2. (Continued)

Table 2B (Continued)

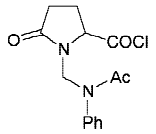
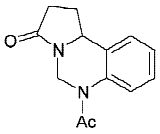
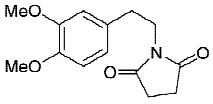
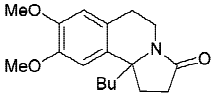
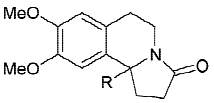
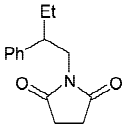
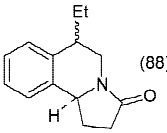
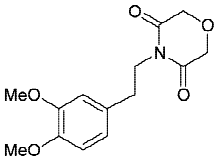
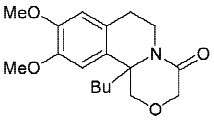
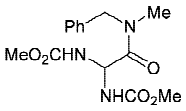
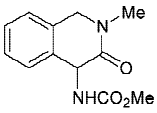
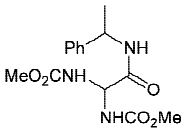
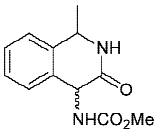
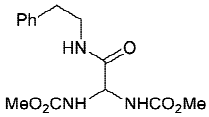
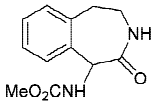
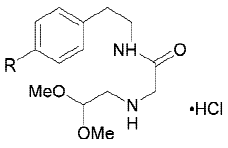
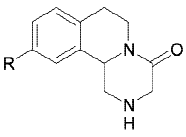
substrate	conditions	product(s) and yield(s) (%)	ref
C_{14}			
	$AlCl_3$, CH_2Cl_2, reflux	 (49)	337
	THF, –78°, 6 h		291
	A: 1. BuLi (1.1 eq) 2. HCl (12 M)	(26)	
	B: 1. BuLi (2.2 eq) 2. HCl (12 M)	(40)	
	C: 1. BuLi (2.2 eq) 2. TFA, rt	(92)	
	1. RLi, THF, –78°, 6 h 2. TFA		291
	CH_2Cl_2, rt, 4 h	R = Me (98)	
	$CHCl_3$, reflux, 120 h	R = *s*-Bu (93)	
	CH_2Cl_2, reflux, 36 h	R = Ph (98)	
	CH_2Cl_2, reflux, 6 h	R = CH_2=$CHCH_2$ (97)	
	1. $NaBH_4$, MsOH, EtOH 2. PPA, 100°, 6 h	 (88), α:β = 39:61	114
	1. BuLi, THF, -78°, 6 h 2. TFA, CH_2Cl_2, rt, overnight	 (93)	291
	MsOH, 0°-rt, 24 h	 (98)	377
	MsOH, 0°-rt, 6 h	 (83)	377 386
			377 386
	A: MsOH, 0°-rt, 72 h	(67)	
	B: MsOH, toluene, 0°-rt, 24 h	(76)	
	H_2SO_4, 5°-rt, 3.5 h	 R = H (96), Br (91)	408

Table 2. (Continued)

Table 2B (Continued)

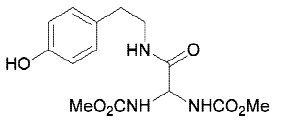
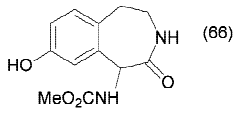
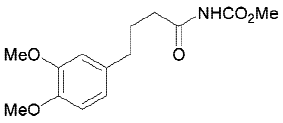
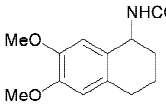
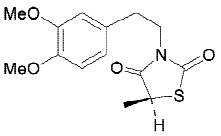
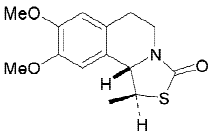
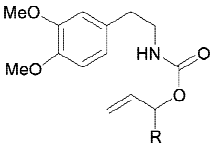
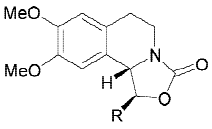
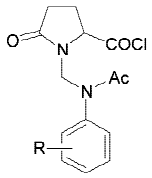
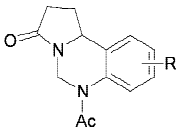
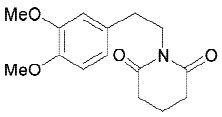
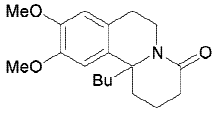
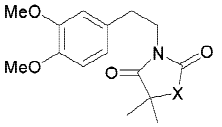
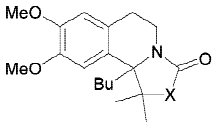
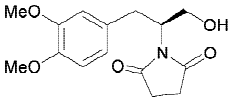
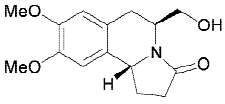
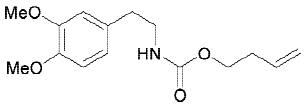
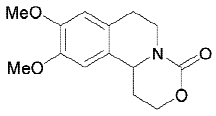
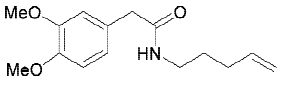
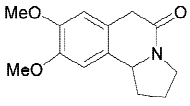
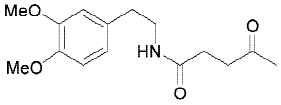
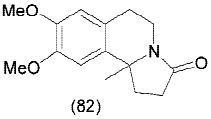
substrate	conditions	product(s) and yield(s) (%)	ref
	TFA, 0°-rt, 72 h	 (66)	377
	1. DIBAL-H, CH_2Cl_2, –78°, 2 h 2. $TiCl_4$, CH_2Cl_2, –78°, 15 min	 (79)	625
	1. $NaBH_4$, CH_2Cl_2/MeOH, –40° to –20°, 5 h 2. BF_3•Et_2O, CH_2Cl_2, 0°-rt, 3 days	 (89)	432 433
C_{14-17}			
	1. O_3, CH_2Cl_2, –78° 2. Me_2S 3. HCO_2H, rt, 14 h	 R: H (75), Me (73), Et (75), Pr (73)	404
C_{15}			
 R: 2-OMe	$SnCl_4$, CH_2Cl_2, reflux	 (17)	337
3-OMe	$AlCl_3$, CH_2Cl_2, reflux	(23)	
4-OMe	$AlCl_3$, CH_2Cl_2, reflux	(38)	
3-OMe	TFA, TFAA, CH_2Cl_2, reflux	(37)	
3-Me	$AlCl_3$, CH_2Cl_2, reflux	(32)	
	1. BuLi, THF, –78°, 6 h 2. TFA, CH_2Cl_2, rt, overnight	 (94)	291
	1. BuLi, THF, –78°, 6 h 2. TFA, CH_2Cl_2, rt, overnight	 X: O (94), S (95)	291
	1. $NaBH_4$, EtOH, 0° 2. HCl, EtOH, rt, 20 h	 (91)	627
	1. O_3, CH_2Cl_2, –78° 2. Me_2S 3. HCO_2H, rt, 14 h	 (70)	404
	1. O_3, CH_2Cl_2, –78° 2. Me_2S 3. HCO_2H, rt, 14 h	 (65)	404
	**A**: H_3PO_4, 100°, 1 h **B**: HCl, THF, rt, 16 h	 (82) (70)	354 643

Table 2. (Continued)

Table 2B (Continued)

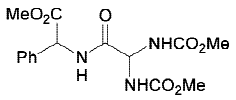
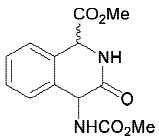
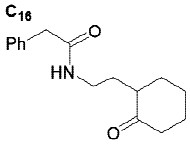
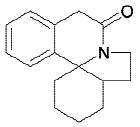
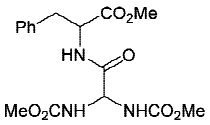
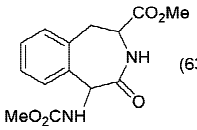
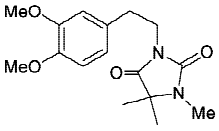
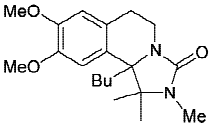
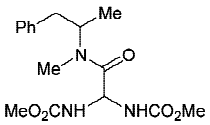
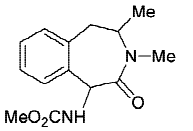
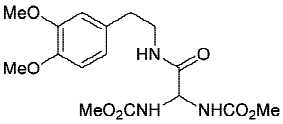
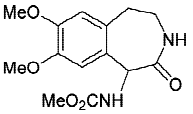
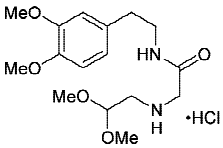
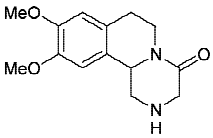
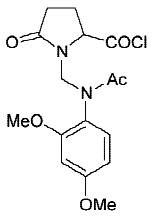
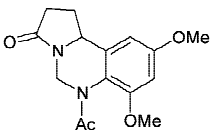
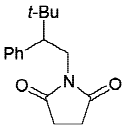
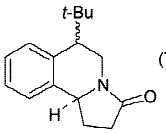
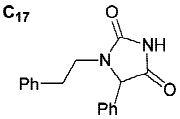
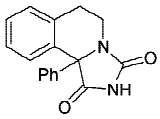
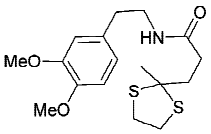
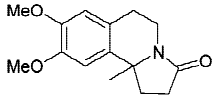
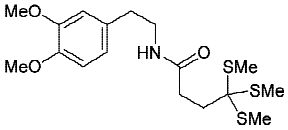
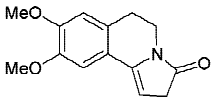
substrate	conditions	product(s) and yield(s) (%)	ref
	MsOH, rt	 (85)	386
C_{16} 	PPA, 100°, 24 h	 (60)	21 23
	H_2SO_4, 0°-rt, 72 h	 (63)	377
	1. BuLi, TMSCl, THF –78°, 6 h 2. TFA, $CHCl_3$, reflux	 (—)	291
	MsOH, 0°-rt, 72 h	 (70)	377
	TFA, 0°-rt, 48 h	 (65)	377 386
	H_2SO_4, 5°-rt, 3.5 h	 (93)	408
	$AlCl_3$, CH_2Cl_2, reflux	 (62)	337
	PPA, 100°, 6 h	 (74), α:β = 15:85	114
C_{17} 	1. Br_2, HOAc, 55-95° 2. $SnCl_4$, 0°, 2 h	 (90)	400
	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2, reflux	 (76)	345
	Me_2SO_4, CH_2Cl_2, reflux	 (46)	345

Table 2. (Continued)

Table 2B (Continued)

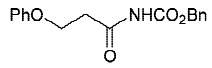
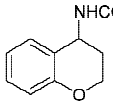
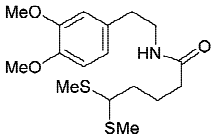
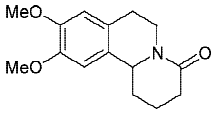
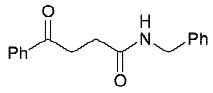
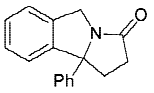
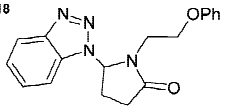
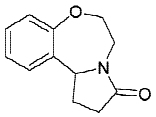
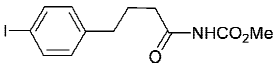
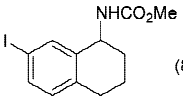
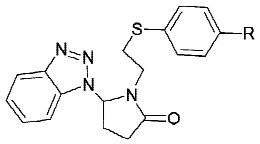
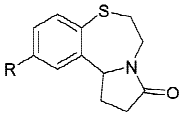
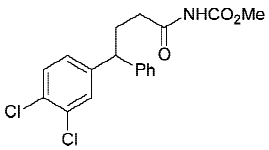
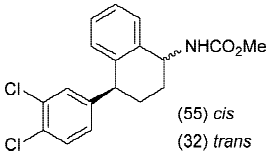
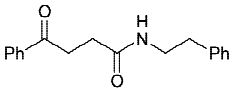
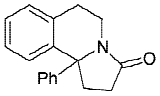
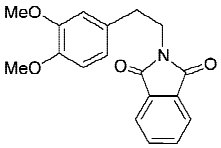
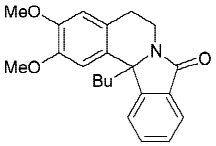
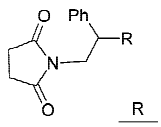
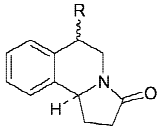
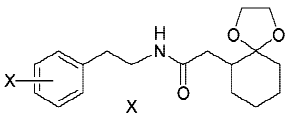
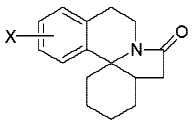
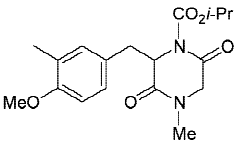
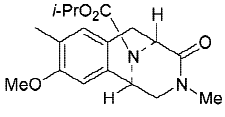
substrate	conditions	product(s) and yield(s) (%)	ref
	1. DIBAL-H, CH_2Cl_2, –78°, 2 h 2. BF_3•Et_2O, CH_2Cl_2, –78°, 40 min	 (86)	625
	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2, reflux	 (100)	343
	PPA, 100°, 50 min	 (0)	354
C_{18} 	$TiCl_4$, CH_2Cl_2, rt, 72 h	 (72)	644
	1. DIBAL-H, CH_2Cl_2, –78°, 2 h 2. $TiCl_4$, CH_2Cl_2, –78°, 2 h	 (84)	625
	$TiCl_4$, rt, 48 h	 R H (81) Cl (67)	644
	1. DIBAL-H, CH_2Cl_2, –78°, 2 h 2. $TiCl_4$, CH_2Cl_2, –78°, 1 h	 (55) *cis* (32) *trans*	625
	PPA, 100°, 50 min	 (45)	354
	1. BuLi, THF, –78°, 6 h 2. TFA, CH_2Cl_2, rt, overnight	 (95)	291
 R Ph C_6H_{11}	1. $NaBH_4$, MsOH, EtOH, –5 to 0° 2. PPA, 100°, 6 h	 (84), α:β = 93:7 (91), α:β = 12:88	45 114
 X 4-F 3-F	PPA, 135°, 12 h PPA, 130°, 12 h	 (46) (40)	66
	1. $LiAlH(OBu\text{-}t)_3$, THF, 0°, 1 h 2. HCO_2H, 70°, 40 min	 (85)	420

Table 2. (Continued)

Table 2B (Continued)

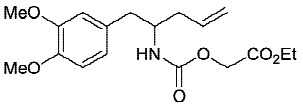
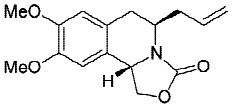
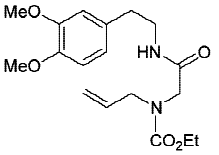
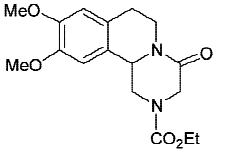
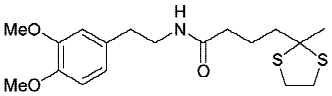
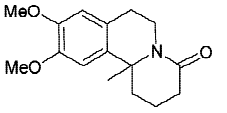
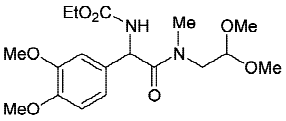
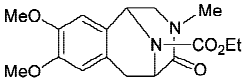
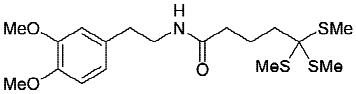
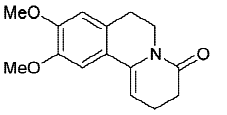
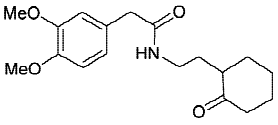
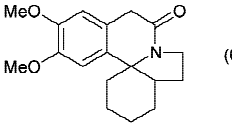
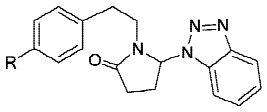
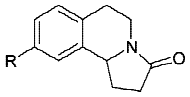
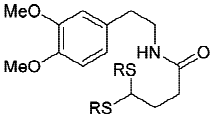
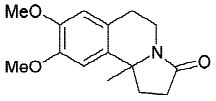
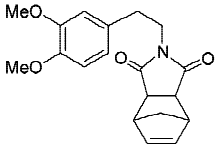
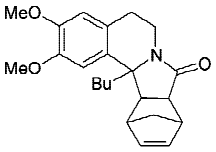
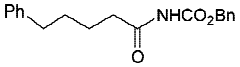
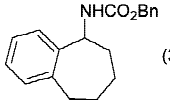
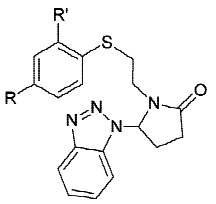
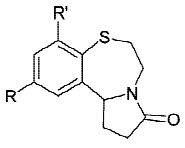
substrate	conditions	product(s) and yield(s) (%)	ref
	1. DIBAL-H, toluene, −78°, 40 min 2. HCO_2H, rt, 14 h	 (63)	368
	1) O_3, CH_2Cl_2, −78° 2) Me_2S 3) HCO_2H, 14 h, rt	 (45)	404
	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2, reflux	 (75)	345
	HCl, MeCN	 (—)	49
	Me_2SO_4, CH_2Cl_2, reflux	 (71)	345
	PPA, 100°, 24 h	 (60)	21 23
C_{18-19} 	$TiCl_4$, toluene, reflux, 24 h	 R: H (75), OMe (80)	645
C_{18-26}  R: Et, Ph	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2, rt	 (98), (64)	345
C_{19} 	1. BuLi 2. TFA	 (—)	353
	1. DIBAL-H, CH_2Cl_2, −78°, 2 h 2. $TiCl_4$, CH_2Cl_2, −78°, 2 h	 (39)	625
	$TiCl_4$, rt, 48 h	 R: Me, R': H (84); R: H, R': Me (80)	644

Table 2. (Continued)

Table 2B (Continued)

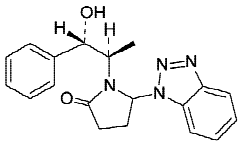
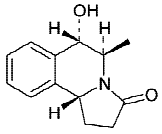
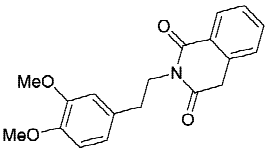
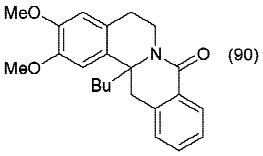
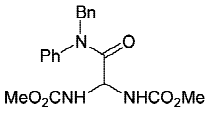
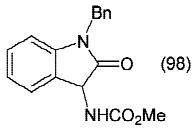
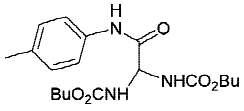
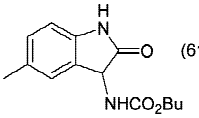
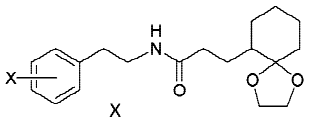
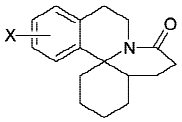
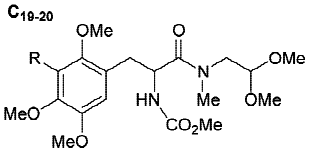
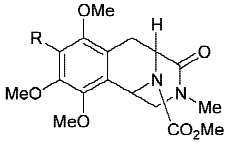
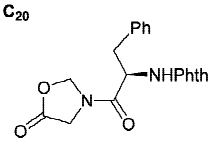
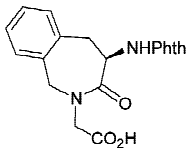
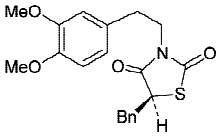
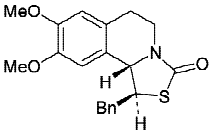
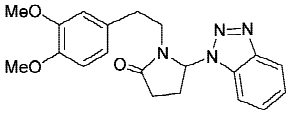
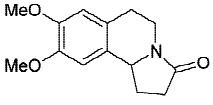
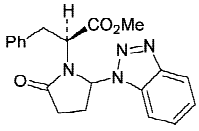
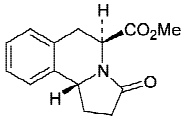
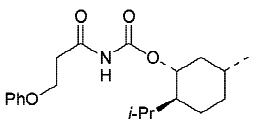
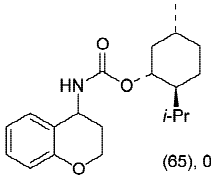
substrate	conditions	product(s) and yield(s) (%)	ref
	$TiCl_4$, toluene, reflux, 24 h	 (40)	645
	1. BuLi, TMSCl, THF, –78°, 6 h 2. TFA, $CHCl_3$, reflux	 (90)	291
	MsOH, 0°-rt, 24 h	 (98)	377
	TFA, rt, 24 h	 (61)	377
 X 4-F H	 PPA, 132°, 12 h PPA, 120°, 12 h	 (11) (25)	66
C_{19-20} 	TFA, reflux, 1.5 h	 R H (91) Me (96)	411
C_{20} 	TfOH, rt, overnight	 (57)	379
	1. $NaBH_4$, CH_2Cl_2/MeOH, –40° to –20°, 5 h 2. BF_3•Et_2O, CH_2Cl_2, 0°-rt, 3 days	 (71)	432 433
	$TiCl_4$, toluene, reflux, 24 h	 (92)	645
	$TiCl_4$, toluene, reflux, 24 h	 (83)	645
	1. DIBAL-H, CH_2Cl_2, –78°, 2 h 2. BF_3•Et_2O, CH_2Cl_2, –78°	 (65), 0% de	625

Table 2. (Continued)

Table 2B (Continued)

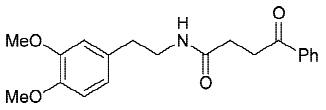
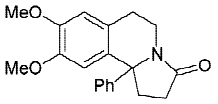
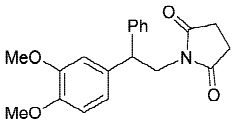
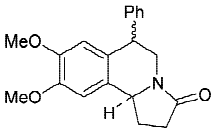
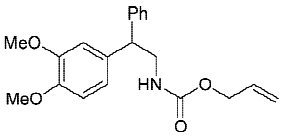
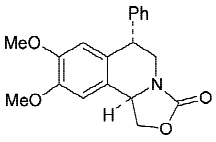
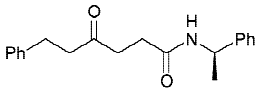
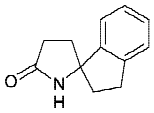
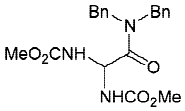
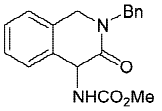
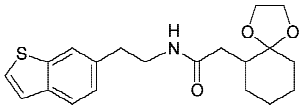
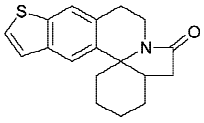
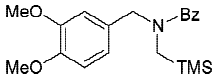
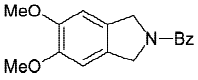
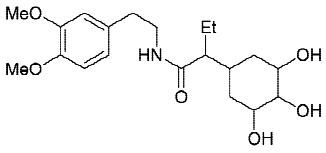
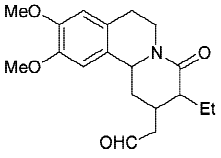
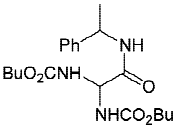
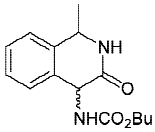
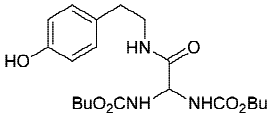
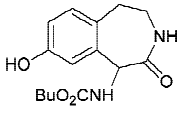
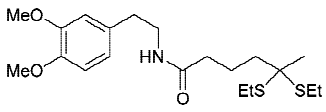
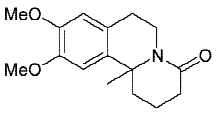
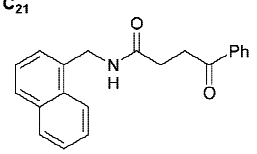
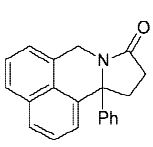
substrate	conditions	product(s) and yield(s) (%)	ref
	H_3PO_4, 100°, 1 h	 (82)	354
	1. $NaBH_4$, MsOH, EtOH, -5 to 0° 2. HCl, EtOH, reflux, 30 min	 (90), α:β = 90:10	45 67
	1. O_3, CH_2Cl_2, –78° 2. Me_2S 3. HCO_2H, rt, 14 h	 (75)	404
	TFA, reflux	 (—)	374
	MsOH, 0°-rt, 24 h	 (70)	377
	HCl, EtOH, rt, 6 days	 (31)	66
	$Ce(NH_4)_2(NO_3)_6$, MeCN, rt	 (7)	330
	1. HIO_4 2. H_3PO_4, reflux	 (—)	34
	MsOH, 0°-rt, 24 h	 (63)	377
	Cl_2CHCO_2H, 0°-rt, 48 h	 (41)	377
	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2, reflux	 (78)	345
C_{21} 	TFA, reflux, 5 h	 (62)	373

Table 2. (Continued)

Table 2B (Continued)

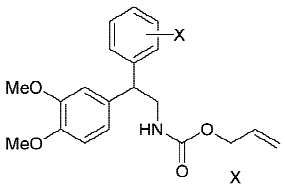
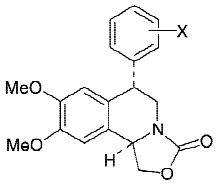
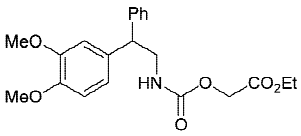
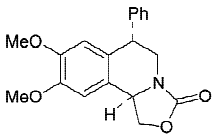
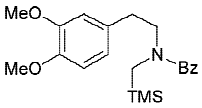
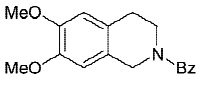
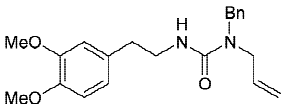
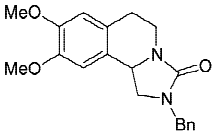
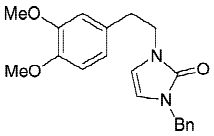
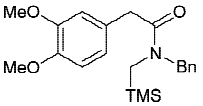
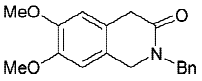
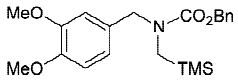
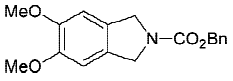
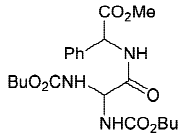
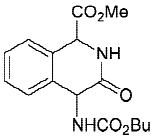
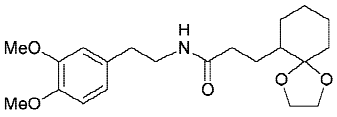
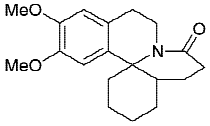
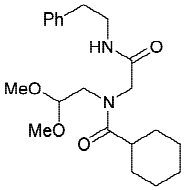
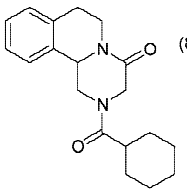
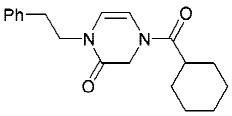
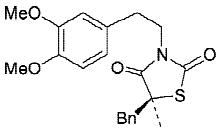
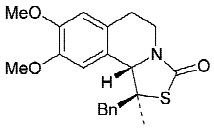
substrate	conditions	product(s) and yield(s) (%)	ref
 X = 2-OMe; 4-Me	1. O_3, CH_2Cl_2, –78° 2. Me_2S 3. HCO_2H, rt, 14 h	 (73); (73)	404
	1. DIBAL-H, toluene, –78°, 40 min 2. HCO_2H, rt, 14 h	 (72)	368
	$Ce(NH_4)_2(NO_3)_6$, MeCN, rt	 (60)	330
	1. O_3, CH_2Cl_2, –78° 2. Me_2S 3. HCO_2H, rt, 14 h	 (3) +  (65)	404
	$Ce(NH_4)_2(NO_3)_6$, MeCN, rt	 (50)	330
	$Ce(NH_4)_2(NO_3)_6$, MeCN, rt	 (13)	330
	MsOH, 0°-rt, 24 h	 (63)	377
	PPA, 100°, 5 h	 (29)	66
	TfOH, CH_2Cl_2, reflux, 6 h	 (85)	409
	TfOH, CH_2Cl_2, rt	 (95)	409
	1. $NaBH_4$, CH_2Cl_2/MeOH, –40° to –20°, 5 h 2. BF_3•Et_2O, CH_2Cl_2, 0°-rt 3 days	 (92)	432 433

Table 2. (Continued)

Table 2B (Continued)

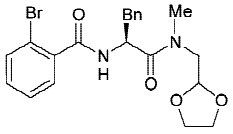
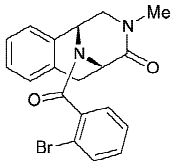
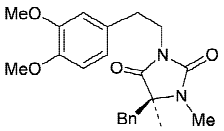
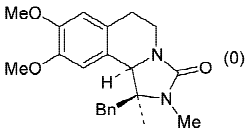
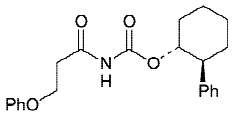
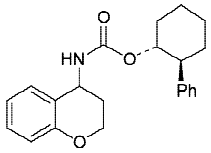
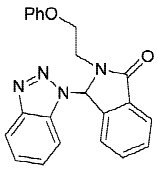
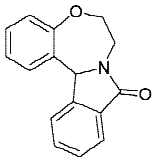
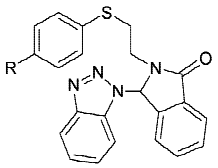
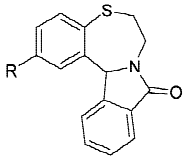
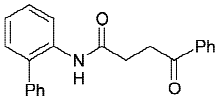
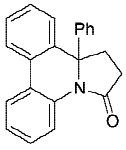
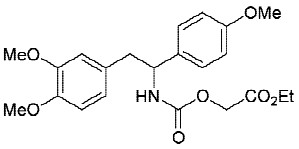
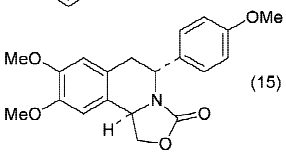
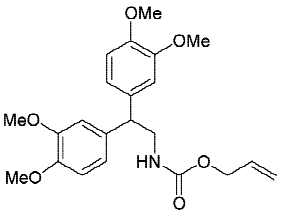
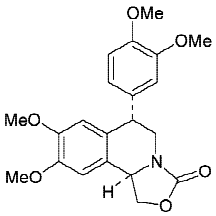
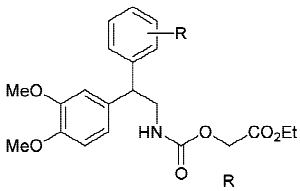
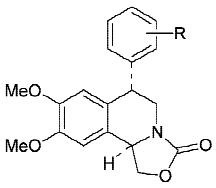
substrate	conditions	product(s) and yield(s) (%)	ref
	MsOH, $MeNO_2$, 60°, 16 h	 (87)	646
C_{22}			
	1. $LiAlH_4$ 2. $BF_3•Et_2O$	 (0)	433
	1. DIBAL-H, CH_2Cl_2, −78°, 2 h **A**: 2. $BF_3•Et_2O$, CH_2Cl_2, −78° **B**: 2. $TiCl_4$, CH_2Cl_2, −78°	 (70), 40% de (70), 11% de	625
	$TiCl_4$, CH_2Cl_2, rt, 48 h	 (89)	644
	$TiCl_4$, rt, 48 h	 R: H (86), Cl (94)	644
	PPA, 200°, 0.75 h	 (62)	373
	1. DIBAL-H, toluene, −78°, 40 min 2. HCO_2H, rt, 14 h	 (15)	368
	1. O_3, CH_2Cl_2, −78° 2. Me_2S 3. HCO_2H, rt, 14 h	 (75)	404
 R: 4-OMe, 2-OMe, 4-Me	1. DIBAL-H, toluene, −78°, 40 min 2. HCO_2H, rt, 14 h	 (70) (65) (70)	368

Table 2. (Continued)

Table 2B (Continued)

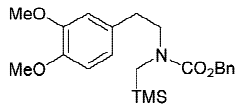
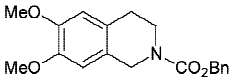
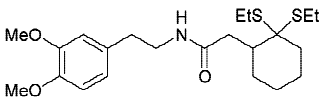
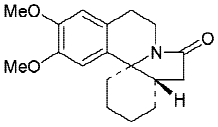
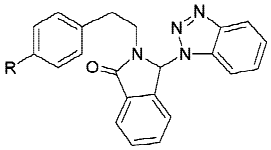
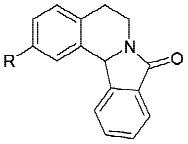
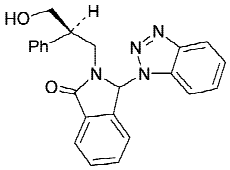
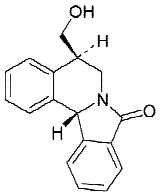
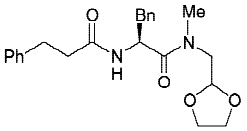
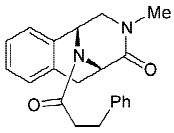
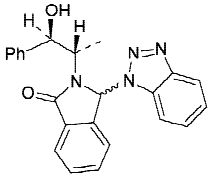
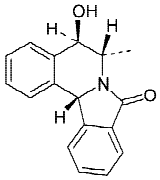
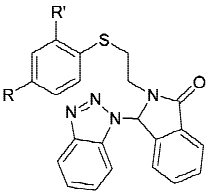
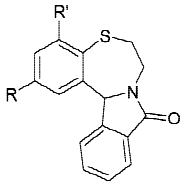
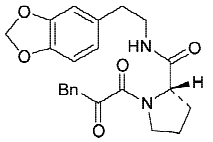
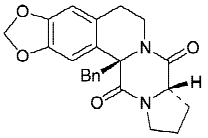
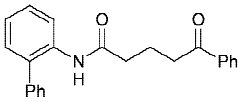
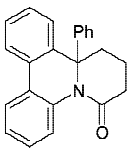
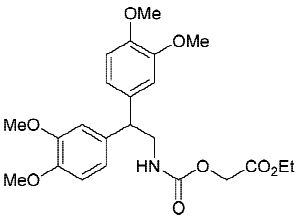
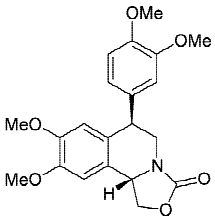
substrate	conditions	product(s) and yield(s) (%)	ref
	$Ce(NH_4)_2(NO_3)_6$, MeCN, rt	 (60)	330
	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2, reflux	 (71)	345
C_{22-23}			
	$TiCl_4$, toluene, reflux, 24 h	 R: H (50), OMe (65)	645
C_{23}			
	$TiCl_4$, toluene, reflux, 24 h	 (60)	645
	MsOH, $MeNO_2$, 60°, 16 h	 (67)	646
	$TiCl_4$, toluene, reflux, 24 h	 (65)	645
	$TiCl_4$, rt, 48 h	 R R': Me H (96), H Me (91)	644
	HCl, MeOH	 $(-)^{\kappa}$	639
	PPA, 150-170°, 75 min	 (35)	373
	1. DIBAL-H, toluene, –78°, 40 min 2. HCO_2H, rt, 14 h	 (70)	368

Table 2. (Continued)

Table 2B (Continued)

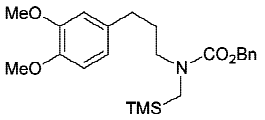
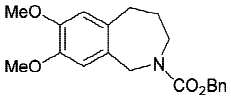
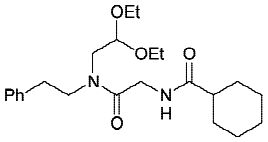
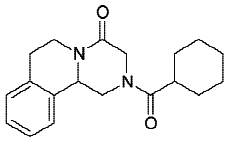
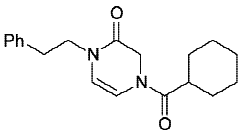
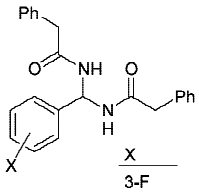
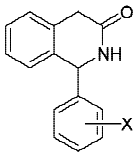
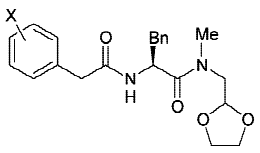
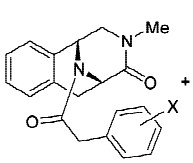
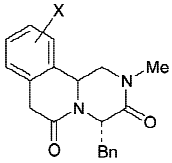
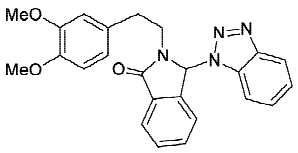
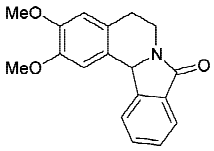
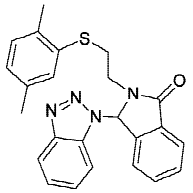
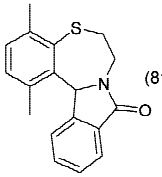
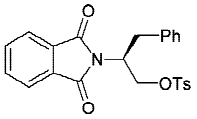
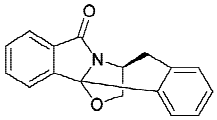
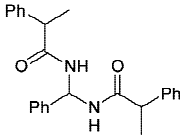
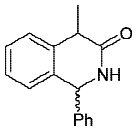
substrate	conditions	product(s) and yield(s) (%)	ref
	$Ce(NH_4)_2(NO_3)_6$, MeCN, rt	 (71)	330
	TfOH, CH_2Cl_2, reflux, 2 days	 (73)	409
	TfOH, CH_2Cl_2, rt	 (91)	409
C_{23-24} 	PPA		608
X			
3-F	100°, 0.5 h	(70)	
2-NO_2	70°, 6 h	(60)	
4-NO_2	25°, 72 h	(78)	
3-CF_3	100°, 0.5 h	(62)	
2-Me	40°, 6 h	(65)	
3-Me	60°, 3 h	(72)	
C_{23-27} 	MsOH, $MeNO_2$, 60°, 16 h	 + 	646
X			
H		(75) (0)	
4-NO_2		(72) (0)	
2-Br		(79) (0)	
3-MeO		(61) (11)	
3,4,5-$(MeO)_3$		(9) (18)	
C_{24} 	$TiCl_4$, toluene, reflux, 24 h	 (75)	645
	$TiCl_4$, rt, 48 h	 (81)	644
	$KPPh_2$, THF, 65-70°, overnight	 (72)	434
C_{25} 	PPA	 (81)	608

Table 2. (Continued)

Table 2B (Continued)

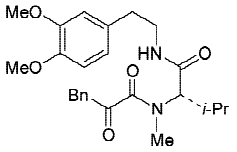
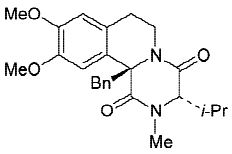
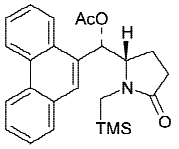
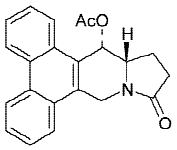
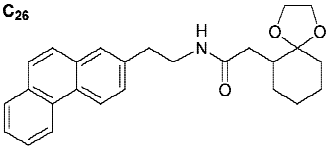
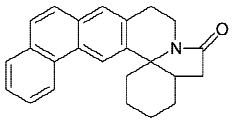
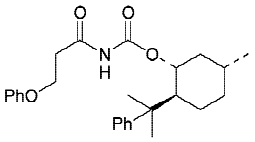
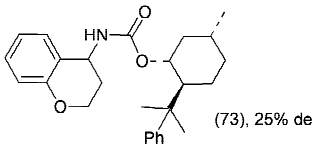
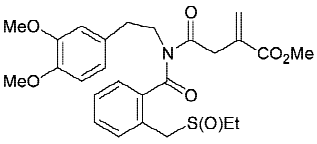
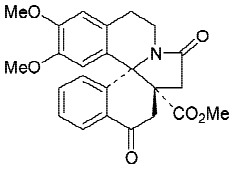
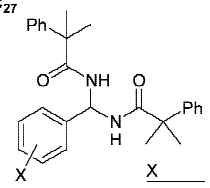
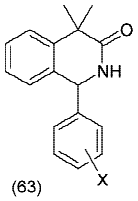
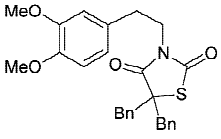
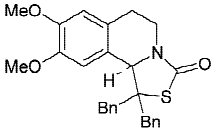
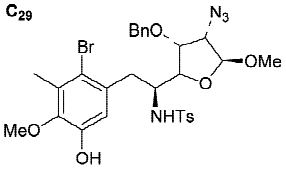
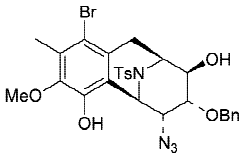
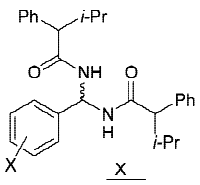
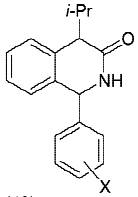
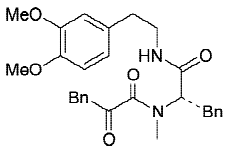
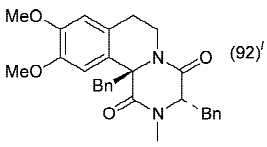
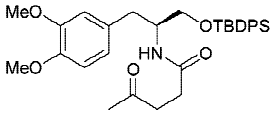
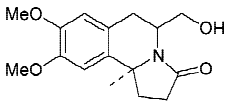
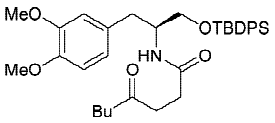
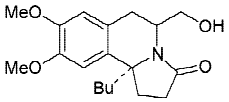
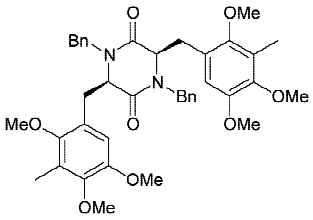
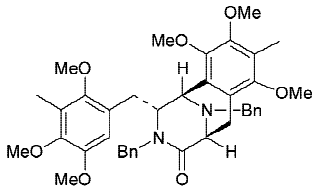
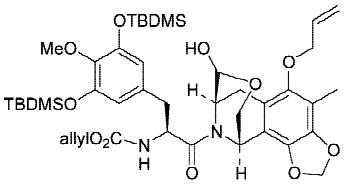
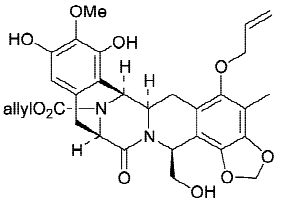
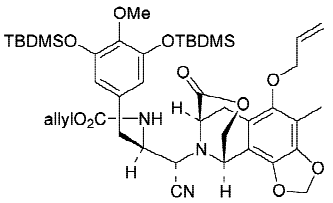
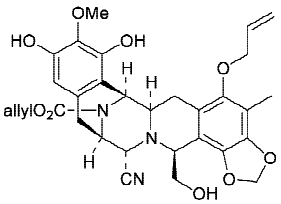
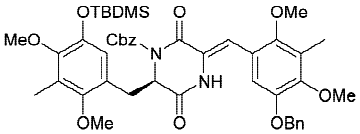
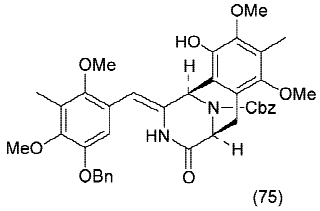
substrate	conditions	product(s) and yield(s) (%)	ref
	HCl, MeOH	 (89)	639
	$Ce(NH_4)_2(NO_3)_6$, MeCN, rt	 (64)	330
C_{26} 	PPA, 100°, 14 h	 (27)	66
	1. DIBAL-H, CH_2Cl_2, –78°, 2 h 2. BF_3•Et_2O, CH_2Cl_2, –78°	 (73), 25% de	625
	1. Ac_2O, TsOH 2. TsOH, reflux	 (65-70)	85 87
C_{27} 	PPA		608
X: H	45°, 3 h	(63)	
X: 2-NO_2	80°, 5 h	(55)	
X: 4-NO_2	40°, 3.5 h	(77)	
	1. $NaBH_4$, CH_2Cl_2/MeOH, –40° to –20°, 5 h 2. BF_3•Et_2O, CH_2Cl_2, 0°-rt 3 days	 (98)	433
C_{29} 	TFA, H_2O, 70°	 (88)	418
	PPA		608
X: H	40°, 3 h	(46)	
X: 4-NO_2	40°, 8 h	(46)	

Table 2. (Continued)

Table 2B (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
	HCl, MeOH	 (92)[f]	639
C_{32}			
	BF_3•Et_2O, CH_2Cl_2, reflux	 (36), 99% ee	647
C_{35}			
	BF_3•Et_2O, CH_2Cl_2, reflux	 (34), 99% ee	647
C_{40}			
	1. $LiAl(OEt)_2H_2$, THF, 0°, 1.5 h 2. TFA, reflux, 36 h	 (73)	426
	1. KF, MeOH, rt, 0.5 h 2. TfOH, CF_3CH_2OH, H_2O, 45°, 7 h	 (87)	425
C_{43}			
	1. DIBAL-H, –78° 2. KF•$2H_2O$ 3. MsOH, MS	 (55)	417
C_{45}			
	1. $NaBH_4$, AcOH, EtOH, –25° 2. HCO_2H, rt 3. Bu_4NF, THF, rt	 (75)	413

[a] An unsaturated cyclized product (5%) was also formed. [b] The compound was a 10:1 mixture of diastereomers. [c] No yields were reported; just product ratios. [d] The compound was a mixture of diastereomers. [e] The compound was a 5:2:1:1 mixture of diastereomers. [f] The compound was a 6:2:3:8 mixture of diastereomers. [g] The compound was a 5.1:4.9 mixture of diastereomers. [h] The compound was a 2:1 mixture of diastereomers. [i] The compound was a 3:1 mixture of diastereomers. [j] The compound was a 4:1 mixture of diastereomers. [k] The compound was a 92:8 mixture of diastereomers. [l] The compound was a 89:11 mixture of diastereomers.

Table 3. Unimolecular Reactions with Furans and Thiophenes

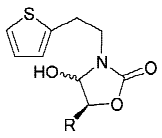
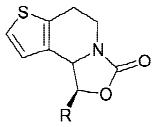
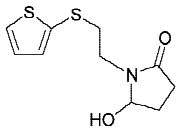
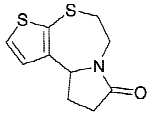
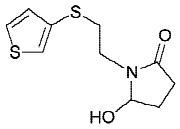
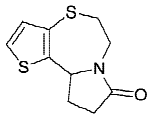
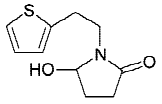
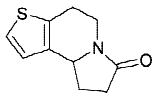
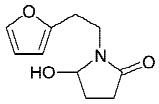
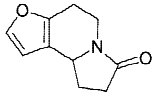
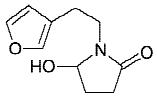
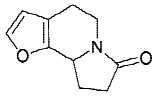
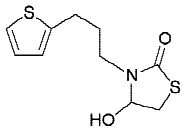
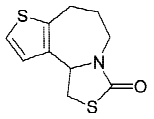
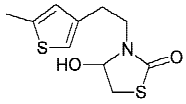
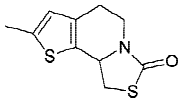
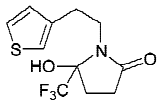
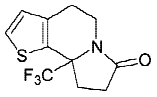
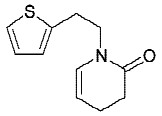
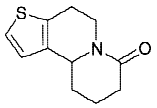
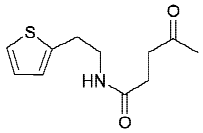
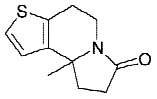
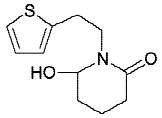
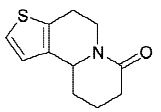
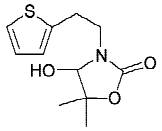
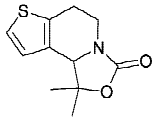
	substrate	conditions	product(s) and yield(s) (%)	ref
C_{9-10}		HCO_2H, rt, 14 h	 R: H (65), Me (68)	120
C_{10}		HCO_2H, 25°, 14 h	 (38)	440
		HCO_2H, 25°, 14 h	 (44)	440
		HCO_2H, 25°	 (50-55)	440
		HCO_2H, C_6H_{12}, 3 min	 (70)	436
		HCO_2H, C_6H_{12}, 3 min	 (66)	436
		TFA, reflux, 3 h	 (67)	441
		HCO_2H, 25°	 (74)	442
C_{11}				358
		TFA, 1.5 days	(77)	
		TfOH, CH_2Cl_2, 1 days	(33)	
		HCO_2H, 25°	 (50-55)	440
		H_3PO_4 (85%), 100°, 40 min	 (68)	354
		HCO_2H, rt	 (50-55)	440
		HCO_2H, rt, 14 h	 (63)	119

Table 3. (Continued)

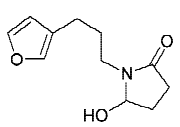
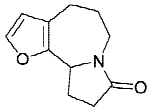
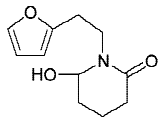
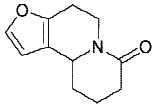
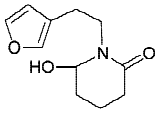
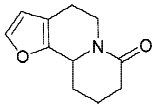
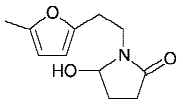
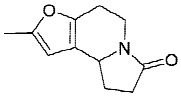
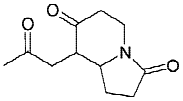
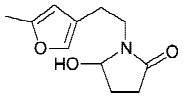
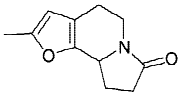
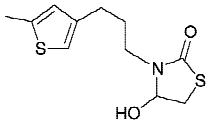
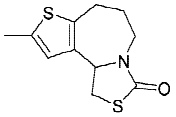
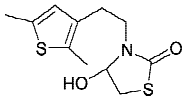
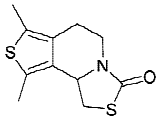
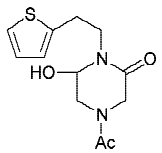
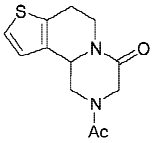
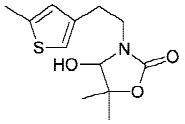
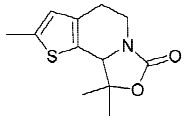
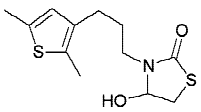
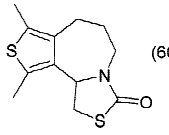
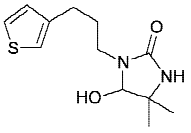
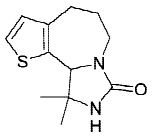
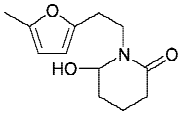
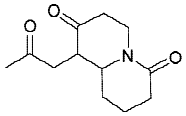
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, C_6H_{12}, 3 min	 (71)	436
	HCO_2H, C_6H_{12}, 3 min	 (71)	436
	HCO_2H, C_6H_{12}, 3 min	 (50)	436
	MsCl, CH_2Cl_2, rt	 (81)	436
	HCO_2H, C_6H_{12}, 3 min	 (75)	436
	HCO_2H, C_6H_{12}, 3 min	 (87)	436
	HCO_2H, 60°, 14 h	 (63)	442
	HCO_2H, 60°, 14 h	 (70)	442
C_{12} 	HCl, 0°, 18 h	 (87)	438
	HCO_2H, 60°, 14 h	 (68)	442
	HCO_2H, 60°, 14 h	 (60)	442
	TFA, reflux, 3 h	 (65)	441
	HCO_2H, C_6H_{12}, 3 min	 (64)	436

Table 3. (Continued)

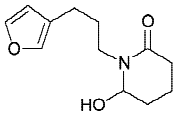
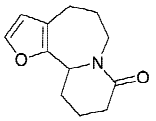
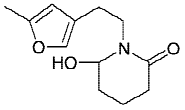
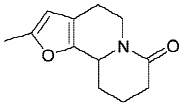
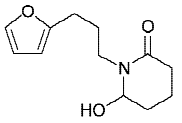
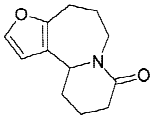
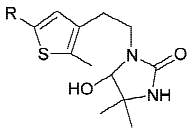
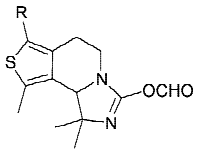
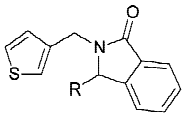
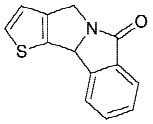
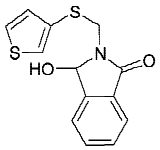
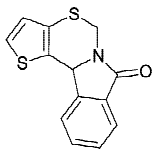
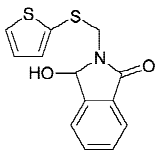
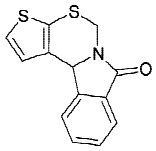
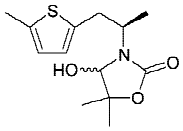
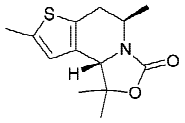
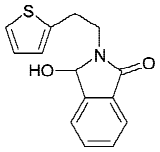
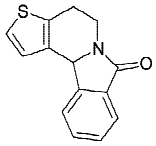
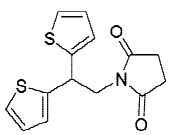
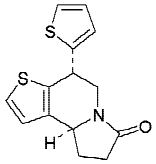
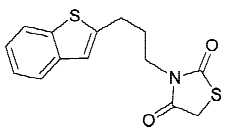
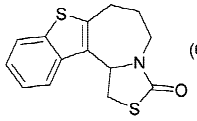
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, C_6H_{12}, 3 min	 (67)	436
	HCO_2H, C_6H_{12}, 3 min	 (48)	436
	HCO_2H, C_6H_{12}, 3 min	 (55)	436
C_{12-13}			
	HCO_2H, 60°, 14 h	 R: H (58), Me (55)	442
C_{13}			
			370
R: Cl	$SnCl_4$	(—)	
R: OH	TFA, rt, overnight	(58)	
	TFA, rt, overnight	 (64)	443
	TFA, rt, overnight	 (72)	443
	HCO_2H, rt, 14 h	 (68)	119
C_{14}			
	$SOCl_2$, CH_2Cl_2, rt, 2 h	 (100)	370
	1. $NaBH_4$, MsOH, EtOH, –5 to 0° 2. HCl, EtOH, reflux, 30 min	 (83)	115
	1. DIBAL-H 2. TFA, reflux, 3 h	 (65)	441

Table 3. (Continued)

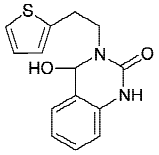
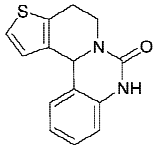
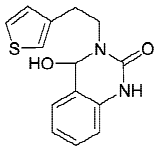
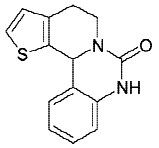
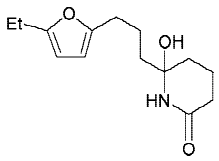
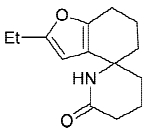
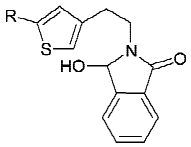
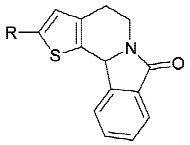
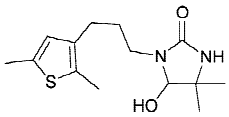
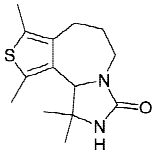
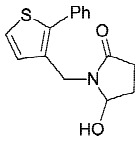
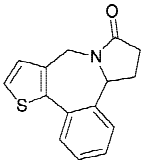
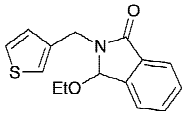
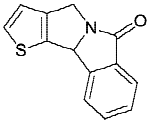
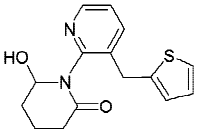
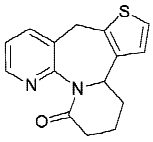
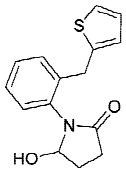
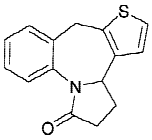
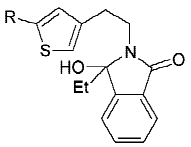
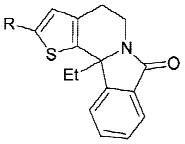
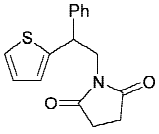
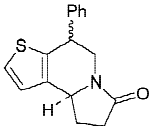
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 14 h	 (65)	406
	HCO_2H, rt, 14 h	 (60)	406
	HCO_2H	 (72)	435
	$SOCl_2$, CH_2Cl_2, rt, 2 h	 R: H (100), Cl (92)	370
	HCO_2H, 60°, 14 h	 (55)	442
C_{15}			
	TFA, CH_2Cl_2, rt, 24 h	 (80)	369
	$TiCl_4$	 (—)	370
	MsOH, rt, 2 h	 (31)	630
	MsOH, CH_2Cl_2, reflux	 (80)	631
C_{16}			
	$SOCl_2$, CH_2Cl_2, rt, 2 h	 R: H (81), Cl (75)	370
	1. $NaBH_4$, MsOH, EtOH, –5 to 0° 2. HCl, EtOH, reflux, 30 min	 (60), α:β = 96:4	45

Table 3. (Continued)

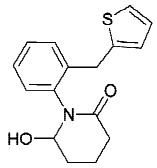
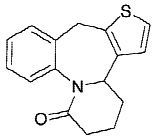
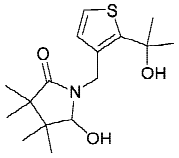
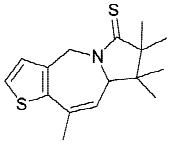
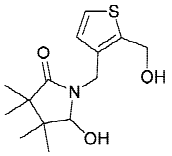
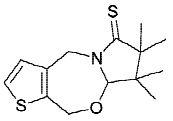
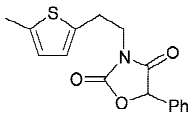
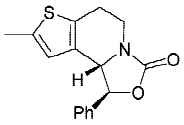
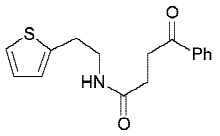
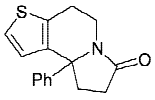
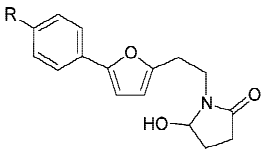
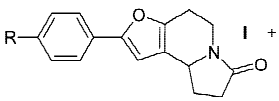
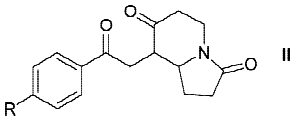
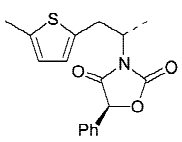
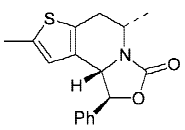
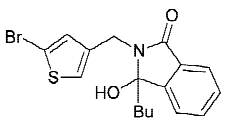
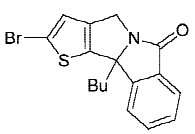
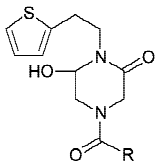
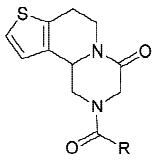
substrate	conditions	product(s) and yield(s) (%)	ref
	MsOH, CH_2Cl_2, reflux	 (99)	631
	TFA, CH_2Cl_2, rt TsOH, toluene, reflux	 (75) (73)	648
	TFA, CH_2Cl_2, rt TsOH, toluene, reflux	 (19) (70)	648
	1. DIBAL-H, toluene, −78°, 1 h 2. HCO_2H, rt, 14 h	 (80)	121
	H_3PO_4 (85%), 100°, 40 min	 (52)	354
C_{16-17}			
	HCO_2H, C_6H_{12}, 3 min	 I +  II R I II CF_3 (30) (34) H (28) (51) OMe (20) (62)	436
C_{17}			
	1. DIBAL-H, toluene, −78°, 1 h 2. HCO_2H, rt, 14 h	 (80)	121
	TsOH, toluene, reflux	 (0)	444
	HCl, 0°, 18 h	 R Ph (81) C_6H_{12} (85)	438

Table 3. (Continued)

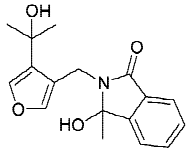
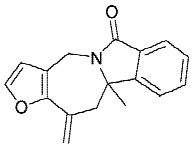
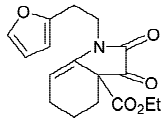
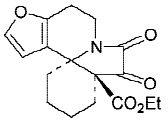
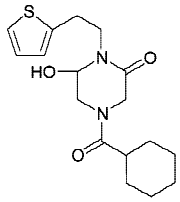
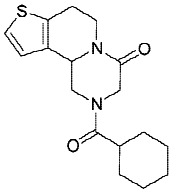
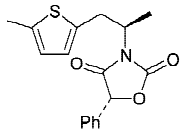
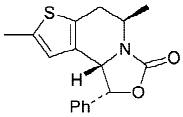
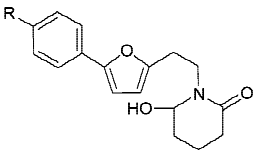
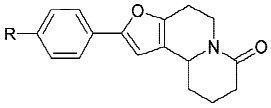
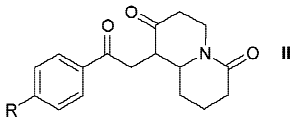
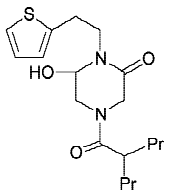
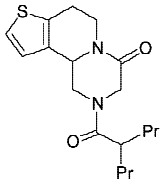
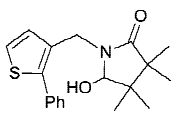
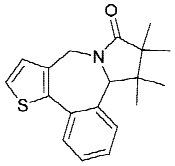
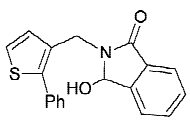
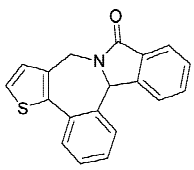
substrate	conditions	product(s) and yield(s) (%)	ref
	TsOH, toluene, reflux	 (55)	500
	PPE, 50°, 2 h	 (85)	80
	HCO_2H, rt	 (—)	440
	1. DIBAL-H, toluene, –78°, 1 h 2. HCO_2H, rt, 14 h	 (8)	121
C_{17-18} 	HCO_2H, C_6H_{12}, 3 min	 **I** +  **II** R I II CF_3 (23) (50) H (10) (51) OMe (5) (50)	436
C_{18} 	HCl, 0°, 18 h	 (76)	438
C_{19} 	TFA, CH_2Cl_2, rt, 24 h	 (85)	369
	TFA, CH_2Cl_2, rt, 24 h	 (88)	369

Table 3. (Continued)

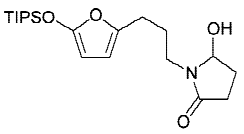
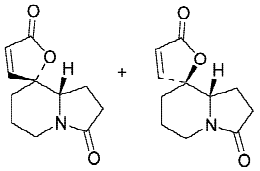
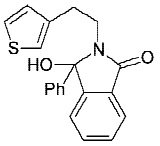
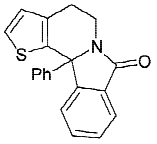
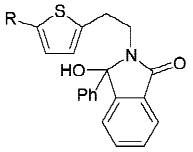
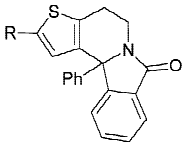
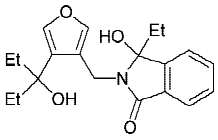
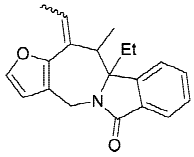
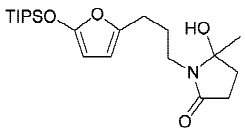
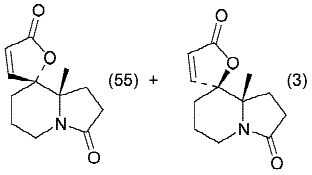
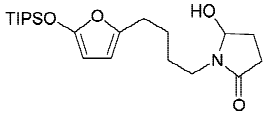
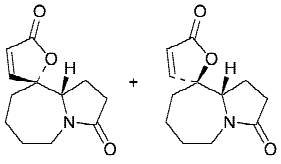
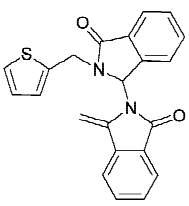
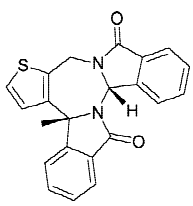
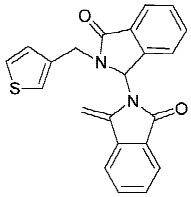
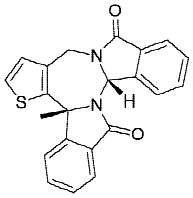
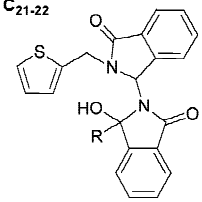
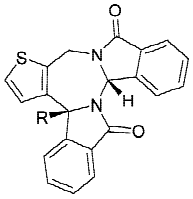
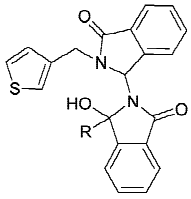
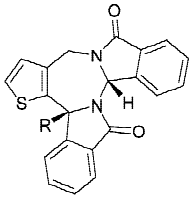
substrate	conditions	product(s) and yield(s) (%)	ref
C_{20}			
			437
	TFAA, *i*-Pr_2NEt, MeCN	(65) (15)	
	$ZnCl_2$, CH_2Cl_2, rt	(56) (6)	
	$ZnCl_2$, MeCN, rt	(41) (10)	
	BF_3•Et_2O, MeCN, rt	(55) (9)	
	Et_2AlCl, MeCN, –20°	(64) (8)	
	Et_2AlCl, MeCN, 0°	(71) (10)	
	Et_2AlCl, MeCN, rt	(71) (12)	
	Et_2AlCl, MeCN, 40°	(64) (13)	
	Et_2AlCl, CH_2Cl_2, rt	(45) (5)	
	Et_2AlCl, THF, rt	(55) (8)	
	$LiClO_4$ (3.0 M), Et_2O, rt	(49) (4)	
	$SOCl_2$, CH_2Cl_2, rt, 2 h	 (96)	370
	$SOCl_2$, CH_2Cl_2, rt, 2 h	 R: H (100), Cl (90)	370
	TsOH, toluene, reflux	 (62)[a]	500
C_{21}			
	$LiClO_4$ (2 M), Et_2O	 (55) + (3)	437
			437
	TFAA, *i*-Pr_2NEt, MeCN	(25) (17)	
	BF_3•Et_2O, MeCN, rt	(33) (25)	
	Et_2AlCl, MeCN, rt	(32) (21)	
	$LiClO_4$ (3.0 M), Et_2O, rt	(31) (16)	
	$LiClO_4$ (2.5 M), Et_2O, rt	(21) (11)	
	TFA, rt	 (98)	439

Table 3. (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
	TFA, rt	 (98)	439
C_{21-22} 	TFA, rt	 R: H (99), Me (96)	439
	TFA, rt	 R: H (99), Me (92)	439

[a] The product was a mixture of isomers.

Table 4. Unimolecular Reactions with Nitrogen-Containing Heterocycles

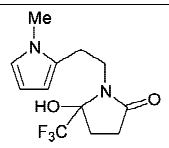
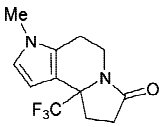
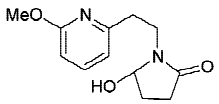
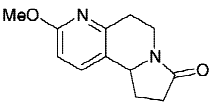
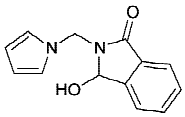
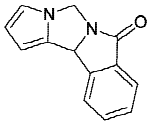
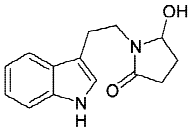
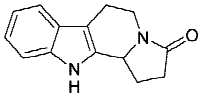
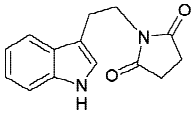
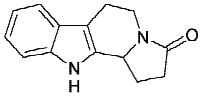
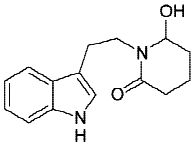
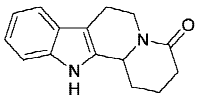
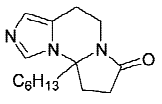
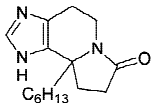
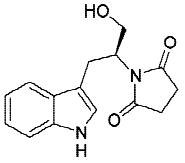
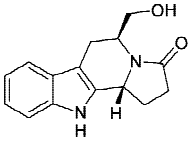
substrate	conditions	product(s) and yield(s) (%)	ref
C_{12} 	TfOH, CH_2Cl_2, 2 days	 (73)	358
	TsOH, C_6H_6, reflux	 (20)	450
C_{13} 	HCO_2H, rt, 3 days	 (27)	445
C_{14} 	HCl, 30°	 (quant.)	470
	1. $NaBH_4$, H^+ 2. HCl, reflux	 (78)	469
C_{15} 	HCl	 (>95)	470
	AcOH	 (—)	448
	1. $NaBH_4$, EtOH 2. HCl, 0°, 20 h	 (45)[a]	622

Table 4. (Continued)

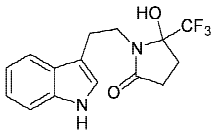
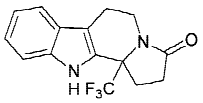
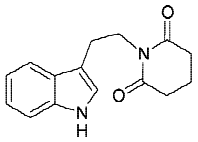
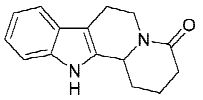
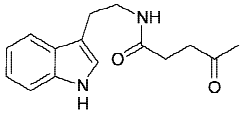
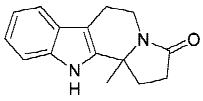
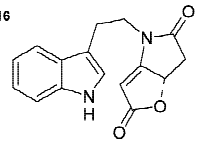
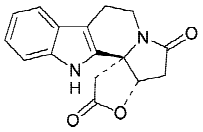
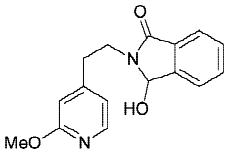
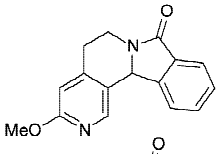
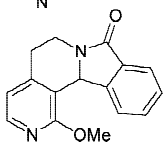
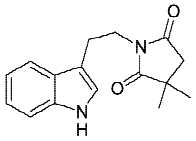
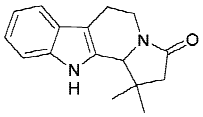
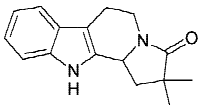
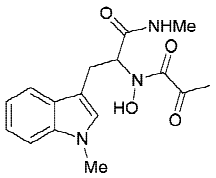
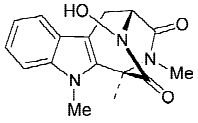
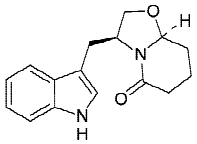
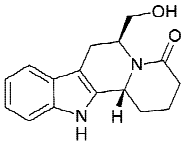
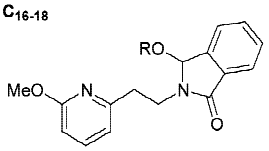
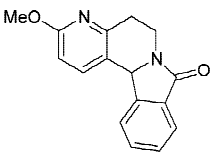
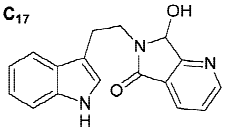
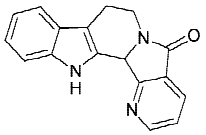
substrate	conditions	product(s) and yield(s) (%)	ref
	TFA, 8 h TFA, CH_2Cl_2, 4 days TfOH, CH_2Cl_2, 1 day	 (57) (91) (77)	358
	1. $NaBH_4$, H^+ 2. HCl, reflux	 (56)	469
	HCl, MeOH, 60°, 4 h	 (87)	354
C_{16} 	TsOH, CH_2Cl_2, reflux	 (79)	320
	TsOH, C_6H_6, reflux	 (53) +  (15)	450
	1. $NaBH_4$, EtOH, 0°, 5 h 2. HCl, EtOH, rt, 20 h	 (73) +  (27)	468
	TFA or HCl, $CHCl_3$ or CH_2Cl_2, rt	 (quant.)	481
	$TiCl_4$, CH_2Cl_2, −78° to rt, 20 h	 $(54)^b$	622
$C_{16\text{-}18}$ 	TsOH, C_6H_6, reflux	 R: H (70), Et (55)	450
C_{17} 	TFA, reflux, 3 h	 (64)	355

Table 4. (Continued)

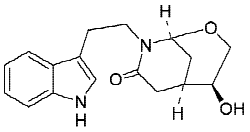
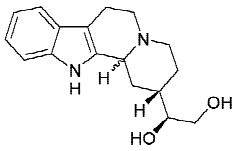
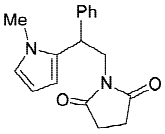
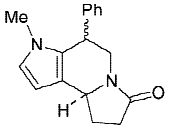
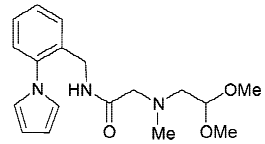
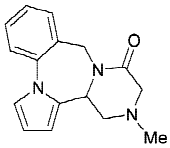
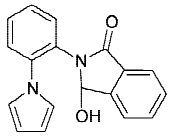
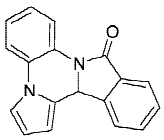
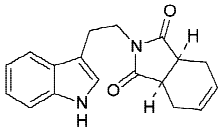
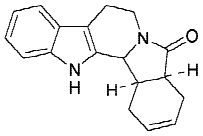
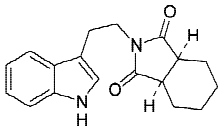
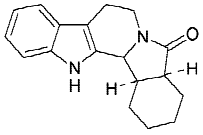
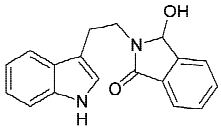
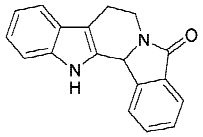
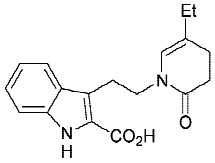
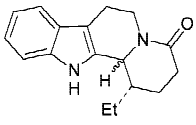
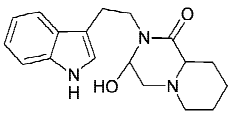
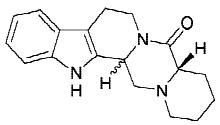
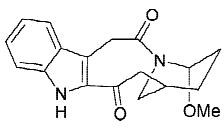
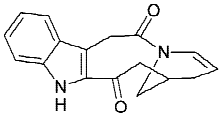
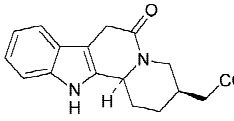
substrate	conditions	product(s) and yield(s) (%)	ref
	AcOH (20%), toluene reflux, 48 h	 (90)	461
	1. $NaBH_4$, MsOH, EtOH, 0° 2. MsOH, rt	 (50), α:β = 74:26	45 115
C_{18}			
	HCl, THF, rt-reflux	 (80)	447
			446
	$SOCl_2$, CH_2Cl_2, rt, 0.5 h TFA, CH_2Cl_2, rt, 1 h	(35) (28)	
	1. $NaBH_4$, H^+ 2. HCl, reflux	 (90)	469
	1. $NaBH_4$, H^+ 2. HCl, reflux	 (69)	469
	HCl, 30°, 30 min or HCl, reflux	 (quant.)	469 470
	AcOH, reflux, 24 h	 (60), α:β = 1:2	93
	HCl (conc.), 40°, 1 h	 (74), α:β = 4:3	472
	TsOH or $KHSO_4$ (cat.) 165-175°	 (70) +	609
		 (small amt.)	

Table 4. (Continued)

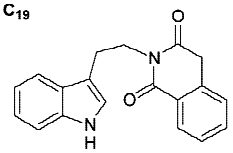
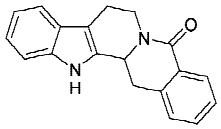
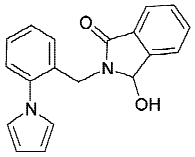
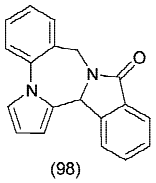
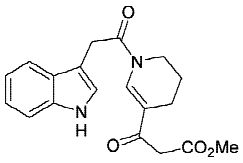
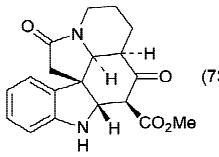
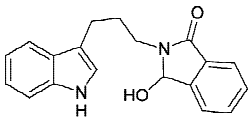
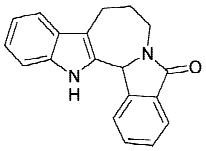
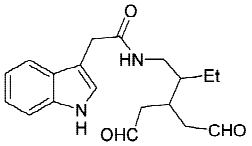
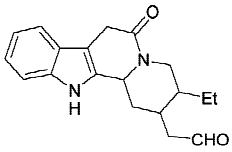
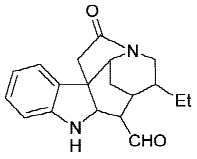
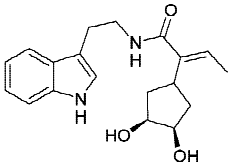
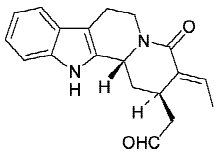
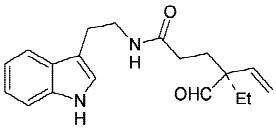
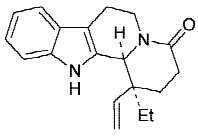
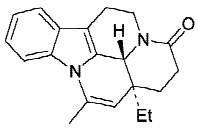
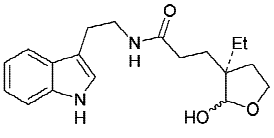
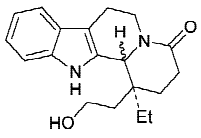
substrate	conditions	product(s) and yield(s) (%)	ref
C_{19} 	1. $NaBH_4$, H^+ 2. HCl, MeOH, reflux	 (86)	467
	$SOCl_2$, CH_2Cl_2, rt, 0.5 h TFA, CH_2Cl_2, rt, 1 h	 (98) (94)	446
	PPA, 20 torr, 100°, 3 h	 (73)	110
	HCl, MeOH, reflux, 24 h	 (85)	463
	AcOH, $CHCl_3$, rt	 (—)	113
	AcOH, NaOAc, H_2O, heat	 (—)	91
	1. HIO_4, AcOH, NaOAc 2. HCl, 60°, 0.5 h	 (69)	111
	TFA, CH_2Cl_2, –55°, 10 h	 (88) +	100
		 (5)	
	1. AcOH, reflux, 48 h 2. NaOH, MeOH, rt, 0.5 h	 (65)	100

Table 4. (Continued)

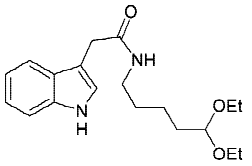
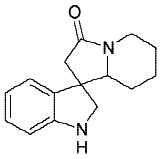
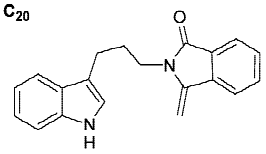
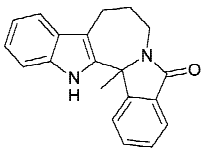
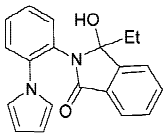
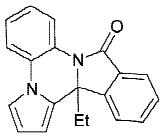
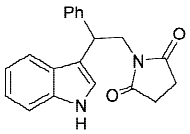
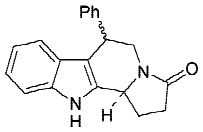
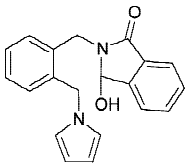
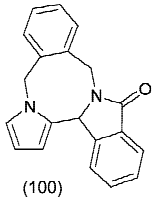
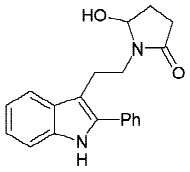
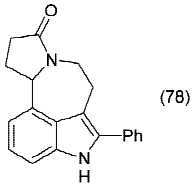
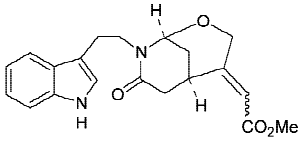
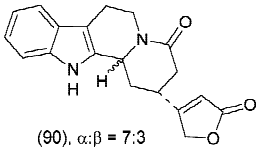
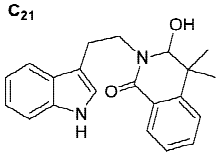
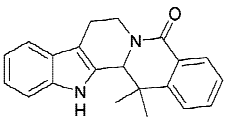
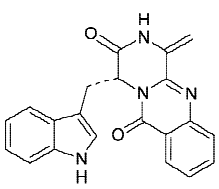
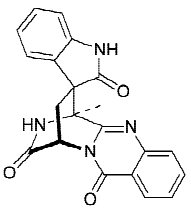
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, Na_2CO_3, H_2O, 100°, 1 h	 (78)	113
C_{20} 	HCl, EtOH, reflux, 24 h	 (80)	463
			446
	$SOCl_2$, CH_2Cl_2, rt, 0.5 h	(35)	
	TFA, CH_2Cl_2, rt, 1 h	(28)	
	1. $NaBH_4$, MsOH, EtOH, 0°		45
	2. MsOH, rt		115
		(70), α:β = 92:8	
			446
	$SOCl_2$, CH_2Cl_2, rt, 0.5 h	(100)	
	TFA, CH_2Cl_2, rt, 1 h	(92)	
	HCO_2H, reflux	 (78)	381
	AcOH, toluene, reflux, 48 h		103
		(90), α:β = 7:3	
C_{21} 	DMSO, 10 days	 (11)	635
	$AlCl_3$, THF, 0°, 1 h	(87)	
	TFA, 70°, 2 h	 (89)	482 649

Table 4. (Continued)

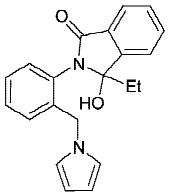
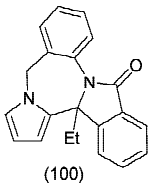
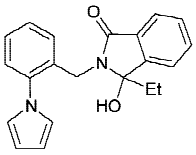
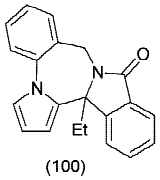
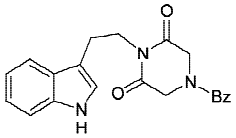
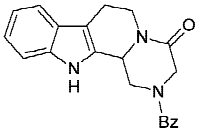
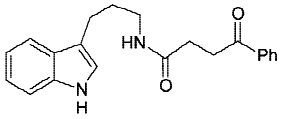
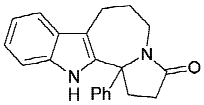
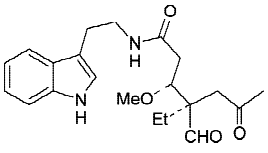
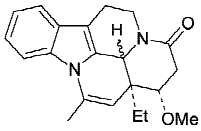
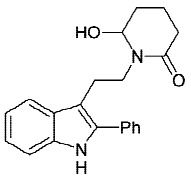
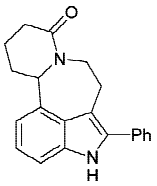
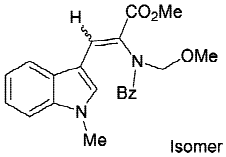
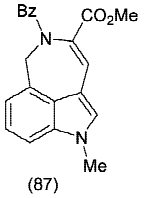
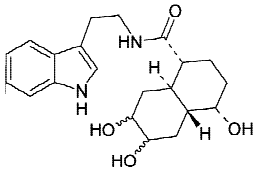
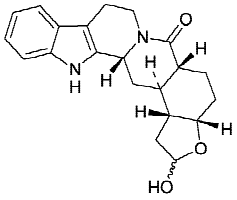
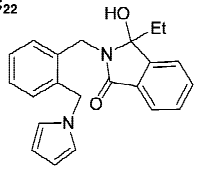
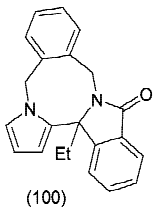
substrate	conditions	product(s) and yield(s) (%)	ref
	$SOCl_2$, CH_2Cl_2, rt, 0.5 h TFA, CH_2Cl_2, rt, 1 h	 (100) (93)	446
	$SOCl_2$, CH_2Cl_2, rt, 0.5 h TFA, CH_2Cl_2, rt, 1 h	 (100) (94)	446
	$NaBH_4$, MsOH, EtOH, –5°, 4 h	 (67)	476
	HCl, MeOH, 45°, 48 h	 (79)	463
	TFA, CH_2Cl_2, rt, 15 h	 (77), α:β = 1.6:1	95
	HCO_2H, reflux	 (73)	381
 Isomer *E* *Z*	Ac_2O-AcOH, 80°	 (87) (89)	446
	1. $NaIO_4$, acetone, H_2O, 60-70°, 20 s 2. H_3PO_4, 60-70°, 20 min	 (60)[c]	89
C_{22} 	$SOCl_2$, CH_2Cl_2, rt, 0.5 h TFA, CH_2Cl_2, rt, 1 h	 (100) (92)	446

Table 4. (Continued)

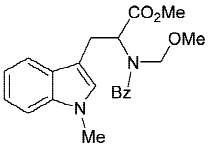
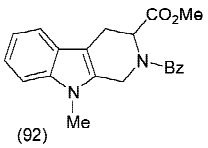
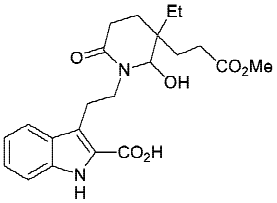
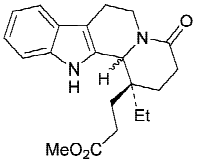
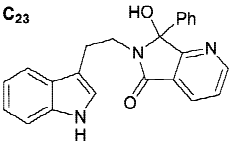
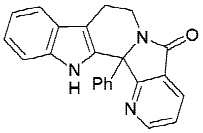
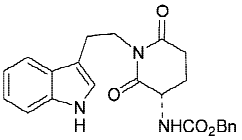
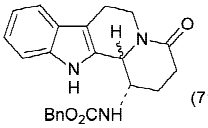
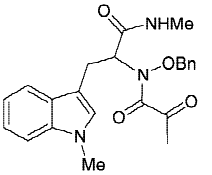
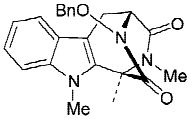
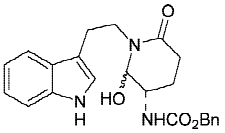
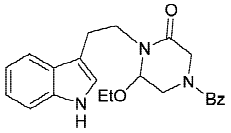
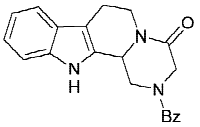
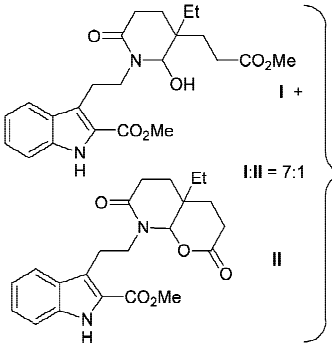
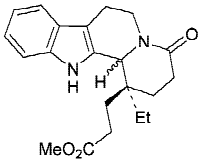
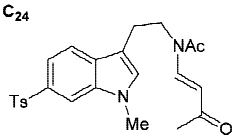
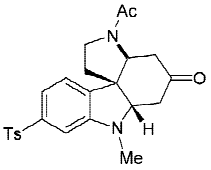
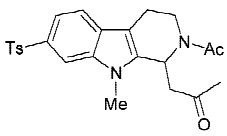
substrate	conditions	product(s) and yield(s) (%)	ref
	Ac_2O, AcOH 120° DMSO, 150°	 (92) (90)	383
	AcOH, reflux, 20 h	 (—), α:β = 1:1	446
C_{23} 	TFA, reflux, 3.5 h	 (58)	446
	1. $NaBH_4$, EtOH, 2. TFA, CH_2Cl_2, rt, 3 h	 (71), α:β = 9:1	471
	TFA or HCl, $CHCl_3$ or CH_2Cl_2, rt	 (76)	481
	BF_3•Et_2O, MeCN, –78 to 10°, 5 h	 (66)	397
	TsOH, C_6H_6, reflux, 3 h	 (56)	476
 I + I:II = 7:1 II	AcOH, reflux, 20 h	 (96), α/β = 1:1	93
C_{24} 	BF_3•Et_2O, 90°, 16 min	 (89) +  (2)	108

Table 4. (Continued)

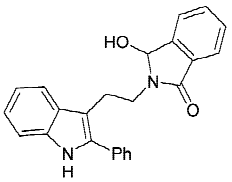
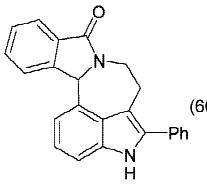
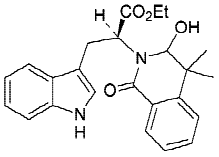
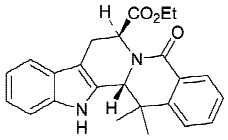
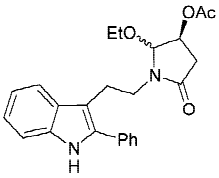
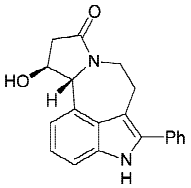
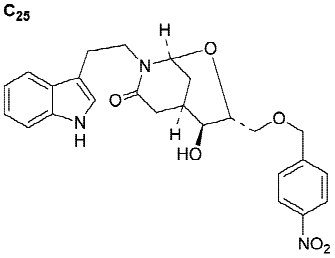
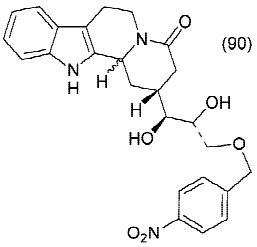
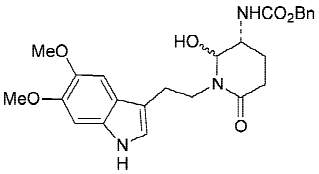
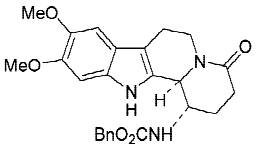
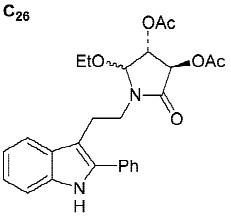
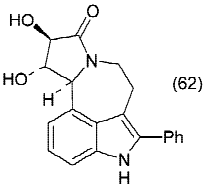
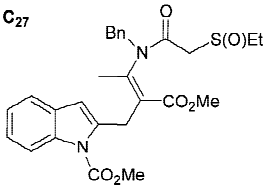
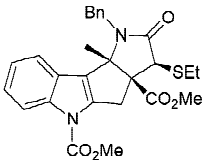
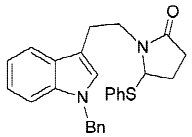
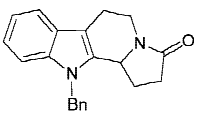
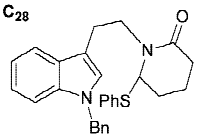
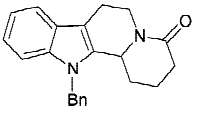
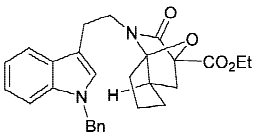
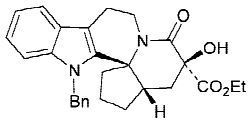
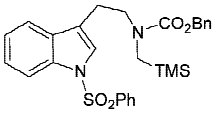
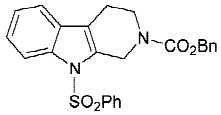
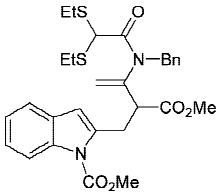
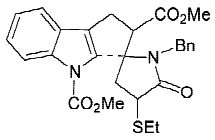
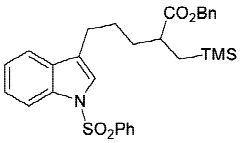
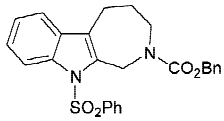
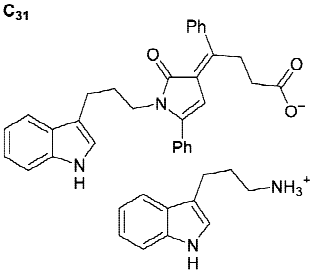
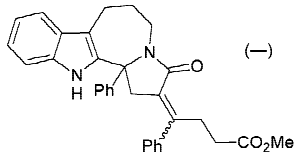
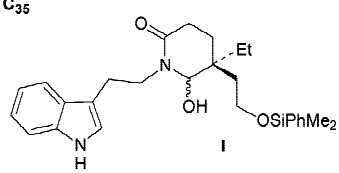
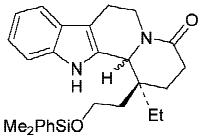
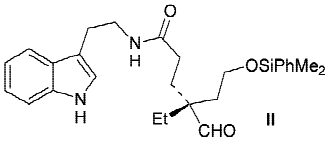
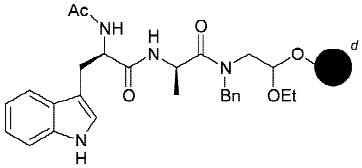
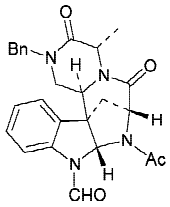
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, reflux	 (60)	381
	HCl, CH_2Cl_2	 (77)	635
	1. HCO_2H, reflux 2. AcCl, EtOH, rt	 (67)	381
C_{25} 	AcOH, toluene, reflux, 48 h	 (90)	461
	BF_3•Et_2O, CH_2Cl_2, −78 to 10°, 5 h	 (94)	397
C_{26} 	1. HCO_2H, reflux 2. AcCl, EtOH, rt	 (62)	381
C_{27} 	TsOH, C_6H_6, reflux	 (80)	344
	BF_3•2AcOH, CH_2Cl_2, 25°	 ("excellent")	343 346
C_{28} 	BF_3•2AcOH, CH_2Cl_2, 25°	 ("excellent")	343 346

Table 4. (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
	$BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 6 h	 (60)	86
	$Ce(NH_4)_2(NO_3)_6$, MeCN, rt	 (86)	330
C_{29}			
	$(Me_2SSMe)^+BF_4^-$	 (59)	344
C_{30}			
	$Ce(NH_4)_2(NO_3)_6$, MeCN, rt	 (45)	330
C_{31}			
	HCl, MeOH	 (—)	463
C_{35}			
 I			
 II	Nafion-H, toluene, rt, 18 h	(95), α:β = 1:2	101
I + II = 1.7:1	TFA, CH_2Cl_2, -42° to rt, 16 h	(95), α:β = 1:3	650
	HCO_2H, 60°	 (63)	543

[a] The product was a 9:1 mixture of diastereomers. [b] The product was a 5:2 mixture of diastereomers. [c] Other isomers were detected by NMR. [d] TentaGel-OH resin (black circle) was used for the solid-phase reaction.

Table 5. Unimolecular Reactions with Alkenes

Table 5A. Unimolecular Reactions with Alkenes: α-Hydroxy/Alkoxy/Thioalkoxy/Acyloxy/Halo Amides

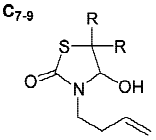
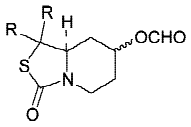
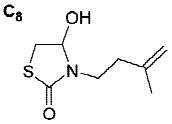
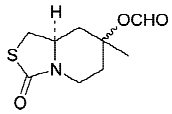
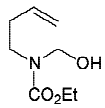
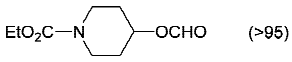
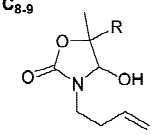
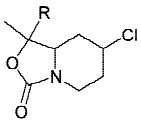
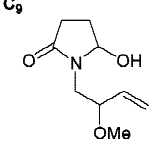
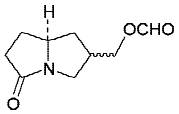
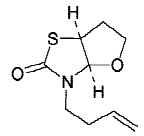
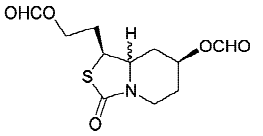
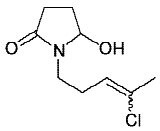
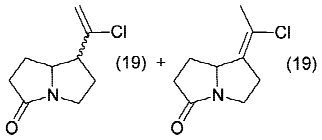
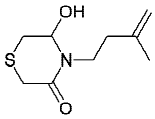
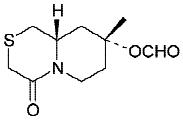
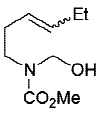
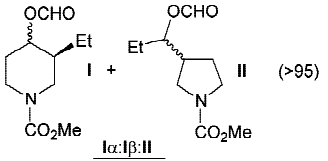
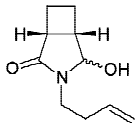
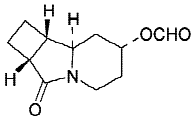
substrate	conditions	product(s) and yield(s) (%)	ref
$C_{7\text{-}9}$ 	HCO_2H, rt	 α:β = 3:1	
R: H	18 h	(80)	124
H	142 h	(82)	429
Me	2 h	(80)	124
Me	2 h	(92)	429
C_8 	HCO_2H, rt, 18 h	 (85), α:β = 5:2	429
	HCO_2H, rt, 24 h	 (>95)	161
$C_{8\text{-}9}$ 	$TiCl_4$, CH_2Cl_2, reflux, 2 h	 R: H (58), Me (65)	170
C_9 	HCO_2H, rt, 18 h	 (55), α:β = 5:1	154, 156
	HCO_2H, 60°, 24 h	 (50), α:β = 2:1	610
	PPA, rt, 50 min	 (19) + (19)	499
	HCO_2H, rt, 16 h	 (55)	610
 Isomer: *E*, *Z*	HCO_2H, rt, 24 h	 I + II (>95); Iα:Iβ:II: 88:4:8, 18:73:9	161
C_{10} 	HCO_2H, rt, overnight	 (quant.), α:β = 9:1	142

Table 5. (Continued)

Table 5A (Continued)

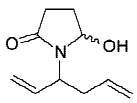
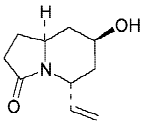
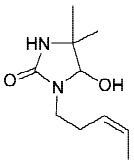
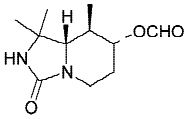
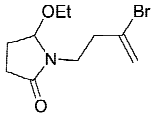
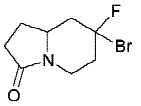
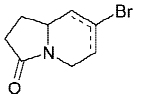
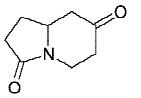
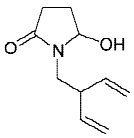
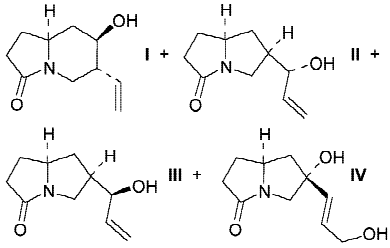
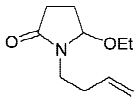
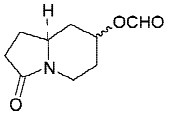
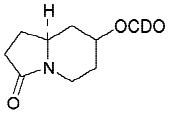
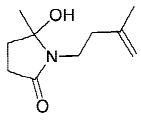
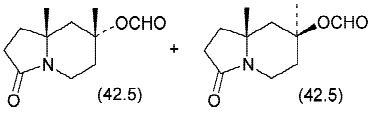
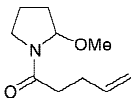
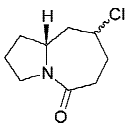
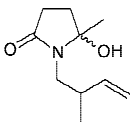
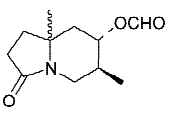
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 1 h; saponified	 (70)	159
	HCO_2H, CH_2Cl_2, reflux, 24 h	 (49)	520
	HF, 0°, 3 h	 (35)	506
	TfOH, CH_2Cl_2, rt, 15-17 h	 (48.5)	506
	TFA, rt, 16-24 h	 (47)	506
			159
	TFA, 22°, 1.5 h; saponified	I: (0); II-IV: (—)	
	HCO_2H, AcOH, rt, 5 days; saponified	I: (31); II-IV: (69)	
	HCO_2H, rt, 1 h	 α (<10); β (>90)	124
	DCO_2D, rt, 1 h	 (80) monodeutero	124
	HCO_2H, rt, 30 min	 (42.5) (42.5)	136
	$TiCl_4$, CH_2Cl_2, –78° to rt, 33 h	 (80)	493
	HCO_2H, rt, 18 h	 (81), α:β = 86:14	137

Table 5. (Continued)

Table 5A (Continued)

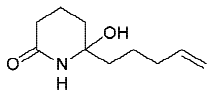
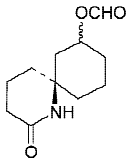
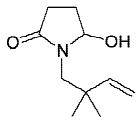
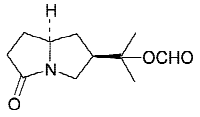
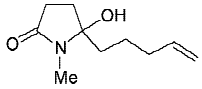
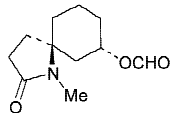
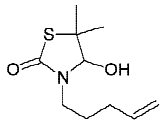
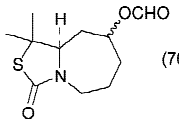
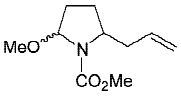
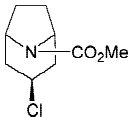
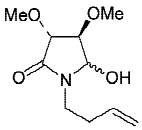
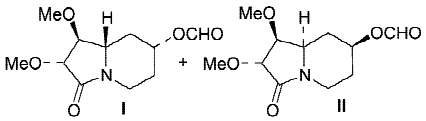
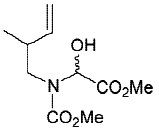
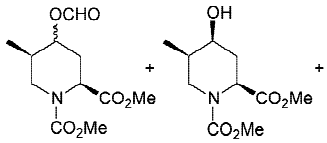
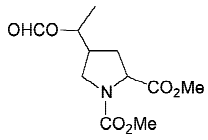
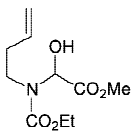
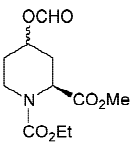
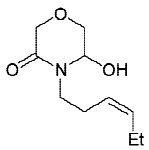
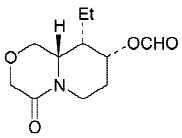
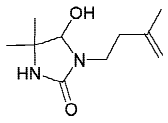
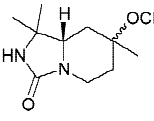
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 4 days	 (43), α:β = 1:4	509
	HCO_2H, rt, 5 min	 (quant.)	154 156
	HCO_2H, 18 h	 (quant.)	133
	HCO_2H, rt, 118 h	 (76), α:β = 3:1	429
	$TiCl_4$, CH_2Cl_2, rt	 (89)	511
	HCO_2H, rt, 18 h	 (quant.), I:II = 2:1	138
	HCO_2H, rt, 18 h	 α (35); β (10) (5)	161
		 (29)[a]	
	HCO_2H, rt, 3 days	 (87), α:β = 1:1.2	161
	HCO_2H, rt, 19 h	 (100)	610
	HCO_2H, CH_2Cl_2, reflux, 96 h	 (50), α:β = 1:1	520

Table 5. (Continued)

Table 5A (Continued)

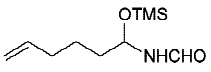
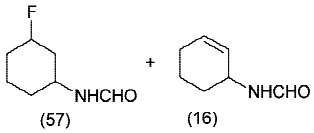
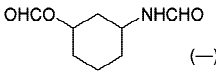
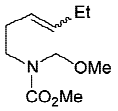
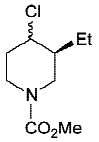
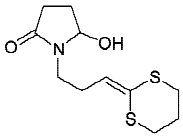
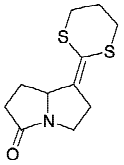
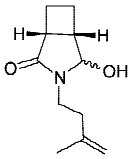
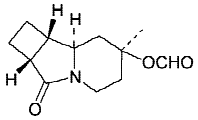
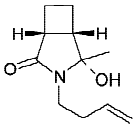
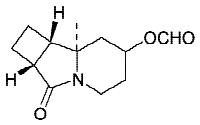
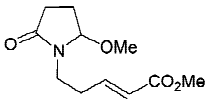
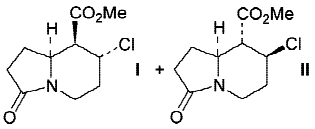
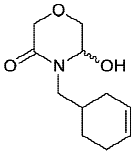
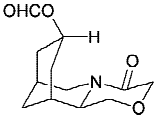
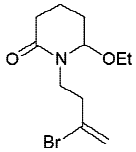
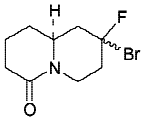
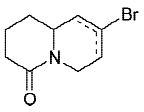
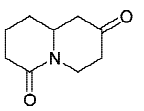
substrate	conditions	product(s) and yield(s) (%)	ref
	BF_3•Et_2O, CH_2Cl_2, rt, 50 min	 (57) (16)	303
	HCO_2H, rt, 40 min	 (—), *cis*:*trans* = 79:14	303
 Isomer: *E*; *Z*	$SnCl_4$, CH_2Cl_2, −78° to rt, 2 h	 α: (95); (33) β: (5); (67)	166
C_{11}			
	MsCl, Et_3N, CH_2Cl_2, −30 to 20°	 (86)	178
	HCO_2H, rt, 1 h	 (100), α:β = 3:2	142
	HCO_2H, rt, overnight	 (quant.)	142
	$SnCl_4$, DCE, 0-70°, 18 h	 I + II (28)	503
	HCO_2H, rt, 19 h	 (71)	610
	HF, 0°, 3 h	 (27)	506
	TfOH, CH_2Cl_2, rt, 15-17 h	 (36)	506
	TFA, rt, 16-24 h	 (—)	506

Table 5. (Continued)

Table 5A (Continued)

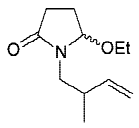
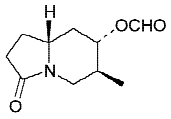
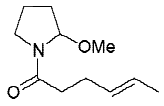
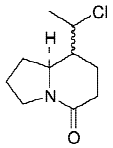
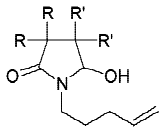
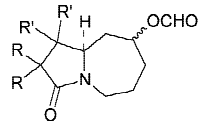
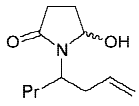
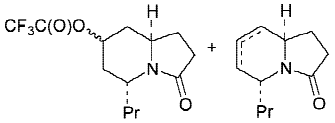
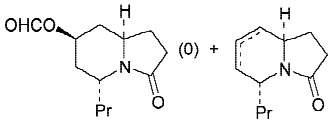
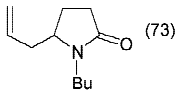
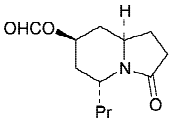
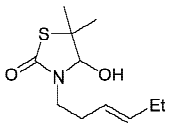
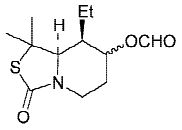
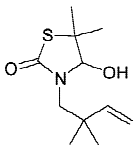
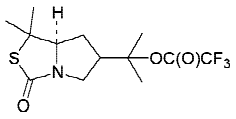
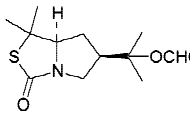
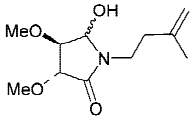
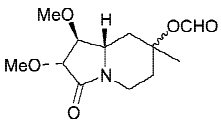
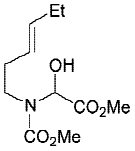
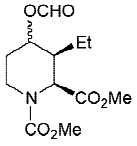
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 18 h	 (89)[b]	137
	$TiCl_4$, CH_2Cl_2, −78° to rt, 33 h	 (50)[a]	493
 R R' H Me Me H	HCO_2H, rt	 (63), α:β = 3:1 (31), α:β = 3:1	429
	TFA, CH_2Cl_2, 25°, 5 min	 (62), α:β = 1:3.8 (12)	150 152
	Et_3SiH, HCO_2H, CH_2Cl_2, 25°, 10 h	 (0) + (0) +  (73)	150 152
	HCO_2H, rt, 0.75 h	 (65)	487
	HCO_2H, rt, 72 h	 (96), α:β = 100:1	429 484
	TFA, 0°, 0.5 h	 (70)	156
	HCO_2H, rt, 1.75 h	 (66)	154 156
	HCO_2H, rt, 18 h	 (quant.), α:β = 1.5:1	138
	HCO_2H, rt, 3 days	 (75), α:β = 1:3.7	161

Table 5. (Continued)

Table 5A (Continued)

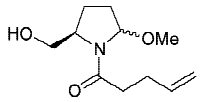
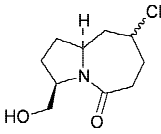
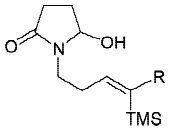
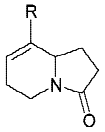
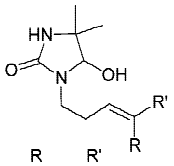
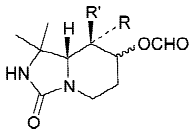
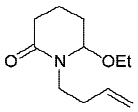
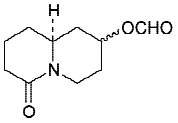
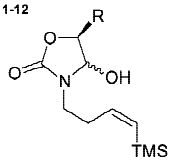
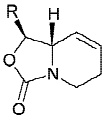
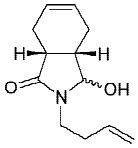
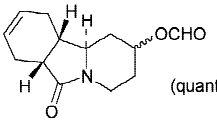
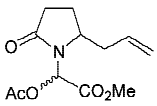
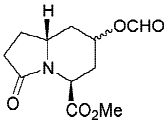
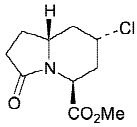
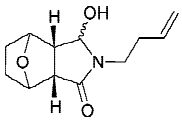
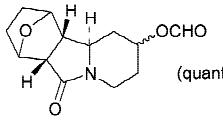
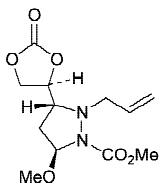
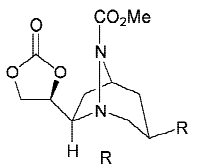
substrate	conditions	product(s) and yield(s) (%)	ref
	$TiCl_4$, CH_2Cl_2, –78° to rt, 33 h	 (68)[a,c]	493
 R: H; Br	TFA, rt, 0.25 h TFA, reflux, 2.5 h	 (92) (70)	167
 R: H, Et; R': Et, H	HCO_2H, CH_2Cl_2, reflux, 11 days	 α: (54), (42); β: (23), (0)	520
	HCO_2H, rt, 18 h	 (quant.)	130
C_{11-12} 	$TiCl_4$, CH_2Cl_2, reflux, 2 h	 R: Me (65); Et (70)	170
C_{12} 	HCO_2H, rt, overnight	 (quant.), α:β = 4:1	142
	HCO_2H, rt, 17 h	 (52), α:β = 1:1.6	161
	1. $SnCl_4$, CH_2Cl_2, 0°, 3 h 2. $NaHCO_3$, 0°	 (69)	166 215
	HCO_2H, rt, overnight	 (quant.), α:β = 4:1	142
	$SnCl_4$, CH_2Cl_2, –78° to rt, 4 h HCO_2H, rt, 18 h	 R: Cl (56); OCHO (76)	427

Table 5. (Continued)

Table 5A (Continued)

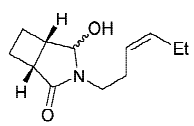
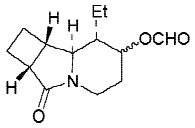
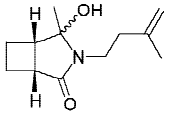
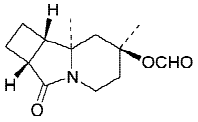
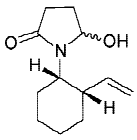
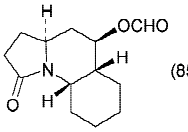
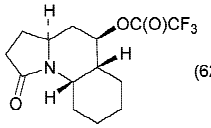
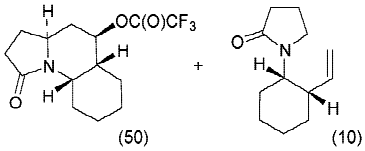
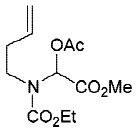
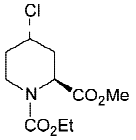
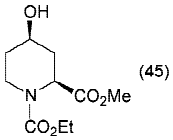
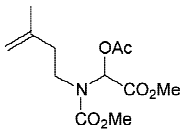
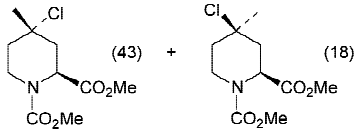
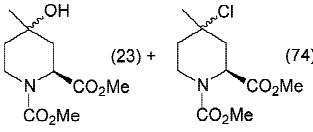
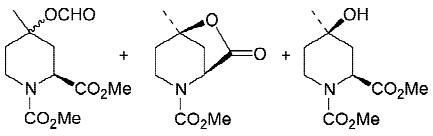
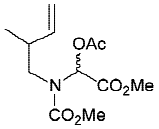
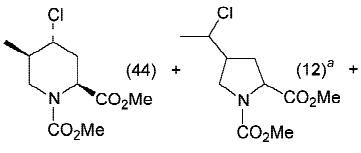
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 1 h	 (94)[a]	142
	HCO_2H, rt, 1 h	 (91)	142
	HCO_2H, rt, 0.5 h	 (85)	140 143
	TFA, CH_2Cl_2, rt, 0.25 h	 (62)	140
	TFA, CH_2Cl_2, Et_3SiH, rt, 0.25 h	 (50) + (10)	140
	1. $SnCl_4$, CH_2Cl_2, 2 h, –78 to 20° 2. $NaHCO_3$, 20°	 (77)	166 215
	1. $SnCl_4$, CH_2Cl_2, 2.5 h, –78° 2. $NaHCO_3$, –78°	 (45)	166 215
	1. $SnCl_4$, CH_2Cl_2, 4 h, –78 to 20° 2. $NaHCO_3$, 20°	 (43) + (18)	166
	1. $SnCl_4$, CH_2Cl_2, 4 h, –78° 2. $NaHCO_3$, –78°	 (23) + (74), α:β = 1:1.3	166
	HCO_2H, 40 h, rt	 (44), α:β = 6:1 (15) (13)	161
	1. $SnCl_4$, CH_2Cl_2, –78 to 20°, 2.5 h 2. $NaHCO_3$, 20°	 (44) + (12)[a] + (9)	166

Table 5. (Continued)

Table 5A (Continued)

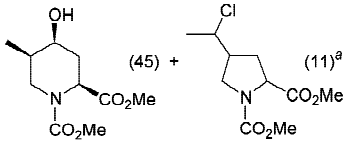
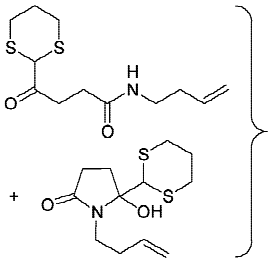
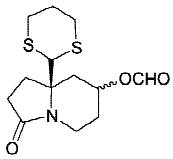
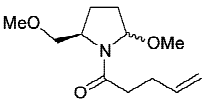
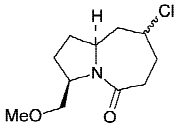
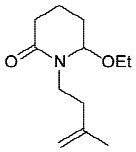
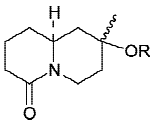
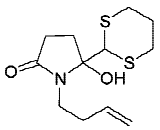
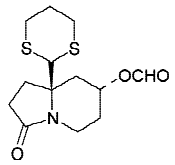
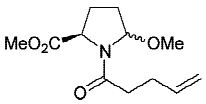
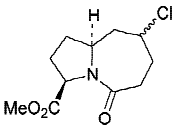
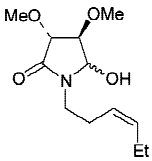
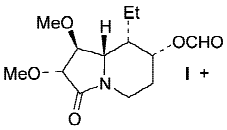
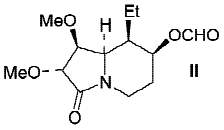
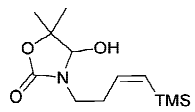
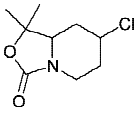
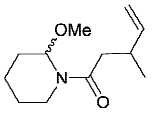
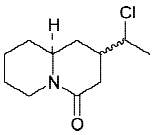
substrate	conditions	product(s) and yield(s) (%)	ref
	1. $SnCl_4$, CH_2Cl_2, –78°, 4 h 2. $NaHCO_3$, –78°	 (45) + (11)[a]	166
	HCO_2H, rt, 7 days	 (67), α:β = 12:1	136
	$TiCl_4$, CH_2Cl_2, –78° to rt, 33 h	 (77)	493
			130
	HCO_2H, 1 h	R = CHO, α:β = 57:43	
	AcOH, 23 h	R = Ac, α:β = 60:40	
	AcOH, H_2O, 2 h	R = H, α:β = 60:40	
	Cl_2CHCO_2H, 2 h	R = C(O)$CHCl_2$, α:β = 70:30	
	HCO_2H, Et_2O, 19 h	R = CHO, α:β = 57:43	
	HCO_2H, HCO_2Na, 18 h	R = CHO, α:β = 56:44	
	HCO_2H, 18 h, rt	 (—)	136
	$TiCl_4$, CH_2Cl_2, 33 h, –78°	 (89)[d]	493
	HCO_2H, rt, 18 h	 I +	124
		 II (quant.), I:II = 100:1	138
	$TiCl_4$, CH_2Cl_2, 2 h, reflux	 (22)	170
	$TiCl_4$, CH_2Cl_2	 (60)	498

Table 5. (Continued)

Table 5A (Continued)

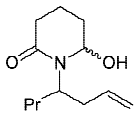
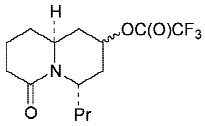
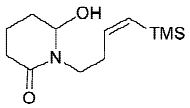
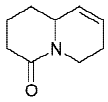
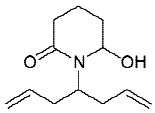
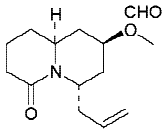
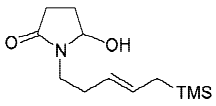
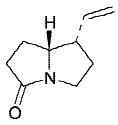
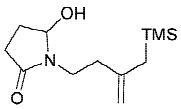
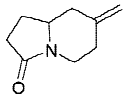
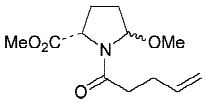
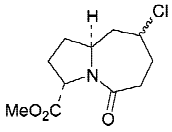
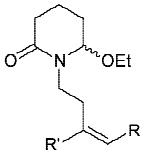
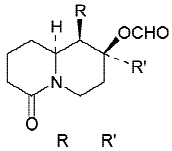
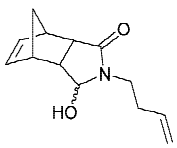
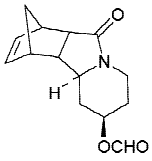
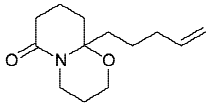
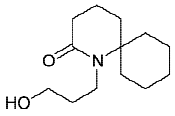
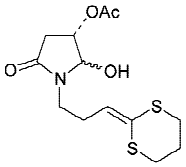
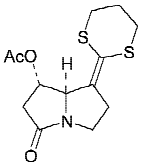
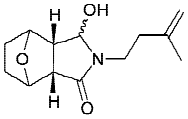
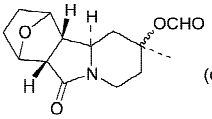
substrate	conditions	product(s) and yield(s) (%)	ref
	TFA, CH_2Cl_2, Et_3SiH	 (22)	152
	TFA, rt, 0.25 h	 (90)	167
	HCO_2H, 25°, 8-10 min	 (71)	143
	TFA, CH_2Cl_2, 0°, 1 h	 (72)	188
	1. NaH, EtI, THF 2. $TiCl_4$, CH_2Cl_2, 25°	 (72)	185
	$TiCl_4$, CH_2Cl_2, 0°-rt	 (89)	496
	HCO_2H		130
	rt, 18 h	R = Me, R' = H (quant.)	
	rt, 2 h	R = H, R' = Me (quant.)[e]	
C_{13}			
	HCO_2H, rt, 12 h	 (92)	611 612
	1. $ZrCl_4$, CH_2Cl_2, rt 2. H_2/Pd-C, EtOH, Bu_3SnH, AIBN	 (82)	651
			
	TfCl, Et_3N	(75-80)	179, 181
	MsCl, Et_3N, CH_2Cl_2	(68)	179
	HCO_2H, rt, overnight	 (quant.), α:β = 3:2	142

Table 5. (Continued)

Table 5A (Continued)

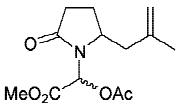
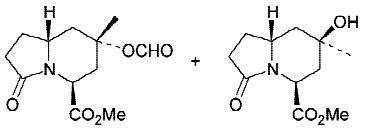
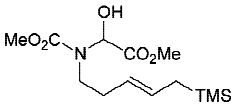
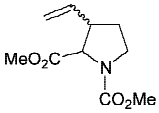
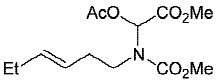
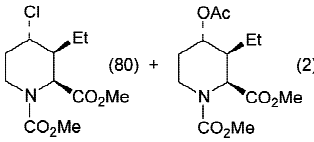
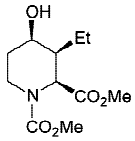
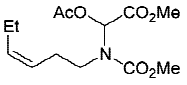
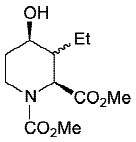
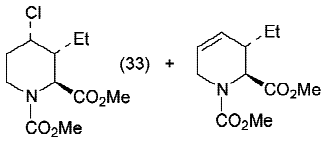
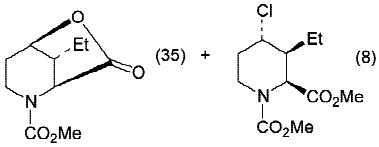
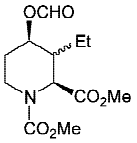
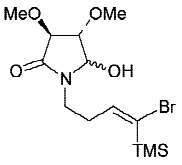
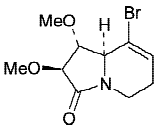
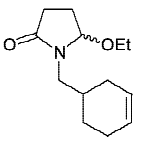
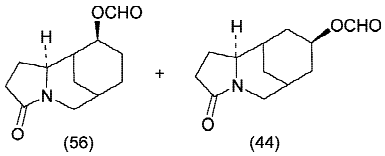
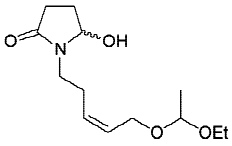
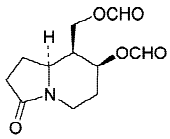
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 50 h	 (47) (33)	161
	1. MsCl, MeCN, Et_3N, rt 2. Reflux, 3 h	 (88), *trans*:*cis* = 78:22	189
	1. $SnCl_4$, CH_2Cl_2, –78 to 20°, 4 h 2. $NaHCO_3$, 20°	 (80) (2)	166 215
	1. $SnCl_4$, CH_2Cl_2, –78°, 2 h 2. $NaHCO_3$, –78°	 (49)	166 215
	1. $SnCl_4$, CH_2Cl_2, –78°, 2.25 h 2. $NaHCO_3$, –78°	 (81), α:β = 9:1	166 215
	1. $SnCl_4$, CH_2Cl_2, –78 to 20°, 2 h 2. $NaHCO_3$, 20°	 (33) (8)	166 215
		 (35) (8)	
	HCO_2H, rt, 2 days	 (77), α:β = 1.3:1	161
	TFA, reflux, 6 h	 (74)	171
	HCO_2H	 (56) (44)	130
	HCO_2H, rt, 18 h	 (20)	505

Table 5. (Continued)

Table 5A (Continued)

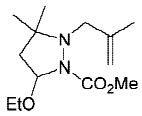
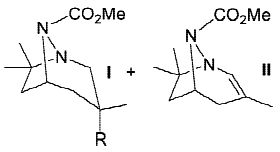
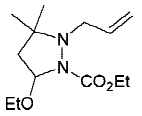
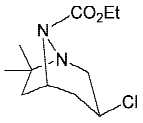
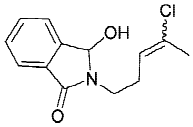
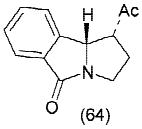
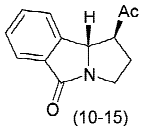
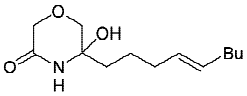
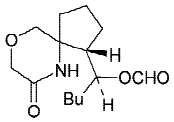
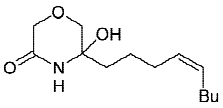
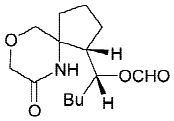
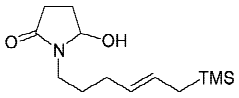
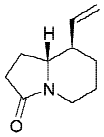
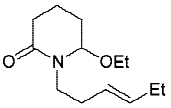
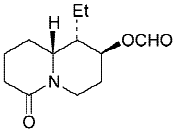
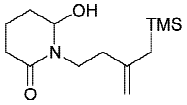
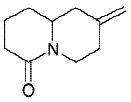
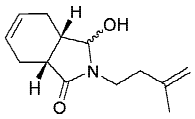
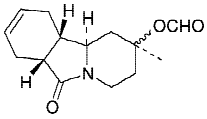
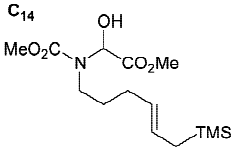
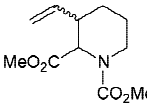
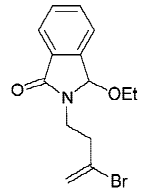
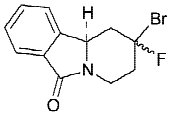
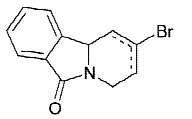
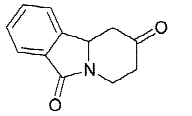
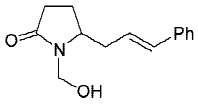
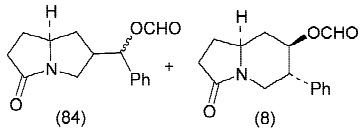
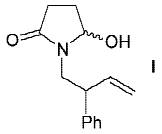
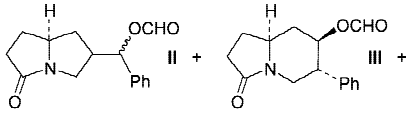
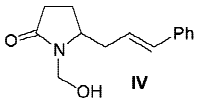
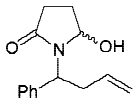
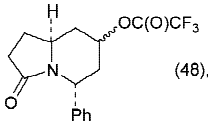
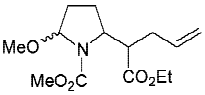
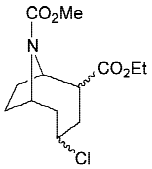
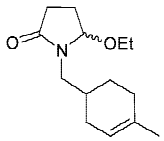
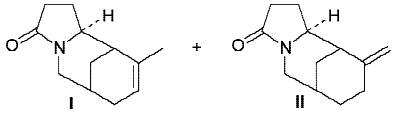
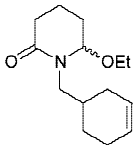
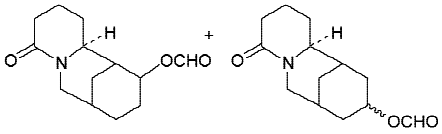
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H $TiCl_4$	 R I II OCHO (37) (34) Cl (56) (16)	205
	$TiCl_4$, CH_2Cl_2, –78-20°	 (95)	205
	H_2SO_4, 0°, 50 min	 (64) +  (10-15)	215
	HCO_2H, 42°, 10 days	 (41)	139
	HCO_2H, 42°, 14 days	 (47)	139
	TFA, CH_2Cl_2, 0°, 1 h	 (—)	188
	HCO_2H, rt, 95 h	 (quant.)	130
	TFA, CH_2Cl_2, 0°, 4 h	 (94)	185 194
	HCO_2H, rt, overnight	 (quant.), α:β = 3:2	142
C_{14} 	1. MsCl, MeCN, Et_3N, rt 2. Reflux, 3 h	 (79), *trans:cis* = 55:45	189
	HF, 0°, 3 h	 (76.5)	506

Table 5. (Continued)

Table 5A (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
	$TfOH, CH_2Cl_2$, rt, 15-17 h	 (79)	506
	TFA, rt, 16-24 h	 (69)	506
	HCO_2H, rt, 18 h	 (84) (8)	155
 I	HCO_2H, 20°	 II + III +  IV	155

Time	I:II:III:IV
0.17 h	84:0:0:16
1 h	32:12:0:56
4 h	4:26:5:65
20 h	0:66:7:27
68 h	0:88:10:2

	TFA, CH_2Cl_2, rt	 (48), α:β = 1:4.3	152
	$TiCl_4$	 (70)	512
	HCO_2H	 I + II (—) I:II = 9:1	613
			130

HCO_2H, rt, 18 h	(54)	(46)
HCO_2H, HCO_2Na, 45°, 50 h	(60)	(40)
HCO_2H, reflux, 0.5 h	(51)	(49)
HCO_2H, H_2O (15%), rt, 18 h	(70)	(30)
HCO_2H, Et_2O (1:10), rt, 6 days	(—)	(—)[f]
Cl_2CHCO_2H, rt, 18 h	(30)	(70)
AcOH, rt, 6 days	(—)	(—)[g]

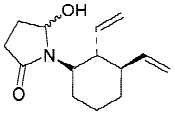
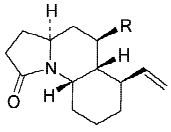
	HCO_2H, CH_2Cl_2, rt, 0.5 h		R		488
			OCHO	(79)	
			OH	(1)	

Table 5. (Continued)

Table 5A (Continued)

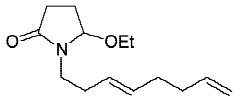
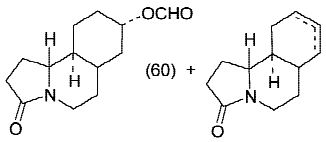
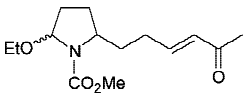
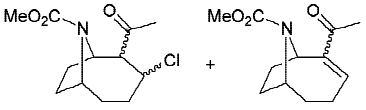
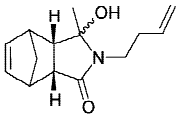
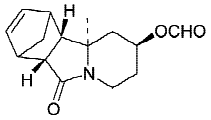
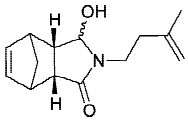
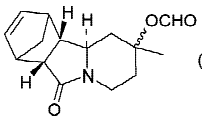
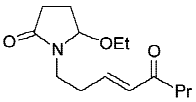
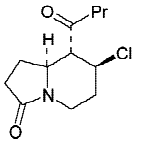
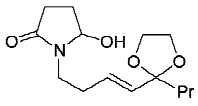
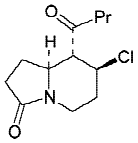
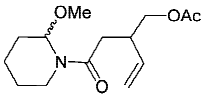
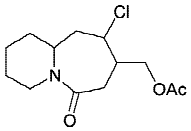
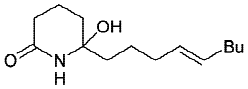
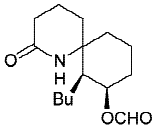
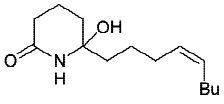
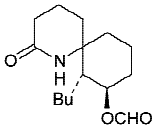
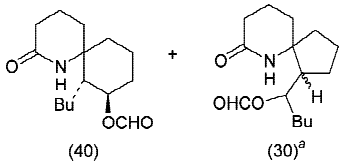
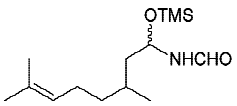
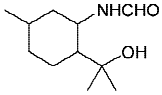
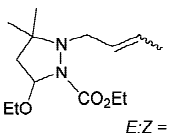
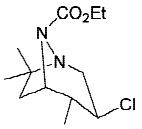
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 18 h	 (60) + (—)	129
	HCl, MeOH, −50 to 20°, 18 h	 (47) + (11)	504
	HCO_2H, rt, 65 h	 (85)	142
	HCO_2H, rt, 12 h	 (—), α:β = 3:2	142
	HCl, MeOH	 (quant.)	504
	HCl, MeOH, rt, 18 h	 (100)	505
	$TiCl_4$, CH_2Cl_2	 (>75)	498
	HCO_2H, 42°, 10 days	 (22)	124 134 139
	HCO_2H, 44°, 8 days	 (23)	124 134 139
	HCO_2H, 25°, 32 h	 (40) + (30)[a]	508
	HCO_2H, rt, 2 h	 (82)	303
 *E*:*Z* = 77:23	$TiCl_4$, CH_2Cl_2, −78 to 20°	 (53)	205

Table 5. (Continued)

Table 5A (Continued)

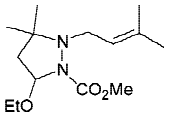
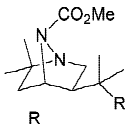
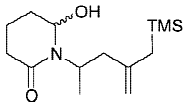
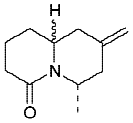
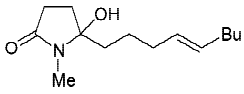
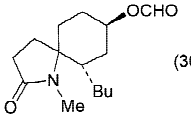
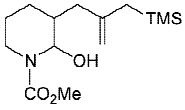
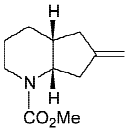
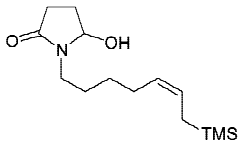
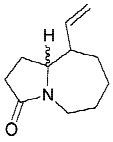
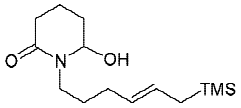
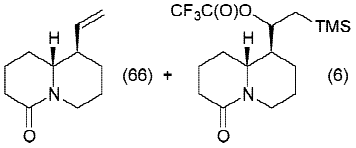
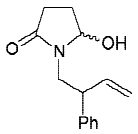
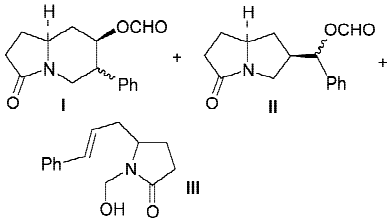
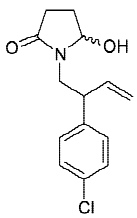
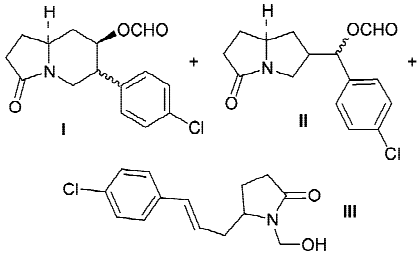
substrate	conditions	product(s) and yield(s) (%)	ref
			205
	HCO_2H	R = OCHO (84)	
	$TiCl_4$	R = Cl (84)	
	TFA, CH_2Cl_2, 0°, 4 h	 (100), α:β = 7:3	193, 198
	HCO_2H, 42°, 14 days	 (30)	139
	MsCl, Et_3N, CH_2Cl_2, -20 to 20°, 16 h	 (45)	194
	TFA, CH_2Cl_2, 0°, 2 h	 (70-90)[h]	204
	TFA, CH_2Cl_2, 0°, 4 h	 (66) + (6)	188
			160
	HCO_2H, 4 h	I (11), II (89), III (0)	
	HCO_2H:AcOH (2:3), 18 h	I (7), II (77), III (4)	
	TFA, CH_2Cl_2, 5°, 0.5 h	I (0), II (44), III (53)	
			160
	HCO_2H, 4 h	I (19), II (81), III (0)	
	HCO_2H:AcOH (2:3), 3.5 h	I (—), II (—), III (60)	

Table 5. (Continued)

Table 5A (Continued)

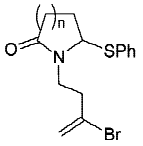
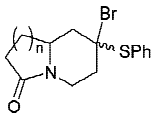
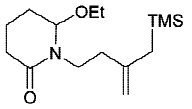
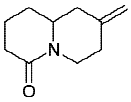
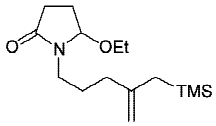
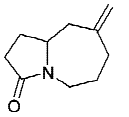
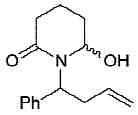
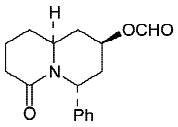
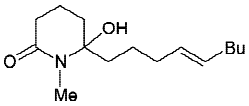
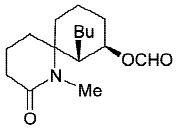
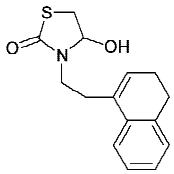
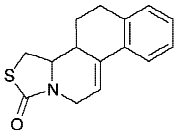
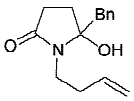
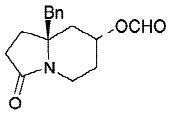
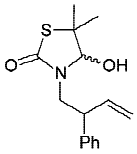
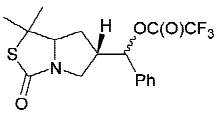
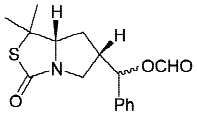
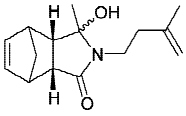
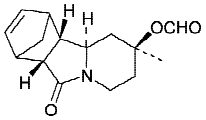
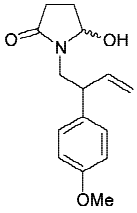
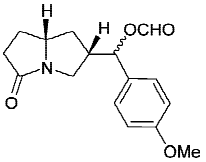
substrate	conditions	product(s) and yield(s) (%)	ref
C_{14-15}			
	1. BF_3•2AcOH, CH_2Cl_2, rt, 24 h 2. HCO_2H, $Hg(OAc)_2$, rt, 12 h		(64), n = 1 (58), n = 2	343 346
C_{15}			
	$TiCl_4$, CH_2Cl_2, 25°, 5 min		(80)	185
	$TiCl_4$, CH_2Cl_2, 0°, 4 h		(78)	194
	HCO_2H, 25°, 8-10 min		(63)	143 489
	HCO_2H, heat		(low)	139
	HCO_2H, rt, 1 h		(85)	514
	HCO_2H, rt, 18 h		(>65)	136
	TFA, rt, 0.5 h		(80)	156
	HCO_2H, rt, overnight		(79)[i]	156
	HCO_2H, rt, 29 h		(quant.)	142
	HCO_2H, rt, 18 h		(91)	155

Table 5. (Continued)

Table 5A (Continued)

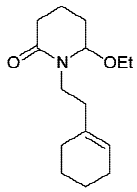
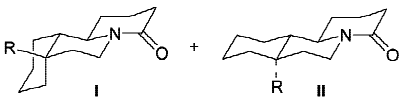
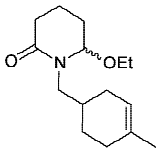
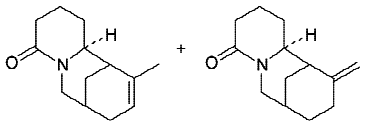
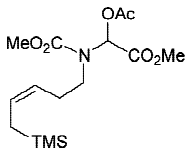
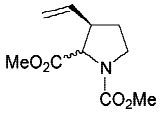
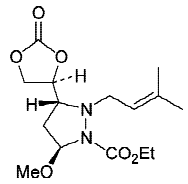
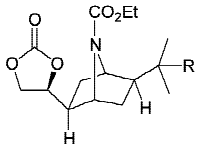
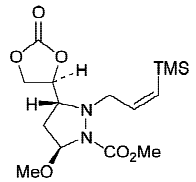
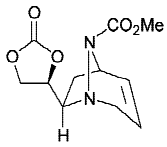
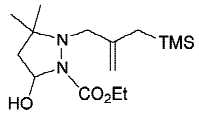
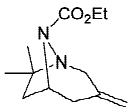
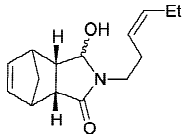
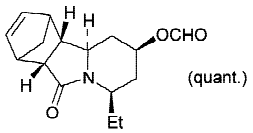
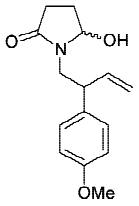
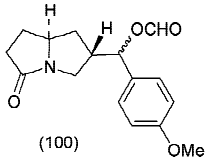
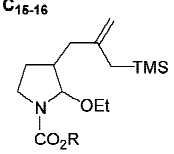
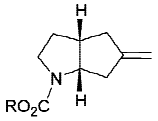
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, 2 h HCO_2H, 16 h HCO_2H, 120 h AcOH, H_2O, 2 h	 I + II R = OCHO (80) I:II = 61:39 R = OCHO (80) I:II = 34:66 R = OCHO (80) I:II = 34:66 R = OH (85) I:II = 69:31	124 130
	HCO_2H, rt, 20 h	 (90) (10)	130
	Et_2AlCl, CH_2Cl_2, 0-20°, 2 h	 (78), α:β = 3.5:1	189 215
	$SnCl_4$, CH_2Cl_2, –78° to rt, 4 h HCO_2H, rt, 18 h	 R = Cl (77) R = OCHO (63)	427
	HCO_2H, rt, 18 h	 (73)	427
	HCO_2H BF_3•Et_2O	 (85) (61)	205
	HCO_2H, rt, 18 h	 (quant.)	142
	HCO_2H, 4 h TFA, CH_2Cl_2, 5°, 0.5 h	 (100) (94)	160
C_{15-16}			
	TFA, CH_2Cl_2, 0°, 4 h	 R = Me (60) R = Et (62)	207

Table 5. (Continued)

Table 5A (Continued)

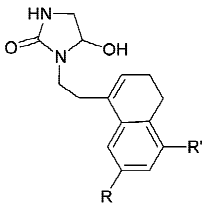
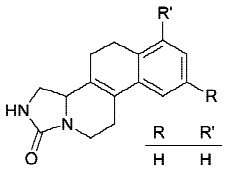
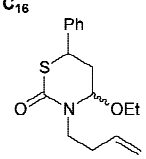
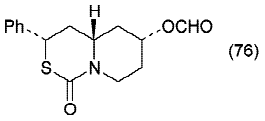
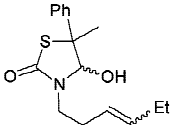
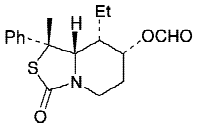
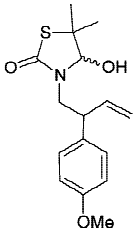
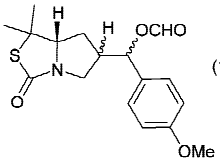
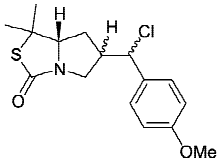
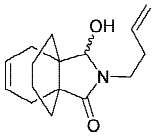
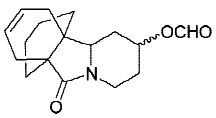
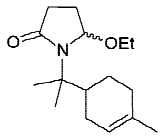
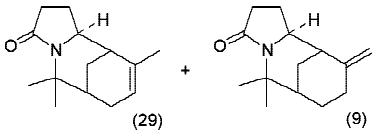
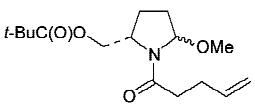
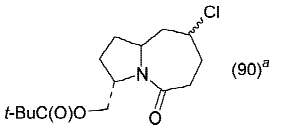
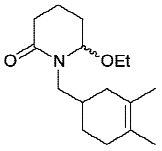
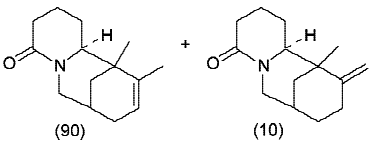
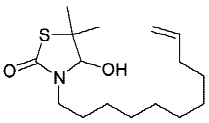
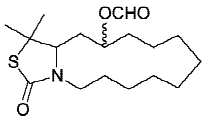
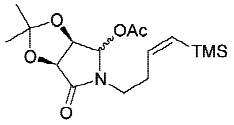
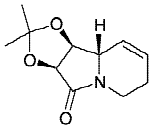
substrate	conditions	product(s) and yield(s) (%)	ref
	PPA, 100°, 6 h	 R R' H H (67) Me H (60) H Cl (39)	652
C_{16}			
	HCO_2H, rt, 4 days	 (76)	610
	HCO_2H	 (87)	429
	HCO_2H, rt, 19 h	 (12)	156
	HCl, MeOH, 17 h, rt	 (11)	156
	HCO_2H, rt, 18 h	 (100)	142
	HCO_2H, rt, 16 h	 (29) (9)	613
	$TiCl_4$, CH_2Cl_2, –78° to rt, 33 h	 (90)[a]	493
	HCO_2H, rt, 5 h	 (90) (10)	130
	HCO_2H, 43°, 913 h	 (84)	156
	BF_3•Et_2O, CH_2Cl_2, rt, 4 h	 (72)	172

Table 5. (Continued)

Table 5A (Continued)

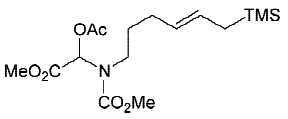
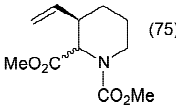
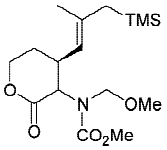
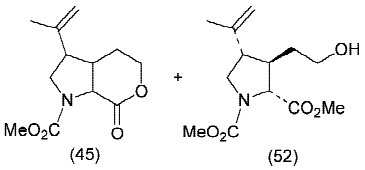
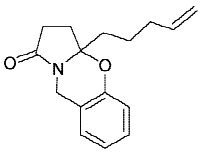
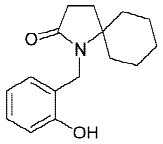
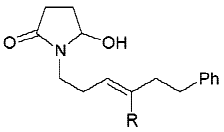
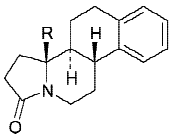
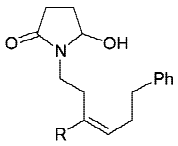
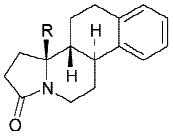
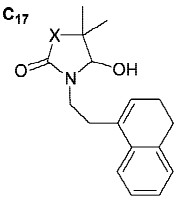
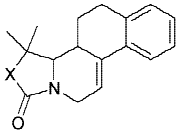
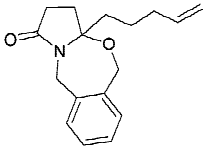
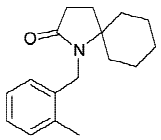
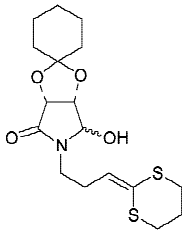
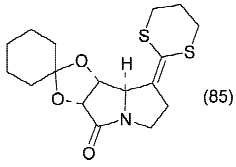
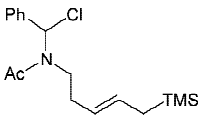
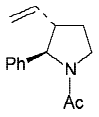
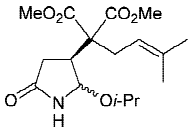
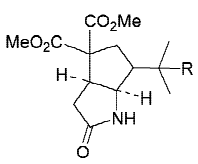
substrate	conditions	product(s) and yield(s) (%)	ref
	Et_2AlCl, CH_2Cl_2, 0-20°, 2 h	 (75), α:β = 1.2:1	189
	1. $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 3.5 h 2. MeOH, rt, 3 h	 (45) + (52)	192
	1. $TiCl_4$, CH_2Cl_2, rt 2. H_2/Pd-C, EtOH, Bu_3SnH, AIBN	 (65)	651
C_{16-17}			
	HCO_2H, rt, 18 h	 R: H (quant.), Me (quant.)	124
	HCO_2H, rt, 69 h	 R: H (quant.), Me (quant.)	124
C_{17}			
	HCO_2H, rt, 1 h	 X: O (65), NH (88)	514
	1. $TiCl_4$, CH_2Cl_2, rt 2. H_2/Pd-C, EtOH, Bu_3SnH, AIBN	 (85)	651
	MsCl, Et_3N, $CHCl_3$, MeCN, 20°, 1 day	 (85)	181
	Et_2AlCl, CH_2Cl_2, 0°-rt, 2 h	 (69)	187
	HCO_2H $TiCl_4$	 R: CO_2H α (57), β (16); Cl α (50), β (30)	395

Table 5. (Continued)

Table 5A (Continued)

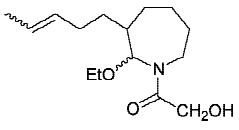
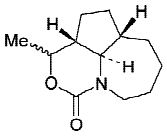
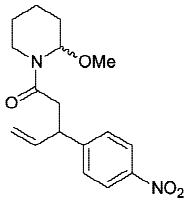
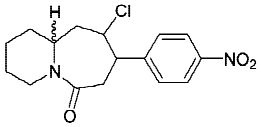
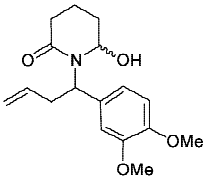
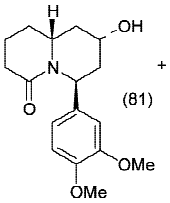
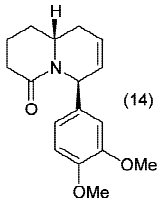
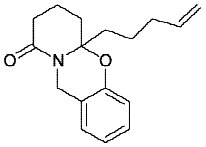
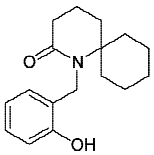
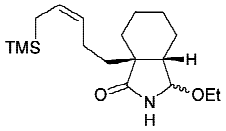
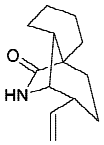
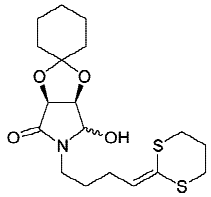
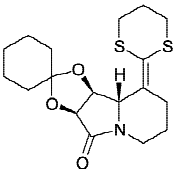
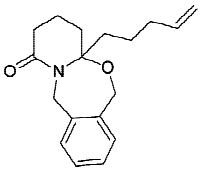
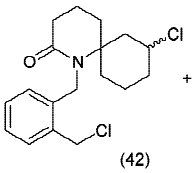
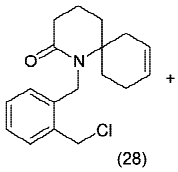
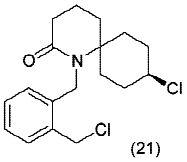
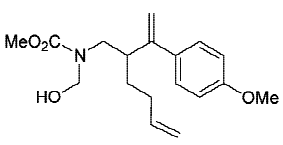
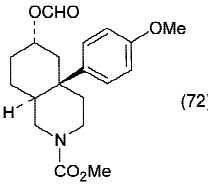
substrate	conditions	product(s) and yield(s) (%)	ref
	$SnCl_4$, CH_2Cl_2, -23°		224
Isomer / Time		α / β	
E / 1.5 h		(0) / (78)	
Z / 8 h		(80) / (0)	
	$TiCl_4$, CH_2Cl_2	 (63)	498
	1. HCO_2H, rt, 1 h 2. KOH, EtOH, 0-5°, 1.5 h	 (81) +  (14)	492
	1. $TiCl_4$, CH_2Cl_2, rt 2. H_2/Pd-C, EtOH, Bu_3SnH, AIBN	 (82)	651
C_{18}			
	HCO_2H, rt, 0.5 h	 (89)	202
	1. MsCl, Et_3N, CH_2Cl_2, 30 min 2. MeCN, rt, overnight	 (60)	183
	$TiCl_4$, CH_2Cl_2, rt, 2 h	 (42) +  (28) +  (21)	651
	HCO_2H	 (72)	145

Table 5. (Continued)

Table 5A (Continued)

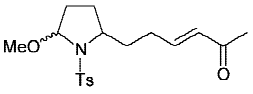
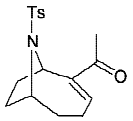
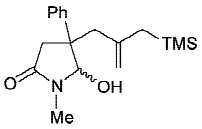
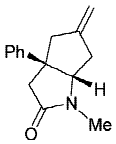
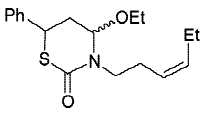
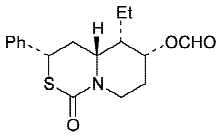
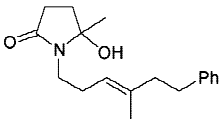
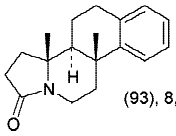
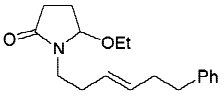
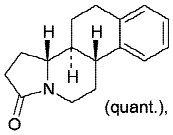
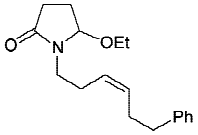
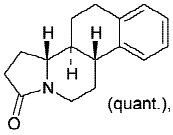
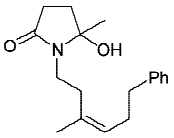
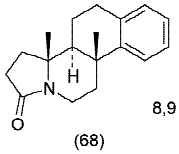
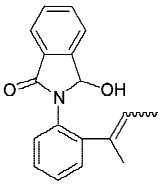
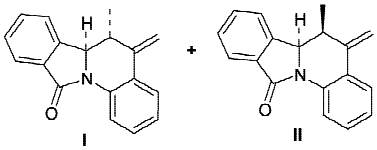
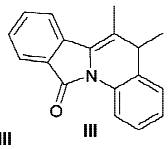
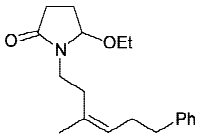
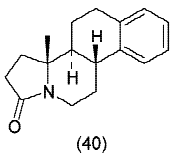
substrate	conditions	product(s) and yield(s) (%)	ref
	1. MeOH, HCl, CH_2Cl_2, –78° 2. DBU, toluene, reflux	 (67)	209
	TFA, CH_2Cl_2, 0-40°, 20 h	 (88)	207
	HCO_2H, rt, 3 days	 (25)	610
	Cl_2CHCO_2H, 0.5 h	 (93), 8,9 *trans;* 8,14 *anti*	124
	HCO_2H, rt, 18 h	 (quant.), 8,9 *trans;* 8,14 *anti*	129 131
	HCO_2H, rt, 18 h	 (quant.), 8,9 *trans;* 8,14 *anti*	129 131
	HCO_2H, rt, 1 h Cl_2CHCO_2H, rt, 0.5 h	 8,9 *trans;* 8,14 *anti* (68) (93)	136
	toluene, reflux	 I + II +  III **I : II : III** 32 : 34 : 34 27 : 27 : 46 **III** (48) **III** (75)	614
	HCO_2H, rt, 18 h Cl_2CHCO_2H, 5°, 0.5 h Ac_2O, AcOH, rt, 20 h HCl, EtOH, 0-10°, 2 h TsOH, C_6H_6, rt, 70 h TFA, CH_2Cl_2, 5°, 0.5 h	 (40) (75) (70) (49) (29) (89)	131

Table 5. (Continued)

Table 5A (Continued)

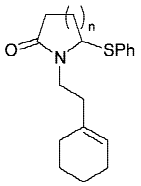
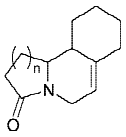
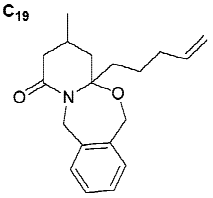
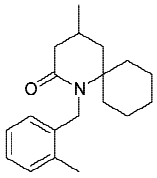
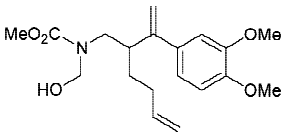
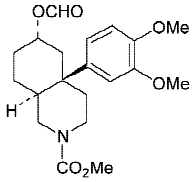
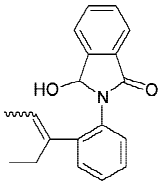
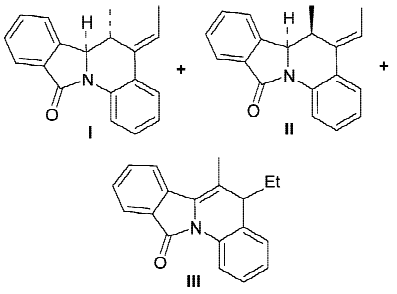
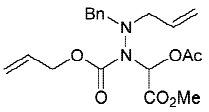
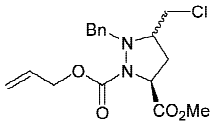
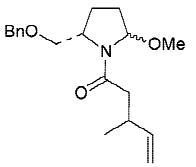
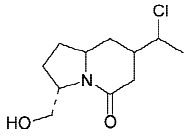
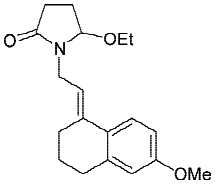
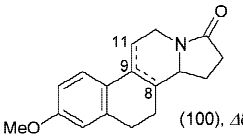
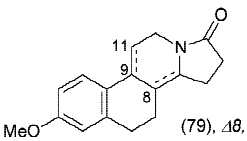
substrate	conditions	product(s) and yield(s) (%)	ref
C_{18-19}			
	BF_3•2AcOH, CH_2Cl_2, 25°	 (54), n = 1 (52), n = 2	343 346
C_{19}			
	1. $TiCl_4$, CH_2Cl_2, rt 2. H_2/Pd-C, EtOH, Bu_3SnH, AIBN	 (99)	651
	HCO_2H	 (74)	145
	toluene, reflux		614
		I II III (25) (65) (0)	
	TsOH (cat.), 40 min		
	TsOH (cat.), 10 days	(22) (57) *E* (21)	
	TsOH (cat.), 25 days	(10) (48) *E* (42)	
	TsOH (1 eq), 1 h	(10) (68) *E* (22)	
	$SnCl_4$, CH_2Cl_2	 (—), *trans*:*cis* = 84:16	428
	$TiCl_4$, CH_2Cl_2	 (82)[a]	621
	C_6H_6, TsOH, heat	 (100), *Δ8,9*:*Δ9,11* = 1:1	653
	1. TsOH, C_6H_6, 80° 2. HCl, MeOH	 (79), *Δ8,9*:*Δ9,11* = 1:1.7	467

Table 5. (Continued)

Table 5A (Continued)

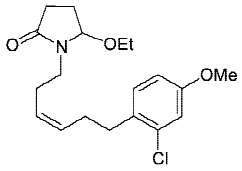
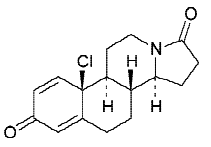
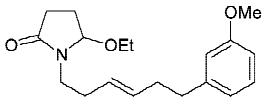
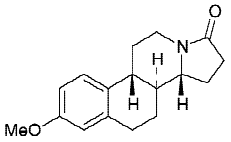
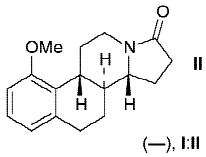
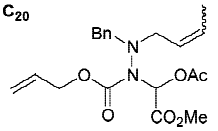
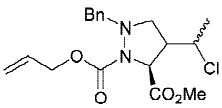
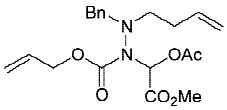
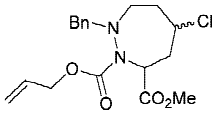
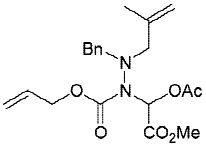
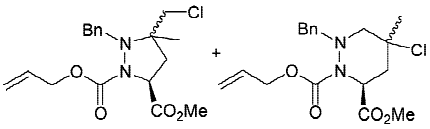
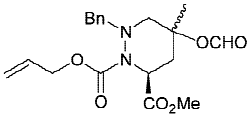
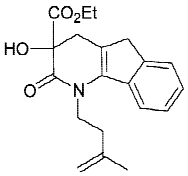
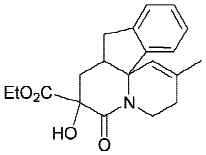
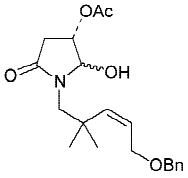
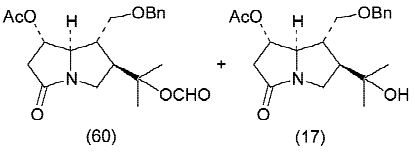
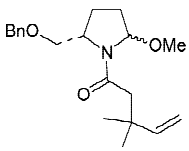
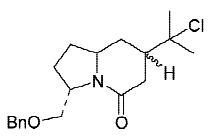
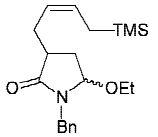
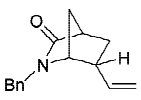
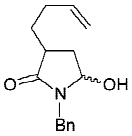
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 18 h	 (30)	513
	HCO_2H, rt	 I +  II (—), I:II = 1.8:1	131
C_{20} 	$SnCl_4$, CH_2Cl_2	 (56)[j]	428
	$SnCl_4$, CH_2Cl_2	 (65)[k]	428
	Et_2AlCl, CH_2Cl_2	 (—), *cis: trans* = 8:19 (—), *cis: trans* = 6:53	428
	HCO_2H, CH_2Cl_2	 (—)	428
	$BF_3{\cdot}Et_2O$, CH_2Cl_2, reflux, 12 h	 (88)	86
	HCO_2H, rt, 24 h	 (60) (17)	152 157
	$TiCl_4$, CH_2Cl_2, –78° to rt	 (89)	621
	HCO_2H, rt, 0.5 h	 (66) +  (27) *endo:exo* = 36:64	202

Table 5. (Continued)

Table 5A (Continued)

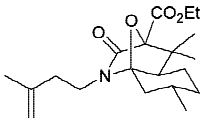
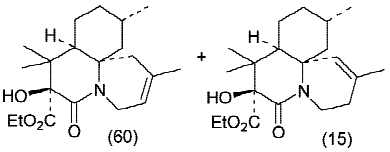
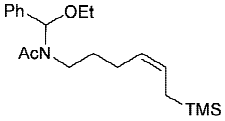
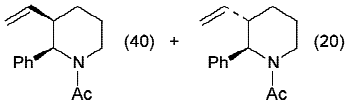
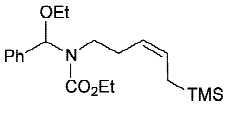
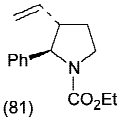
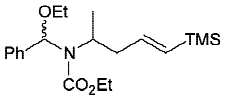
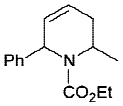
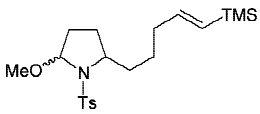
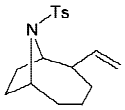
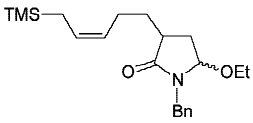
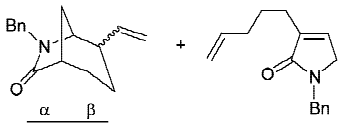
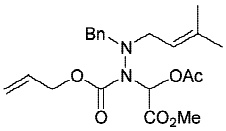
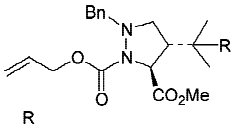
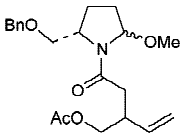
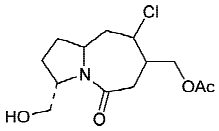
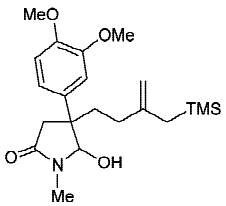
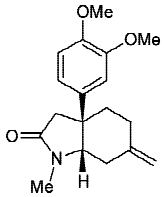
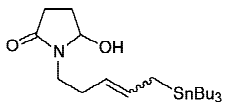
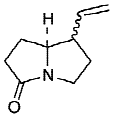
substrate	conditions	product(s) and yield(s) (%)	ref
	BF_3•2AcOH, CH_2Cl_2, rt, 10 h	 (60) + (15)	86, 516
	HCO_2H, rt, 16 h	 (40) + (20)	187
	HCO_2H, rt, 17 h	 (81)	187
	$SnCl_4$, CH_2Cl_2, rt, 2 h	(73)	
	Et_2AlCl, CH_2Cl_2, 0°-rt, 2 h	(69)	
	BF_3•Et_2O, CH_2Cl_2, 0°	 (71)	168
	$TiCl_4$, CH_2Cl_2, –78°	 (76)	209
C_{21}			
	TFA, rt, 0.5-1 h	 α (73) β (4) + (10)	202, 203
	HCO_2H, rt, 0.5-1 h	α (82) β (5) + (<2)	
	CH_2Cl_2		428
	$SnCl_4$	R = Cl (58)	
	HCO_2H	R = OCHO (66)	
	$TiCl_4$, CH_2Cl_2	 (85)	498
	MsCl, Et_3N, CH_2Cl_2, rt, overnight	 (80)	186, 194
	MsCl, Et_3N, CH_2Cl_2, 0°-rt	 (45), α:β = 11:1	211
	Ph_2S_2, Bu_3P; then *hν*	(77), α:β = 74:1	212

Table 5. (Continued)

Table 5A (Continued)

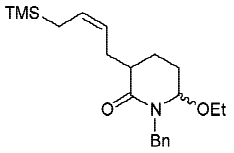
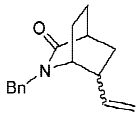
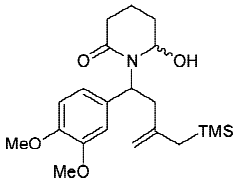
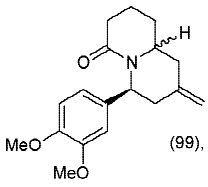
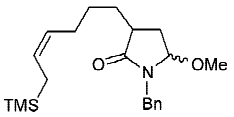
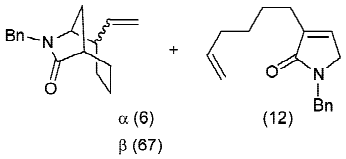
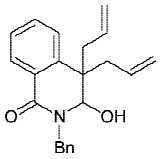
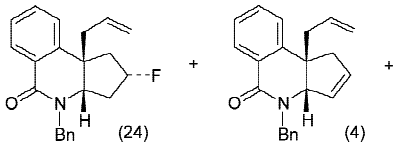
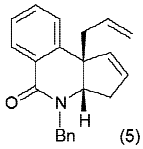
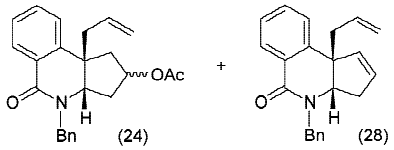
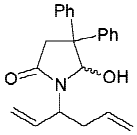
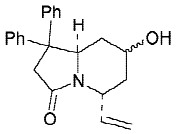
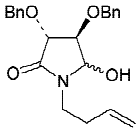
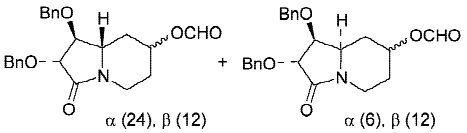
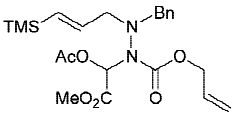
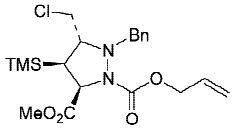
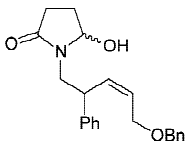
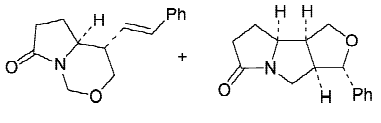
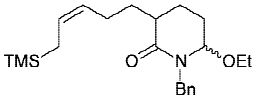
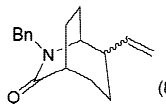
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt , 0.5 h	 (94), *endo*:*exo* = 94:6	202
	TFA, CH_2Cl_2, -78°, 5 h	 (99), α:β = 1:4	197
	TFA, CH_2Cl_2, 0°-rt, 1 h	 α (6) β (67) (12)	202 203
	BF_3•Et_2O, Et_2O, rt, 24 h	 (24) (4)	501
		 (5)	
	1. TMSOTf, -78° 2. BSA, rt, 10.5 h	 (24) (28)	501
	HCO_2H, 22°, 1.5 h	 (70), α:β = 1:13	159
	HCO_2H, rt, 18 h	 α (24), β (12) α (6), β (12)	216
	$SnCl_4$, CH_2Cl_2	 (68)	428
	HCO_2H, rt, 18 h TFA, 60°, 18 h	 (47) (0) (44) (64)	162
	HCO_2H, rt, 0.5-1 h	 (85), α:β = 1:1.4	202 203

Table 5. (Continued)

Table 5A (Continued)

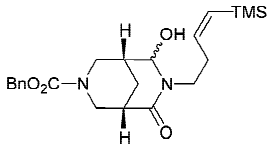
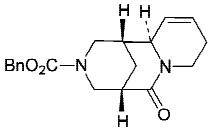
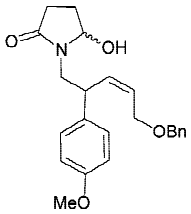
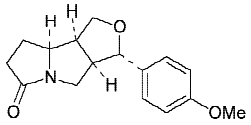
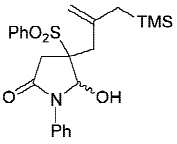
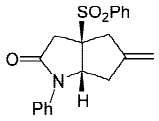
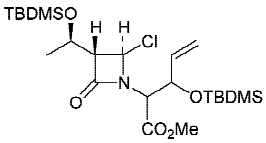
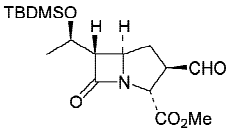
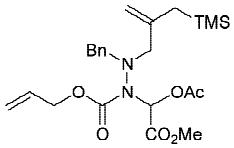
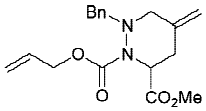
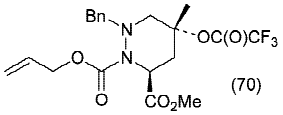
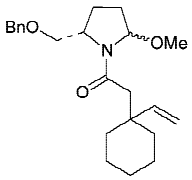
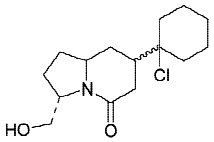
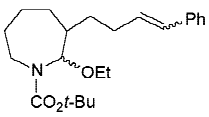
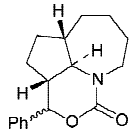
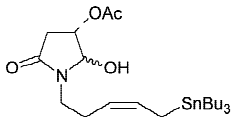
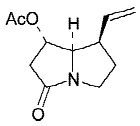
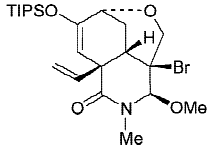
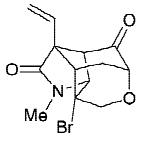
substrate	conditions	product(s) and yield(s) (%)	ref
	TFA, 0°, 6 h	 (72)	175
C_{23}			
	HCO_2H, rt, 70 h HCO_2H, 18 h TFA, 18 h	 (67) (30) (23)	162
	TFA, CH_2Cl_2, 0°, 2 h	 (53)	207
	$AgBF_4$, CH_2Cl_2, –78°	 (33)	165
	Et_2AlCl, CH_2Cl_2	 (83)	428
	TFA, CH_2Cl_2	 (70)	428
	$TiCl_4$, CH_2Cl_2, –78° to rt, overnight	 (94)	497
	$SnCl_4$, CH_2Cl_2, –23°		224
Isomer	Time	α β	
E	1.5 h	(0) (80)	
Z	1 h	(77) (3)	
	MsCl, Et_3N, CH_2Cl_2, rt	 (73)	211
	TFA, reflux, 0.25 h	 (74)	116

Table 5. (Continued)

Table 5A (Continued)

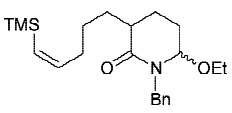
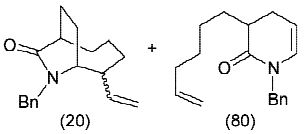
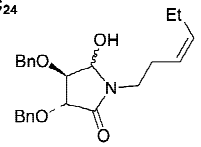
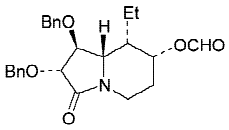
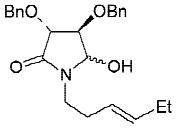
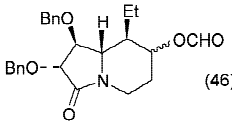
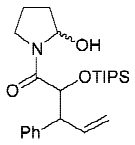
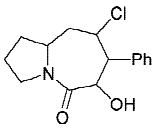
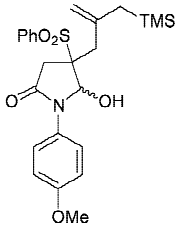
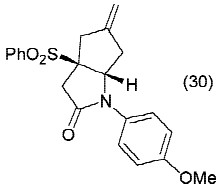
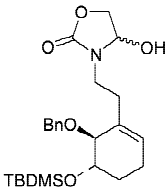
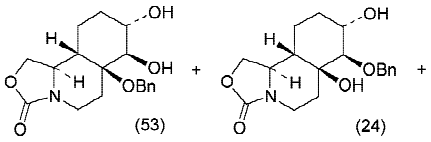
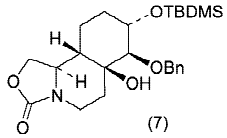
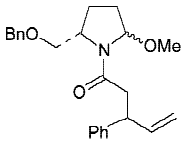
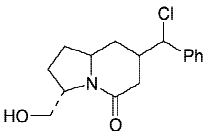
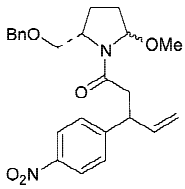
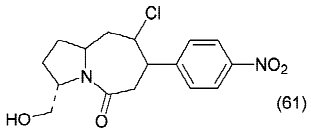
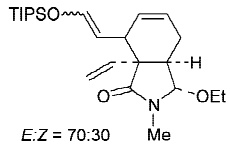
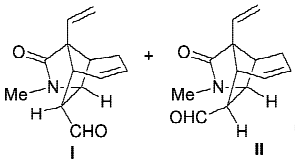
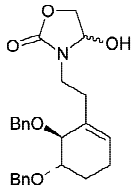
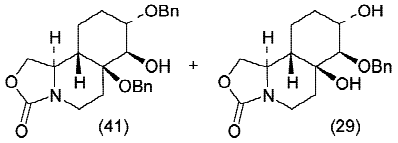
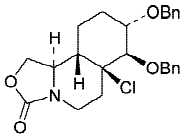
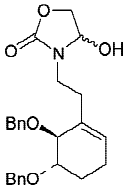
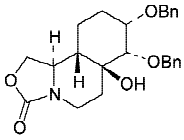
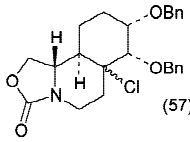
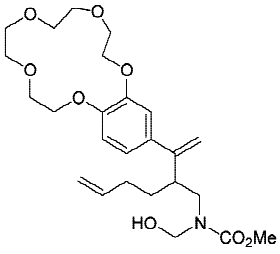
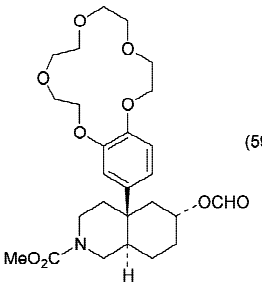
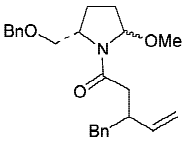
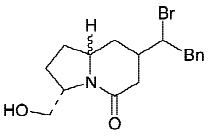
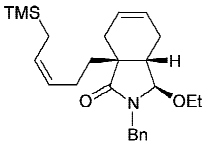
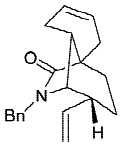
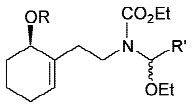
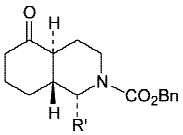
substrate	conditions	product(s) and yield(s) (%)	ref
	$SnCl_4$, CH_2Cl_2, rt, overnight	 (20) (80)	202
C_{24} 	HCO_2H, rt, 18 h	 (62)	216
	HCO_2H, rt, 18 h	 (46), α:β = 3.3:1	216
	$TiCl_4$, CH_2Cl_2	 (51)	308
	TFA, CH_2Cl_2, 0°, 2 h	 (30)	207
	BF_3•Et_2O, CH_2Cl_2, 0°-rt	 (53) (24)  (7)	217
	$TiCl_4$, CH_2Cl_2, –78° to rt	 (90)	496 498
	$TiCl_4$, CH_2Cl_2	 (61)	498
 *E*:*Z* = 70:30	BF_3•Et_2O, CH_2Cl_2, 20°	 I II (—), I:II = 7:3	233

Table 5. (Continued)

Table 5A (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
C_{25}			
	$BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°-rt	 (41) + (29)	217
	1. $AlCl_3$, CH_2Cl_2, rt 2. 0°-rt	 (70)	217
	$BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°-rt	 (55)	217
	1. $AlCl_3$, CH_2Cl_2, rt 2. 0°-rt	 (57), α:β = 3.75:1	217
	HCO_2H	 (59)	145
	$TiBr_4$, CH_2Cl_2	 (89)	498
	HCO_2H, rt, 0.5 h	 (98)	202
$C_{26\text{-}33}$			
	$BF_3{\cdot}Et_2O$, DTBMP, CH_2Cl_2, 0°		616

R	R'	
TIPS	*i*-Pr	(69), 39% ee
TBDPS	*i*-Pr	(91), 88% ee
TIPS	Pr	(87), 87% ee
TBDPS	Pr	(75), 87% ee

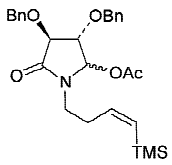
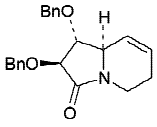
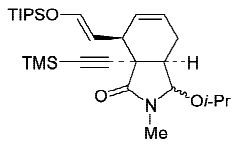
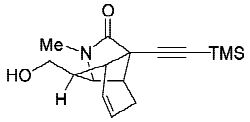
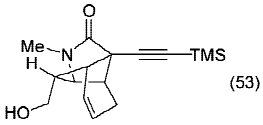
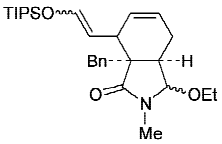
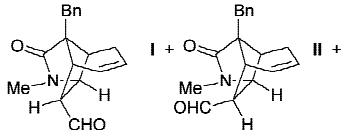
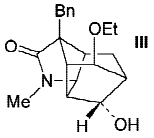
C_{27}			
	$BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 2 h	 (99)	173

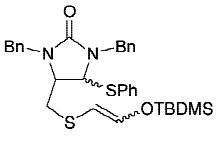
Table 5. (Continued)

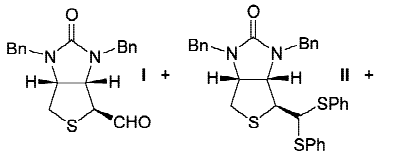
Table 5A (Continued)

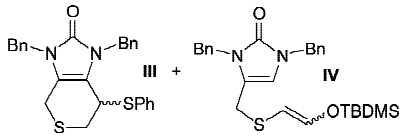
substrate	conditions	product(s) and yield(s) (%)	ref
C_{28}			
	1. TMSOTf, CH_2Cl_2, −15°, 6 h 2. $NaBH_4$, EtOH	 (13) +  (53)	235
C_{29}			
		 	233

E:*Z*		I+II+III	(I+III):II
<10:90	$SnCl_4$, 20 h	(50)	12:88
<10:90	$TiCl_4$, 22 h	(58)	18:82
<10:90	BF_3•Et_2O, 0.6 h	(92)	9:91
>90:10	BF_3•Et_2O, 2 h	(90)	89:11
>90:10	BF_3•Et_2O, 0.45 h	(79)	90:10
>90:10	BF_3•Et_2O, 0.15 h	(80)	94:6

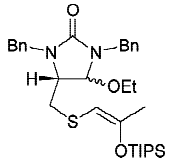
C_{32}



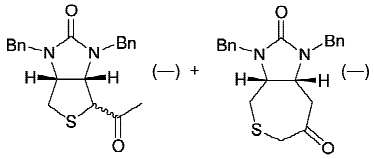




	I	II	III	IV
$AlCl_3$, −78° to rt			(55)	
$TiCl_4$, −78° to rt			(62)	
BF_3•Et_2O, 0°-rt			(43)	
AgOTf, 0°-rt	(5)		(20)	(40)
TBDMSOTf, 0°-rt		(20)	(30)	
PhSH, rt			(61)	
TBDMS-SPh, TBDMSOTf, 0°-rt		(70)		
p-$NO_2C_6H_4CHO$, TBDMSOTf rt, 5 min	(95)			

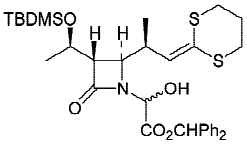


TMSOTf, CH_2Cl_2, −78°, 1 h



237

C_{33}



1. MsCl, Et_3N, MeCN, rt, 1 h
2. Reflux

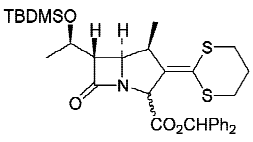
 (73)

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Table 5. (Continued)

Table 5A (Continued)

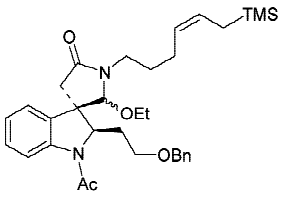
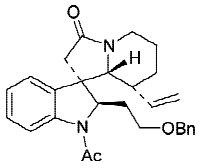
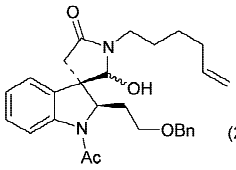
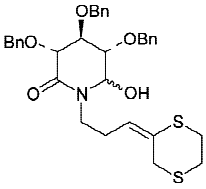
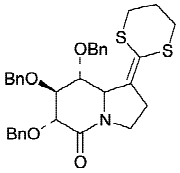
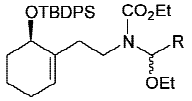
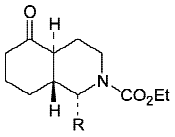
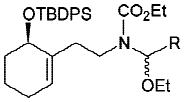
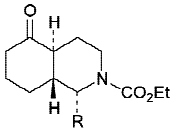
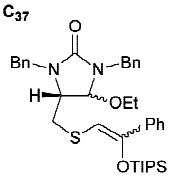
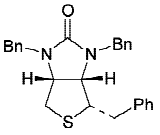
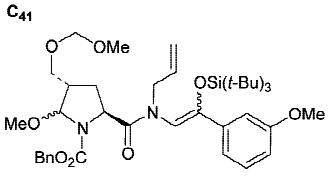
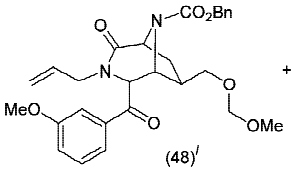
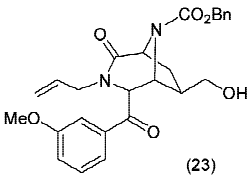
substrate	conditions	product(s) and yield(s) (%)	ref
	$BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 60 h	 (69) +  (26)	191
	MsCl, Et_3N, CH_2Cl_2, –20°, 2 days	 (84)	183
C_{33-34}  R: (*E*)-MeCH=CH; CO_2Et; *t*-Bu	$BF_3{\cdot}Et_2O$, DTBMP, CH_2Cl_2, 0°	 (53), 90% ee; (64), 0-20% ee; (34), 88% ee	616
C_{36-37}  R: Ph; 4-$MeOC_6H_4$; CH_2SPh	$BF_3{\cdot}Et_2O$, DTBMP, CH_2Cl_2, 0°	 (63), 85% ee; (72), 88% ee; (51), 90% ee	616
C_{37}  *E* or *Z* isomer	TMSOTf, CH_2Cl_2, –78°, 1 h	 (91)	237
C_{41} 	$BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°-rt , 0.5 h	 (48)[*l*] +  (23)	236

Table 5. (Continued)

Table 5B. Unimolecular Reactions with Alkenes: Imides, Amides, Enamides, Carbamates, and Ureas

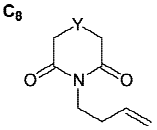
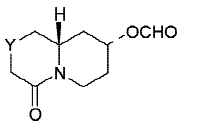
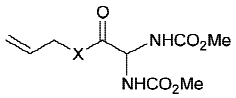
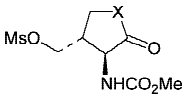
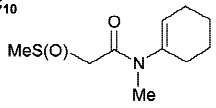
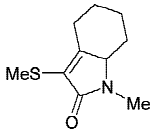
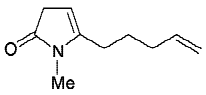
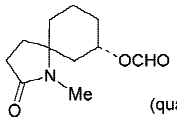
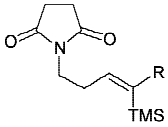
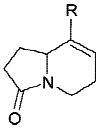
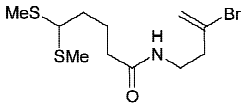
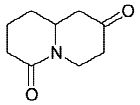
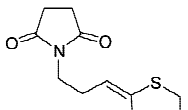
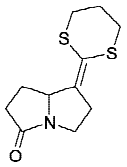
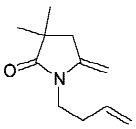
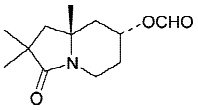
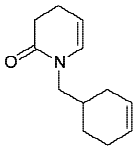
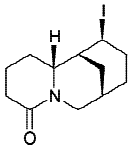
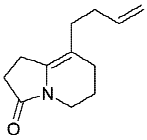
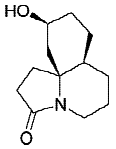
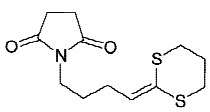
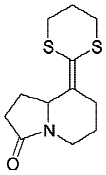
substrate	conditions	product(s) and yield(s) (%)	ref
C_8 	1. $NaBH_4$, HCl, EtOH 2. HCO_2H, rt, 18 h	 Y: O (80), S (78)	510
	MsOH, rt	 X: O (47), NH (51)	517
C_{10} 	TFAA, CH_2Cl_2, 0°	 (22)	72
	HCO_2H, 18 h	 (quant.)	133
C_{11}  R: H, Br	1. $NaBH_4$, MeOH, 0° 2. TFA, T: 25° (H), reflux (Br)	 (92), (63)	169
	1. $(Me_2SSMe)^+BF_4^-$, CH_2Cl_2 –40° to rt 2. 98% HCO_2H, $Hg(OAc)_2$ 12 h	 (58)	345
	1. $NaBH_4$, MeOH, –4°, 1 h 2. MsCl, Et_3N, CH_2Cl_2, –20° to rt, overnight	 (86)	180
	HCO_2H, rt, 18 h	 (69)	322
C_{12} 	TfOH, Bu_4NI, $CHCl_3$, rt	 (73-92)	485
	1. HCO_2H, rt, 2. NH_3, MeOH	 (92)	309
	1. $NaBH_4$, MeOH, -4°, 1 h 2. MsCl, Et_3N, CH_2Cl_2, -20° to rt, overnight	 (70)	180

Table 5. (Continued)

Table 5B (Continued)

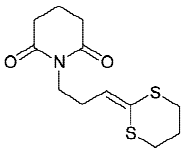
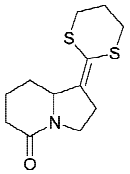
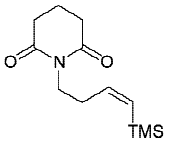
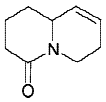
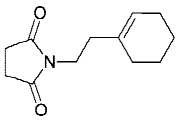
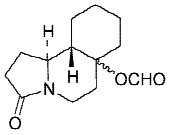
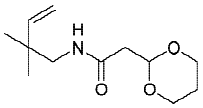
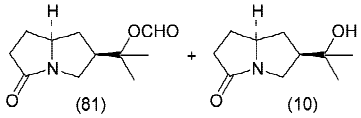
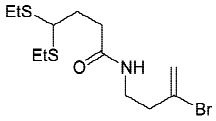
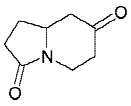
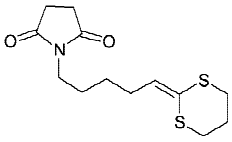
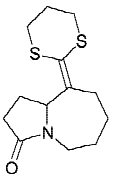
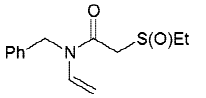
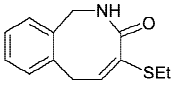
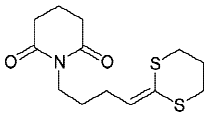
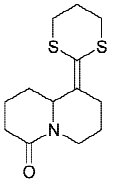
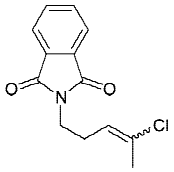
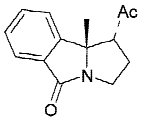
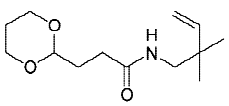
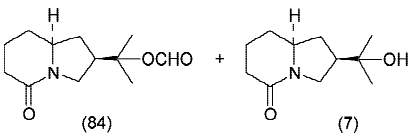
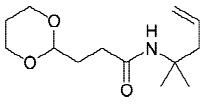
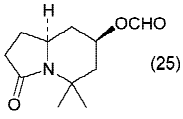
substrate	conditions	product(s) and yield(s) (%)	ref
	1. $NaBH_4$, MeOH, -4°, 1 h 2. MsCl, Et_3N, CH_2Cl_2, -20° to rt, overnight	 (71)	180
	1. $NaBH_4$, MeOH, 0° 2. TFA, rt	 (91)	169
	1. $NaBH_4$, MeOH, 0° 2. HCO_2H, rt, 2 h	 (61)	141
	HCO_2H, rt, 24 h	 (61) (10)	152
	1. $(Me_2SSMe)^+BF_4^-$, CH_2Cl_2 –40° to rt 2. 98% HCO_2H, $Hg(OAc)_2$ 12 h	 (65)	345
C_{13}			
	1. $NaBH_4$, MeOH, -4°, 1 h 2. MsCl, Et_3N, CH_2Cl_2, -20° to rt, overnight	 (48)	180
	Ac_2O, TsOH, C_6H_6, reflux, 3 h	 (42)	655
	1. $NaBH_4$, MeOH, -4°, 1 h 2. MsCl, Et_3N, CH_2Cl_2, -20° to rt, overnight	 (79)	180
	1. MeMgI, Et_2O, rt, 12 h 2. H_2SO_4, 0°, 70 min	 (67)	499
	HCO_2H, rt, 9 h	 (84) (7)	152
	TFA, CH_2Cl_2, Et_3SiH	 (25)	152

Table 5. (Continued)

Table 5B (Continued)

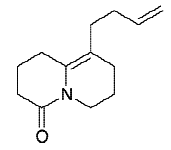
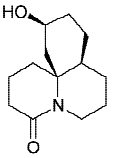
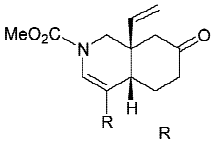
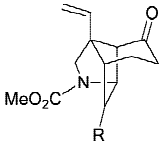
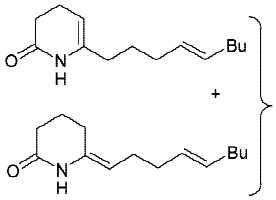
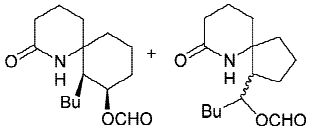
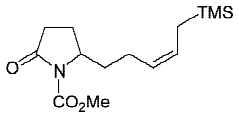
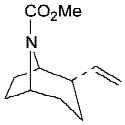
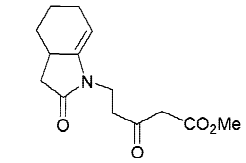
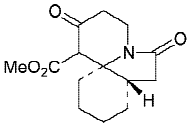
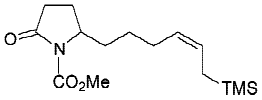
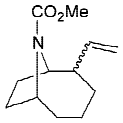
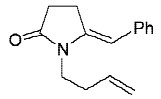
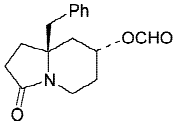
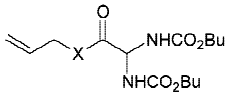
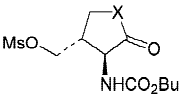
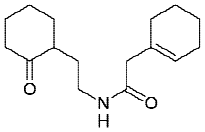
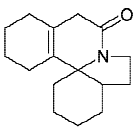
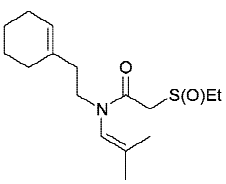
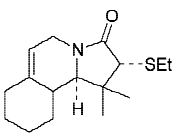
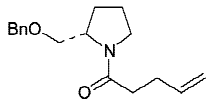
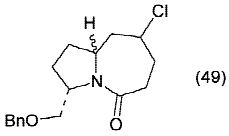
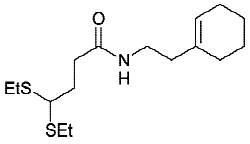
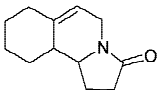
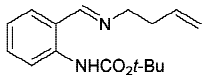
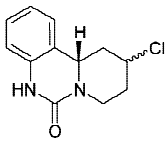
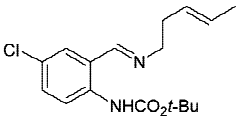
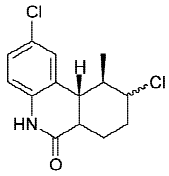
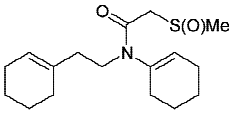
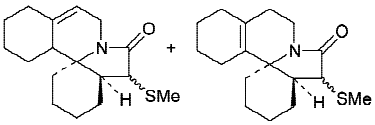
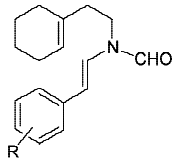
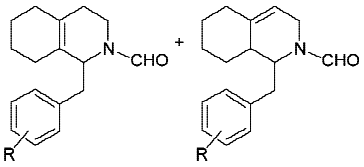
substrate	conditions	product(s) and yield(s) (%)	ref
	1. HCO_2H, rt, 2. NH_3, MeOH	 (60)	309
			231 232
R H Br	HCO_2H, reflux, 4-6 h TFA, reflux, 8-10 h	(65) (85)	
C_{14}			
	HCO_2H, 25°, 32 h	 (40) (30)	507
	1. $NaBH_4$, EtOH, –20° 2. HCO_2H, rt	 (75)	208
	BF_3•Et_2O, CH_2Cl_2, 50°, 1.5 h	 (58)	532
C_{15}			
	1. $NaBH_4$, EtOH, –20° 2. HCO_2H, rt	 (73), α:β = 1:17	208
	HCO_2H, 18 h, rt	 (65)	136
	MsOH, rt	 X: O (64), NH (80)	517
C_{16}			
	PPA, 100°, 20 h PPA, 105°, 21 h	 (61) (—)	24 32
	Ac_2O, TsOH, toluene, reflux, 30 min	 (51)	655

Table 5. (Continued)

Table 5B (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
	1. MeCN, carbon anode, MeOH, Bu_4BF_4 2. $TiCl_4$, CH_2Cl_2, –78° to rt, 40 h	 (49)	496
	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2, rt	 (48)	345
	$TiCl_4$, CH_2Cl_2, reflux	 (65)	339
C_{17}			
	$TiCl_4$, rt	 (40)	339
	TsOH, DCE, reflux, 10 min	 (4) (13)	73
C_{17-18}			
			316

R	conditions		
H	TfOH, CH_2Cl_2, toluene, reflux, 16 h	(60)	(—)
H	TFA:TfOH (8:2), reflux, 2 h	(82)	(—)
H	$H_3PW_{12}O_4$ on SiO_2, toluene, reflux, 20 h	(66)	(—)
H	9-BBNOTf, toluene, rt	(47)	(25)
3-Cl	9-BBNOTf, toluene, rt	(31)	(20)
4-Cl	9-BBNOTf, toluene, rt	(32)	(22)
3-OMe	9-BBNOTf, toluene, rt	(44)	(23)
4-OMe	9-BBNOTf, toluene, rt	(34)	(19)

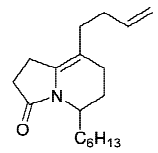
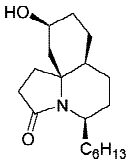
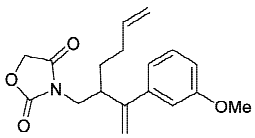
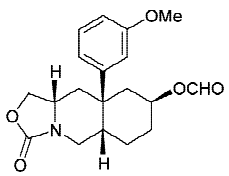
C_{18}			
	1. HCO_2H, rt, 24 h 2. NH_3, MeOH, rt	 (70)	309
	1. DIBAL-H, Et_2O, -78° 2. HCO_2H	 (68)	147

Table 5. (Continued)

Table 5B (Continued)

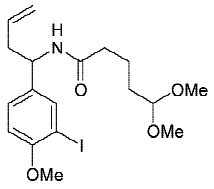
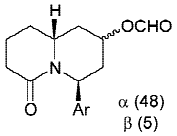
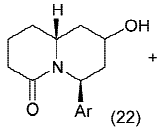
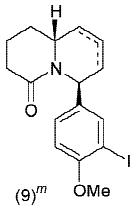
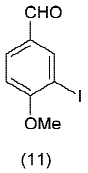
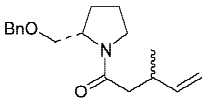
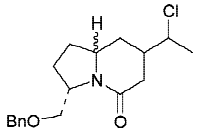
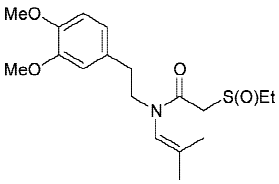
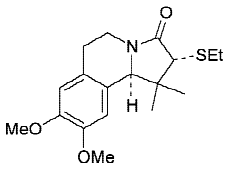
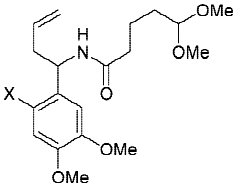
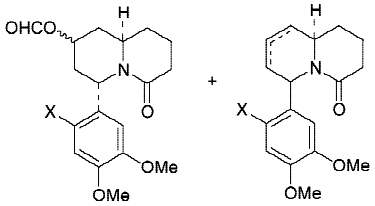
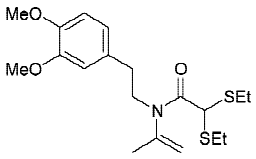
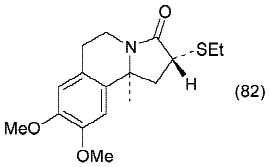
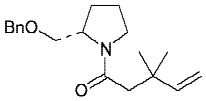
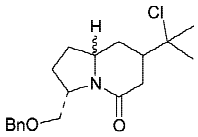
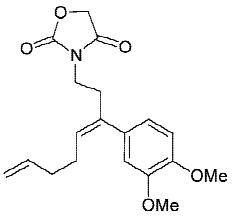
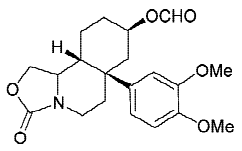
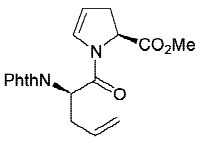
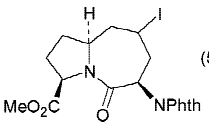
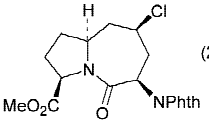
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, CH_2Cl_2	 α (48) β (5) +  (22) +  $(9)^m$ +  (11)	490 491
	1. Pt cathode, Et_4NOTs, MeOH, 26.8 mA 2. $TiCl_4$, CH_2Cl_2, -78° to rt	 (39)	496
	Ac_2O, TsOH, toluene, reflux, 30 min	 (56)	655
C_{19}  X = H, Br, I	HCO_2H, CH_2Cl_2, 25°, 4 h	 (69), α:β = 1:6.7 (21)^m	489
	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2 –40° to rt	 (82)	655
	1. Pt cathode, Et_4NOTs, MeOH, 26.8 mA 2. $TiCl_4$, CH_2Cl_2, -78° to rt	 (59)	496
	1. $NaBH_4$, MeOH, 0°, 10 min 2. HCO_2H, rt, 3 h	 (77)	148
	1. TfOH, Tf_2O, CH_2Cl_2, rt, 3 h 2. NaI, MeC(O)Et, rt, 1.5 h	 (58) +  (21)	313

Table 5. (Continued)

Table 5B (Continued)

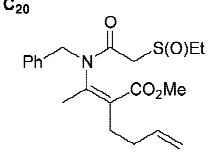
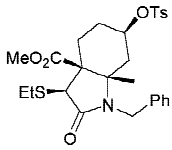
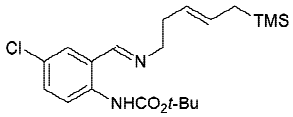
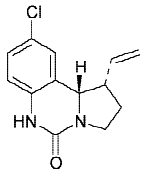
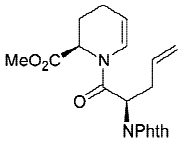
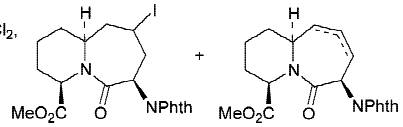
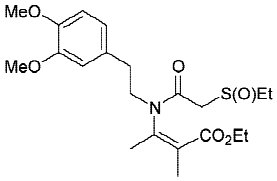
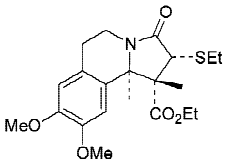
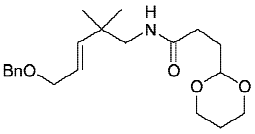
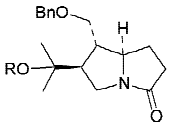
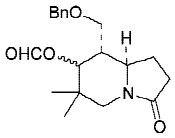
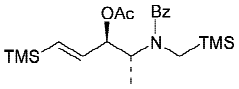
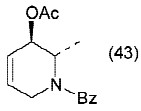
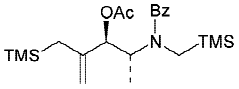
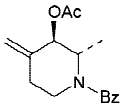
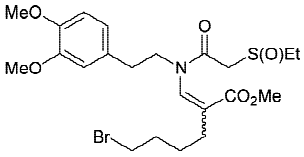
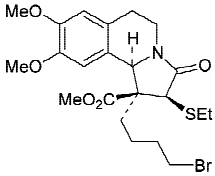
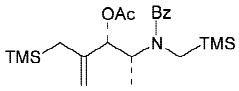
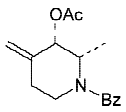
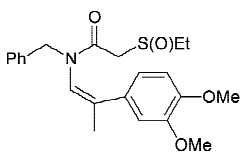
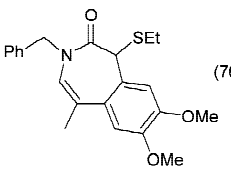
substrate	conditions	product(s) and yield(s) (%)	ref
C_{20} 	$TsOH$, C_6H_6, reflux	 (80)	344, 655
	$TiCl_4$, CH_2Cl_2, rt	 (62-72)	339
	1. $TfOH$, Tf_2O, CH_2Cl_2, rt, 5.5 h 2. CH_2N_2 3. NaI, MeC(O)Et, rt, 1 h	 (59) + (14)[m]	313
C_{21} 	$TsOH$, C_6H_6, reflux	 (78)	655
	HCO_2H, rt, 21 h	 R = CHO, (70) + R = H, (10) +  (9)	151
	1. $Ce(NH_4)_2(NO_3)_6$, MeCN, rt 2. Silica gel	 (43)	177
C_{22} 	1. $Ce(NH_4)_2(NO_3)_6$, MeCN, rt 2. Silica gel	 (48)	177
	CSA, C_6H_6, reflux	 (88)[n]	656
	1. $Ce(NH_4)_2(NO_3)_6$, MeCN, rt 2. Silica gel	 (67)	177
	$TsOH$, C_6H_6, reflux, 20 min	 (76)	656

Table 5. (Continued)

Table 5B (Continued)

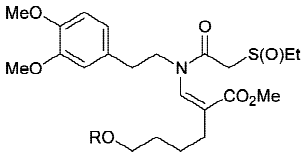
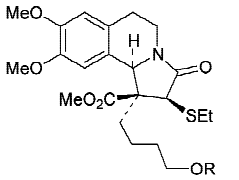
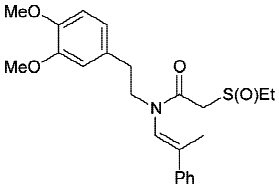
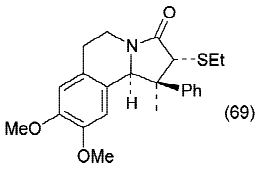
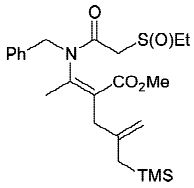
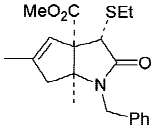
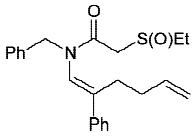
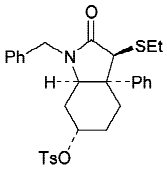
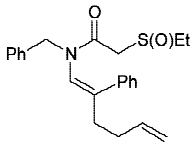
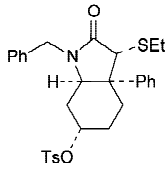
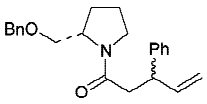
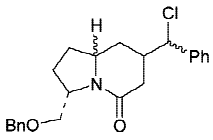
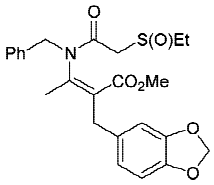
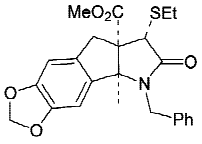
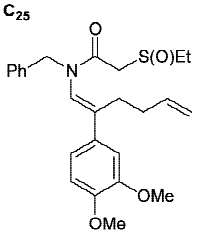
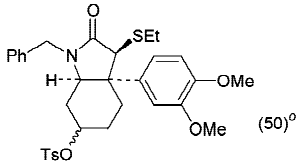
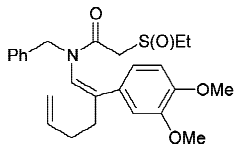
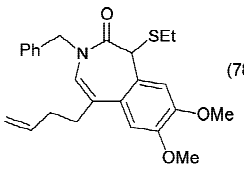
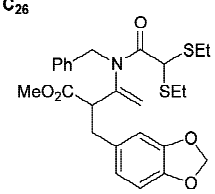
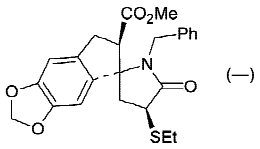
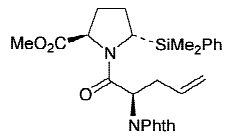
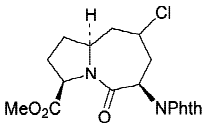
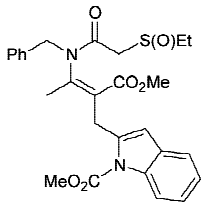
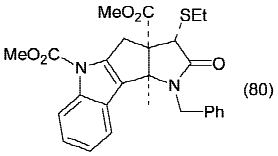
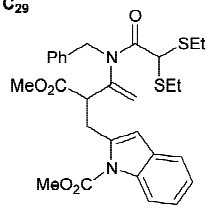
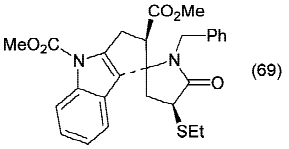
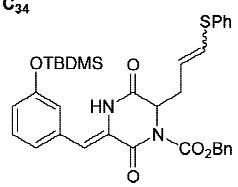
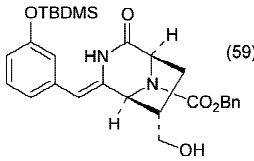
substrate	conditions	product(s) and yield(s) (%)	ref
C_{22-29}			
	CSA, C_6H_6, reflux	 R: CH_2Ph (67); THP (85); TBDMS (80); H (96)	656
	TsOH, C_6H_6, reflux	 (69)	655
	TsOH, C_6H_6, reflux	 (61)	655
	TsOH, C_6H_6, reflux, 20 min	 (76)[j]	656
	TsOH, C_6H_6, reflux, 20 min	 (70)	656
	1. Pt cathode, Et_4NOTs, MeOH, 26.8 mA 2. $TiCl_4$, CH_2Cl_2, –78° to rt	 (54)	496
C_{24}			
	TsOH, C_6H_6, reflux	 (79)	655
C_{25}			
	TsOH, C_6H_6, reflux, 1 h	 (50)[o]	656
	TsOH, C_6H_6, reflux, 1 h	 (78)	656

Table 5. (Continued)

Table 5B (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
C_{26} 	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2, –40°, 1 h	 (—)	655
C_{27} 	$TiCl_4$, CH_2Cl_2, –78° to rt	 (64)	657
	TsOH, C_6H_6, reflux	 (80)	655
C_{29} 	$(Me_2SSMe)^+BF_4^-$, CH_2Cl_2	 (69)	655
C_{34} 	1. $NaBH_4$, MeOH, –20° 2. $HgCl_2$, MeCN, H_2O, 40° 3. $NaBH_4$, MeOH, CH_2Cl_2, 0°	 (59)	182

[a] The compound was a mixture of stereoisomers. [b] Other isomers were detected by NMR. [c] An unsaturated cyclized product (5%) was also formed. [d] The product containg 5−10% of the unsaturated cyclized product. [e] The compound was a mixture of epimers at C_4. [f] The reaction involved enamide formation. [g] The reaction involved enamide/hydroxylactam formation. [h] The compound was a 2:1 mixture of diastereomers. [i] The compound was a 3:2 mixture of diastereomers. [j] The compound was a 5:1 mixture of diastereomers. [k] The compound was a 1:1 mixture of diastereomers. [l] Both products were 2:1 mixtures of epimers adjacent to the benzoyl group. [m] The compound was a mixture of olefin isomers. [n] The compound was a mixture of four diastereomers. [o] The compound was a 3:1 mixture of diastereomers.

Table 6. Unimolecular Reactions with Alkynes and Allenes

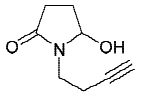
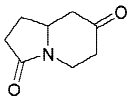
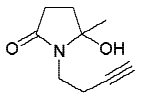
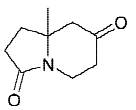
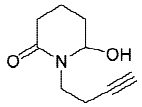
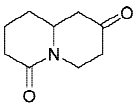
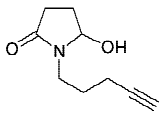
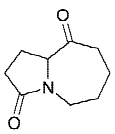
substrate	conditions	product(s) and yield(s) (%)	ref
C_8 	HCO_2H, rt, 72 h	 (high)	124
C_9 	HCO_2H, rt, 90 h	 (45)	136
	HCO_2H, rt, 72 h	 (high)	124
	HCO_2H, rt, 72 h	 (quant.)	124

Table 6. (Continued)

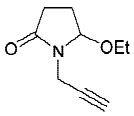
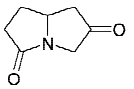
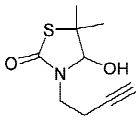
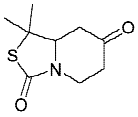
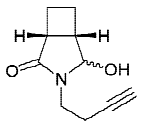
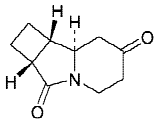
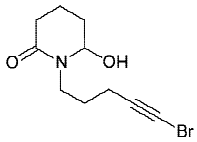
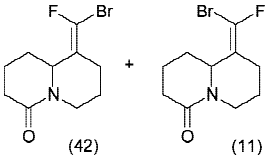
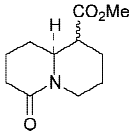
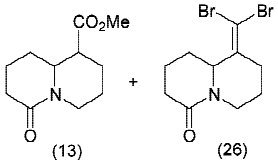
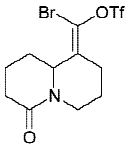
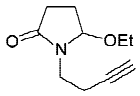
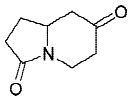
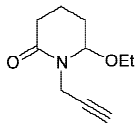
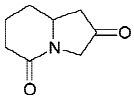
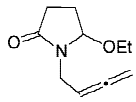
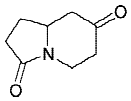
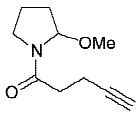
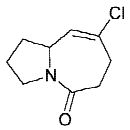
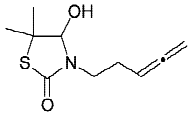
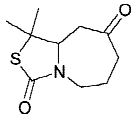
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 72 h	 (97)	46
	HCO_2H, rt, 94 h	 (80)	429
C_{10} 	HCO_2H, rt, 60 h	 (87)	142
	HF, 0°, 3 h	 (42) (11)	225
	1. TFA, 20°, 2 h 2. MeOH, reflux, 3 h	 (60), α:β = 1.2:1	225
	1. TFA, CH_2Cl_2, 20°, 2 h 2. MeOH, reflux, 3 h	 (13) (26)	225
	TFA, TfOH, CH_2Cl_2, 20°, 18 h	 (70)	225
	HCO_2H, rt,		
	72 h	(97)	528
	5 days	(92)	46
	HCO_2H, rt, 92 h	 (88)	46
	HCO_2H, rt, 44 h	 (95)	528
	$TiCl_4$, CH_2Cl_2, –78° to rt, 33 h	 (70)	493
	HCO_2H, reflux, 93 h	 (87)	429

Table 6. (Continued)

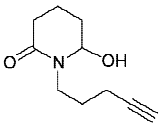
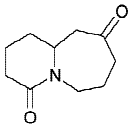
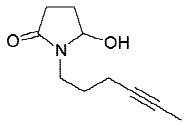
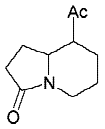
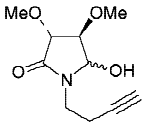
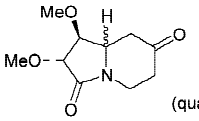
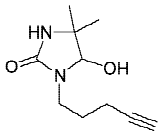
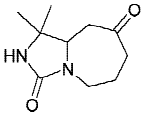
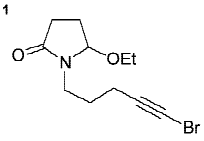
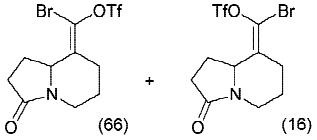
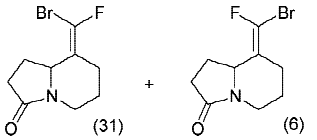
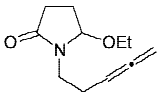
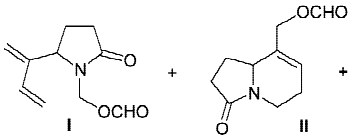
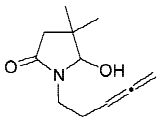
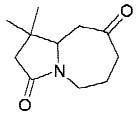
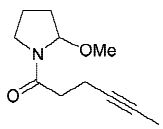
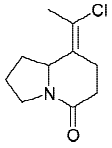
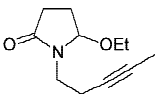
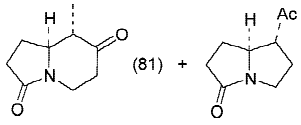
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 72 h	 (quant.)	124
	HCO_2H	 (high)[a]	124
	HCO_2H, 43°, 120 h	 (quant.), α:β = 1:1	138
	TFAA, TFA, CH_2Cl_2, reflux, 65 h	 (46)	520
C_{11} 	TFA, TfOH, CH_2Cl_2, 20°, 24 h	 (66) + (16)	225
	HF, 0°, 3-12 h	 (31) + (6)	225
		 I + II + III	153 528
	HCO_2H, rt, 18 h	I: (II+III) 36:65	
	HCO_2H, HCO_2Na, rt, 18 h	27:73	
	HCO_2H, 76°, 5 h	0:100	
	Cl_2CHCO_2H, rt, 18 h	50:50	
	TFA, CH_2Cl_2, 0-5°, 0.5 h	45:55	
	TsOH, C_6H_6, 80°, 5 h	45:55	
	HCO_2H, CH_2Cl_2, rt, 18 h	47:53	
	HCO_2H, reflux, 93 h	 (75)	429
	$TiCl_4$, CH_2Cl_2, –78° to rt, 33 h	 (82)	493
	HCO_2H, rt, 3 days	 (81) + (9)	658 46

Table 6. (Continued)

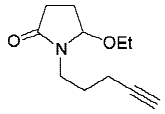
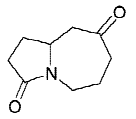
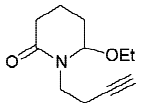
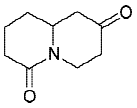
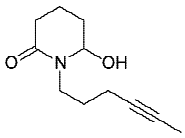
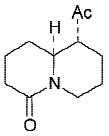
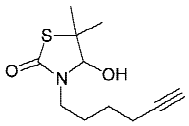
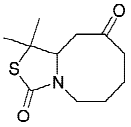
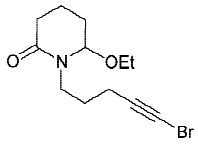
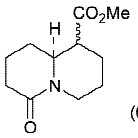
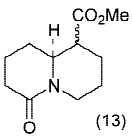
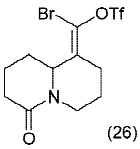
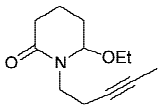
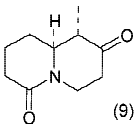
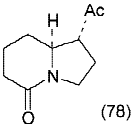
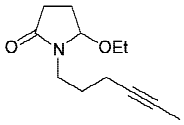
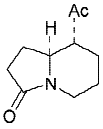
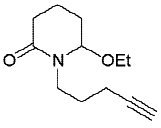
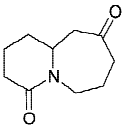
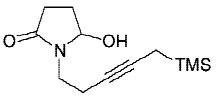
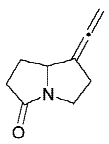
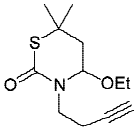
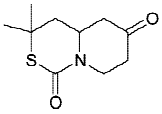
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 3 days	 (100)	658
	HCO_2H, rt, 5 days	(92)	528, 46
	HCO_2H, rt, 3 days	 (100)	658
	HCO_2H, rt, 5 days	(88)	46
	HCO_2H	 (high)	124
	HCO_2H, rt, 43°, 280 h	 (70)	429
C_{12}			
	1. TFA, 20°, 2 h 2. MeOH, reflux, 3 h	 (60), α:β = 1.2:1	226
	1. TFA, CH_2Cl_2, 20°, 2 h 2. MeOH, reflux, 3 h	 (13) +  (26)	226
	HCO_2H, rt, 72 h	 (9) +  (78)	658 46
	HCO_2H, rt, 72 h	 (92)	658 46
	HCO_2H, rt, 14 days	 (90)	46 528
	TFA, CH_2Cl_2, 0°, 2 h	 (70-90)	188 204
	HCO_2H, rt, 7 days	 (45)	610

Table 6. (Continued)

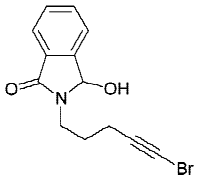
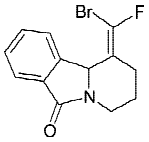
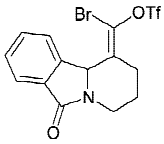
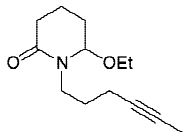
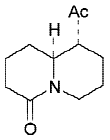
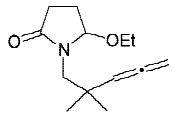
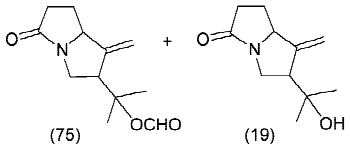
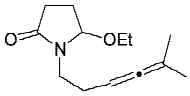
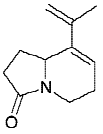
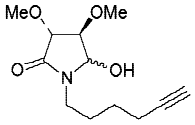
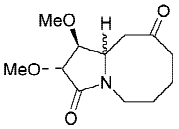
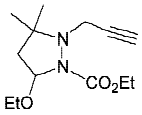
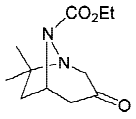
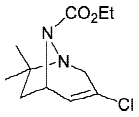
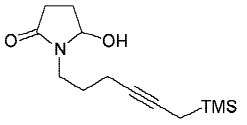
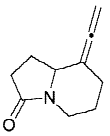
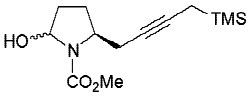
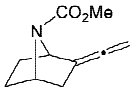
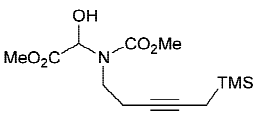
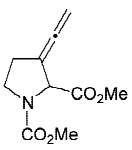
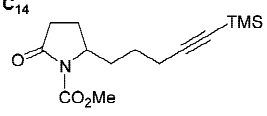
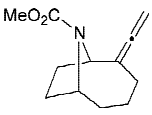
substrate	conditions	product(s) and yield(s) (%)	ref
C_{13}			
	HF, 0°, 3-12 h	 (84)	226
	TFA, TfOH, CH_2Cl_2, 20°, 24 h	 (60)	226
	HCO_2H, rt, 72 h	 (88)	658 46
	HCO_2H, rt, 18 h	 (75) (19)	153
	HCO_2H, rt, 18 h	 (quant.)	153
	HCO_2H, 30°, 13 days	 (quant.), α:β = 1:100	138 216
	HCO_2H	 (47)	205
	$TiCl_4$	 (24)	205
	TFA, CH_2Cl_2, 0°, 1 h	 (85)	188
	HCO_2H, 0°-rt, 10 min	 (74)	221
	1. MsCl, Et_3N, MeCN, rt 2. Reflux, 3 h	 (42)	189
C_{14}			
	1. $NaBH_4$, EtOH, −20° 2. HCO_2H, rt	 (70)	208

Table 6. (Continued)

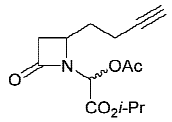
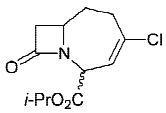
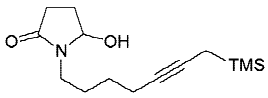
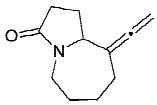
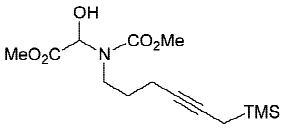
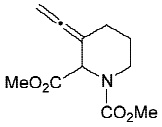
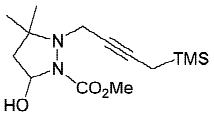
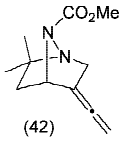
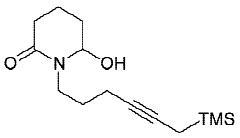
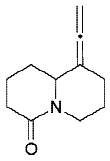
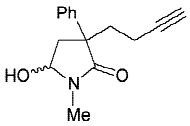
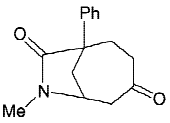
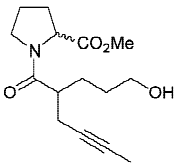
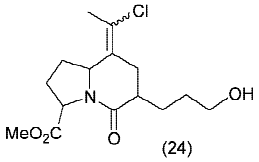
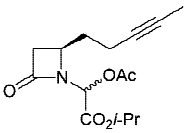
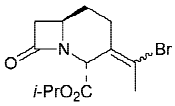
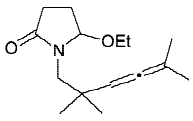
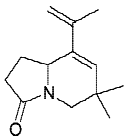
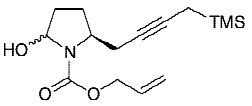
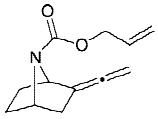
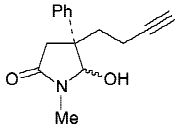
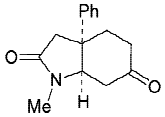
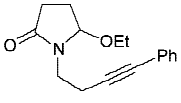
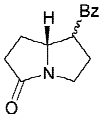
substrate	conditions	product(s) and yield(s) (%)	ref
	$SnCl_4$, CH_2Cl_2, 0°, 6 h	 (12)	223
	TFA, CH_2Cl_2, 0°, 2 h	 (90)	204
	1. MsCl, Et_3N, MeCN, rt 2. Reflux, 3 h	 (—)	189
	HCO_2H $BF_3{\bullet}Et_2O$	 (42) (62)	205
	TFA, CH_2Cl_2, 0°, 2 h	 (95)	188
C_{15}			
	HCO_2H, rt, 45 h	 (37)	127
	1. MeCN, carbon anode, Et_4NBF_4, K_2CO_3, 15.0 mA, 3.18 F/mol 2. $TiCl_4$, CH_2Cl_2, -78° to rt	 (24)	220
	$SnBr_4$, CH_2Cl_2, 0°-rt, 6 h	 (51)[b]	223
	HCO_2H, rt, 18 h	 (quant.)	153
	HCO_2H, 0°-rt, 10 min	 (27)	221
	HCO_2H, rt, 72 h	 (95)	127 132
C_{16}			
	1. HCO_2H, rt, 144 h 2. HCl	 (quant.), α:β = 45:55	218

Table 6. (Continued)

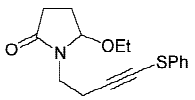
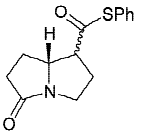
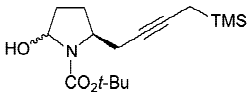
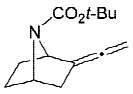
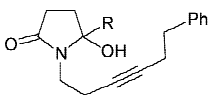
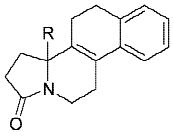
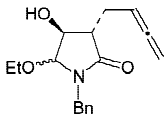
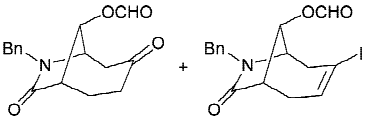
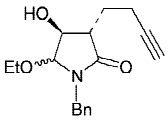
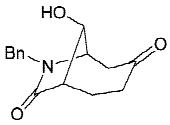
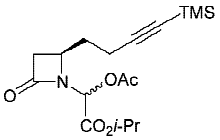
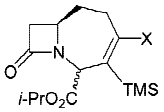
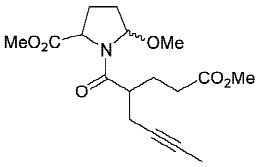
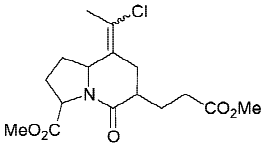
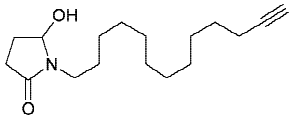
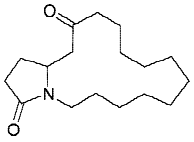
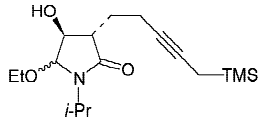
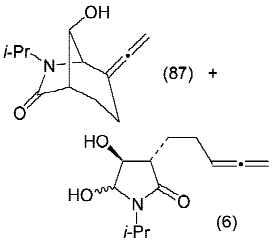
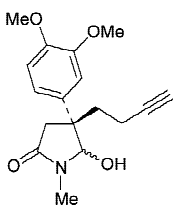
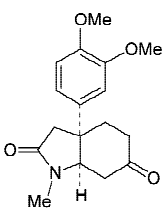
substrate	conditions	product(s) and yield(s) (%)	ref
	1. HCO_2H, rt, 72 h 2. HCl	 (80), α:β = 1:4	218 612
	HCO_2H, 0°-rt, 10 min	 (25)	221
C_{16-17}			
	HCO_2H	 R: H (quant.), Me (quant.)	124
C_{17}			
			
	HCO_2H, 85°, 18 h	(79) (0)	528, 529
	HCO_2H, NaI, 85°, 18 h	(34) (42)	529
	HCO_2H, 85°, 2.5 days	 (52)	528
	SnX_4, CH_2Cl_2, 0°-rt X: Br, Time: 8 h Cl, 4 h	 (70) (70)	223
	$TiCl_4$, CH_2Cl_2, –78° or rt	 (—)	220 391 496
	HCO_2H, 20 days, 43°	 (82)	156
	HCO_2H, NH_3, MeOH	 (87) + (6)	219
	HCO_2H, rt, 120 h	 (85)	132

Table 6. (Continued)

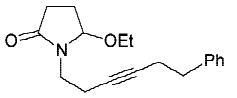
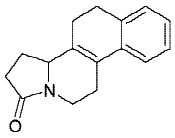
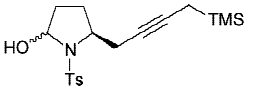
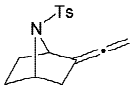
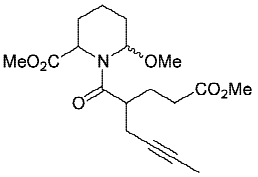
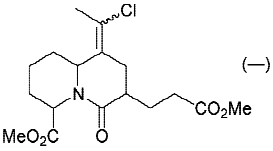
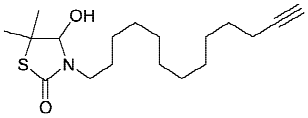
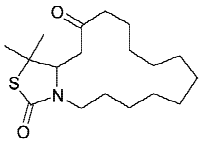
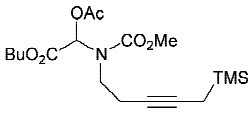
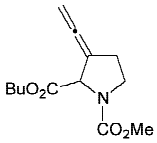
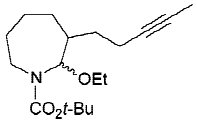
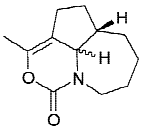
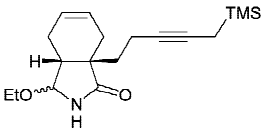
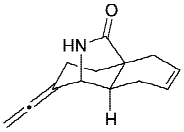
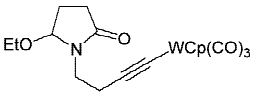
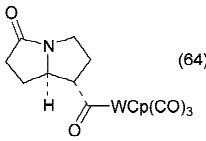
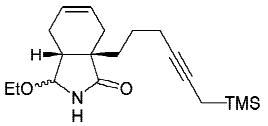
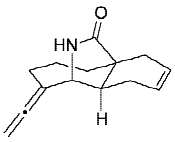
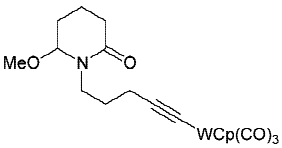
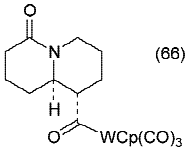
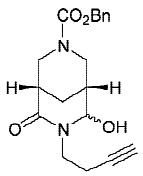
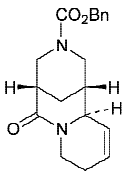
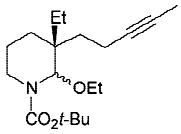
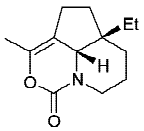
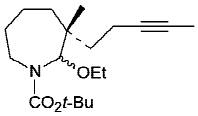
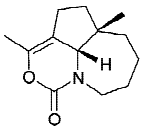
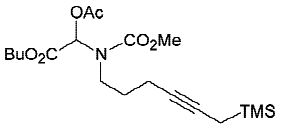
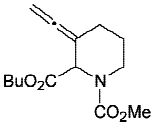
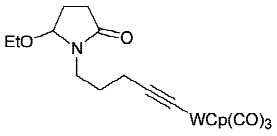
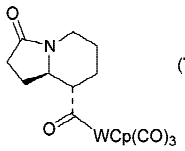
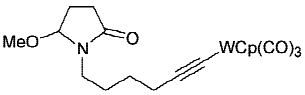
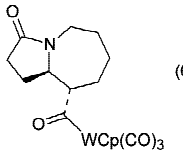
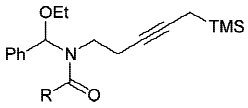
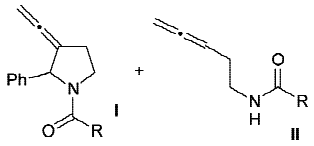
substrate	conditions	product(s) and yield(s) (%)	ref
C_{18}			
	HCO_2H, rt, 18 h	 (quant.)	129, 131
	HCO_2H, 0°-rt, 10 min	 (75)	221
	$TiCl_4$, CH_2Cl_2, -78° to rt	 (—)	220
	HCO_2H, 43°, 451 h	 (75)	156
	Et_2AlCl, CH_2Cl_2, 0°-rt, 2 h	 (50)	189
	$SnCl_4$, CH_2Cl_2, -23°, 1-2 h	 (90), α:β = 2.2:1	224
	HCO_2H, 0.5 h	 (91)	539
	BF_3•Et_2O, Et_2O, –78° to rt	 (64)	659
C_{19}			
	HCO_2H, 0.5 h	 (100)	539
	BF_3•Et_2O, Et_2O, –78° to rt, 3 h	 (66)	659
	HCO_2H, 85°, 36 h	 (65)	175

Table 6. (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
	$SnCl_4$, CH_2Cl_2, –78°, 1 h	 (90)	224
	$SnCl_4$, CH_2Cl_2, -23°, 1 h	 (69)	224
	BF_3•Et_2O, CH_2Cl_2, 0°-rt, 2 h	 (50)	189
	BF_3•Et_2O, Et_2O, –78° to rt	 (71)	659
	BF_3•Et_2O, Et_2O, –78° to rt	 (62)	659
C_{19-20}			
			537

R		I	II	I:II
Me	HCO_2H, rt, 17 h	(68)	(0)	(—)
OEt	HCO_2H, rt, 17 h	(—)	(—)	1:1
OEt	Et_2AlCl, CH_2Cl_2, 0°	(55)	(0)	(—)

C_{20}

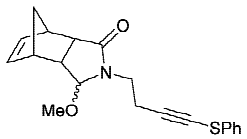
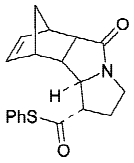
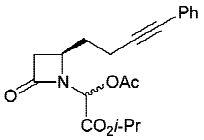
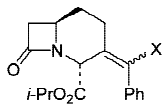
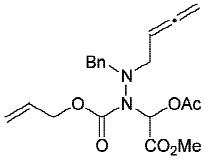
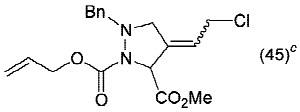
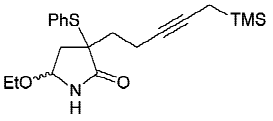
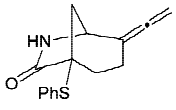
	HCO_2H, rt, 15 h	 (80)	611 612
	SnX_4, CH_2Cl_2, 0° X: Br, Time: 4 h X: Cl, Time: 6 h	 (51) (33)	223
	$TiCl_4$, CH_2Cl_2	 (45)[c]	428
	HCO_2H, rt, 18 h	 (87)	522

Table 6. (Continued)

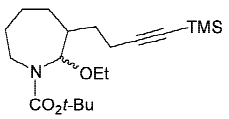
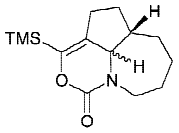
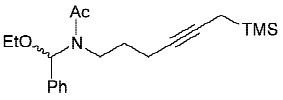
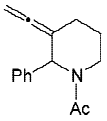
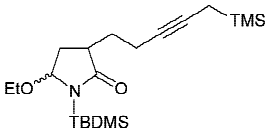
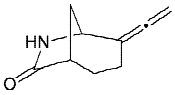
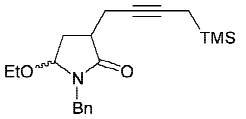
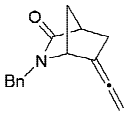
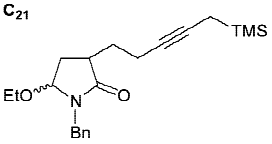
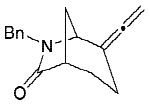
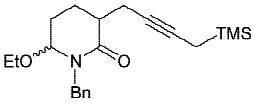
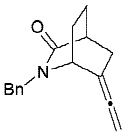
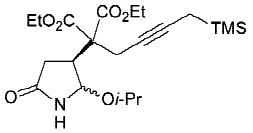
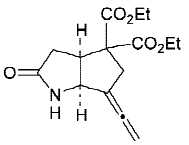
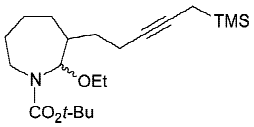
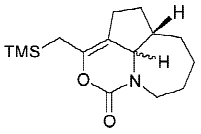
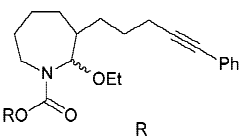
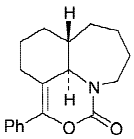
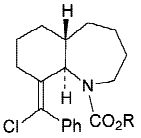
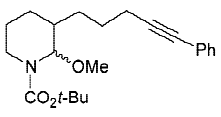
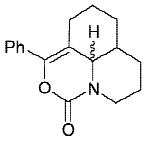
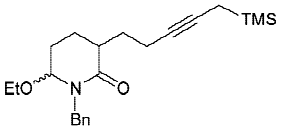
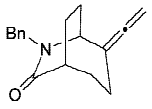
substrate	conditions	product(s) and yield(s) (%)	ref
	$SnCl_4$, CH_2Cl_2, -23°, 1 h	 (86), α:β = 1.75:1	224
	HCO_2H, rt, 17 h	 (74)	537
	HCO_2H, rt, 24 h	 (85)	522
	HCO_2H, rt, 30 min	 (82)	202
C_{21} 	HCO_2H, rt, 0.5 h	 (97)	522
	TFA, rt, 0.5-1 h	(88)	203
	HCO_2H, rt, 0.5 h	 (98)	202
	HCO_2H	 (78)	395
	$SnCl_4$, CH_2Cl_2, –23°, 1 h	 (83), α:β = 30:1	224
$C_{21\text{-}24}$  R: Me; *t*-Bu	$SnCl_4$, CH_2Cl_2, –23°, 2 h	 +  Me: (65), (25); *t*-Bu: (83), (0)	224
C_{22} 	$SnCl_4$, CH_2Cl_2, –23°, 1 h	 (91), α:β = 1:3	224
	HCO_2H, rt, 0.5-1 h	 (93)	203

Table 6. (Continued)

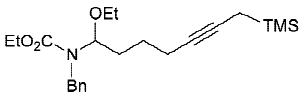
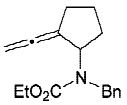
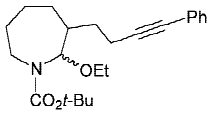
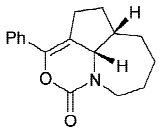
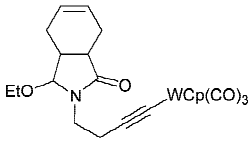
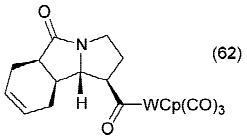
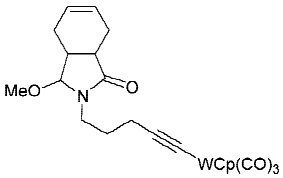
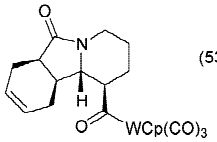
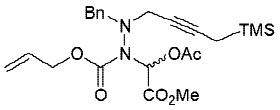
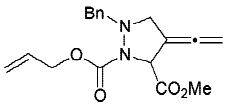
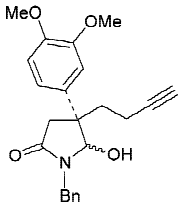
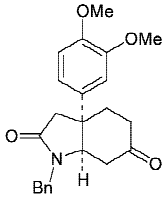
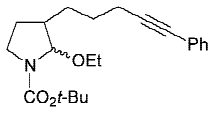
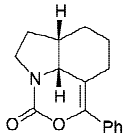
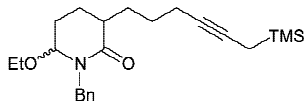
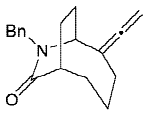
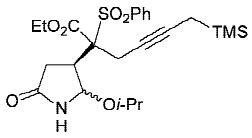
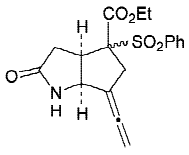
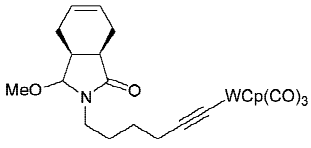
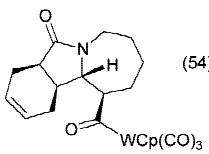
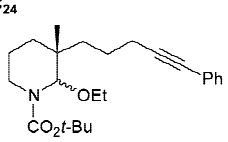
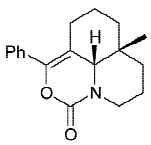
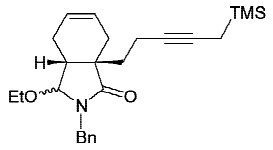
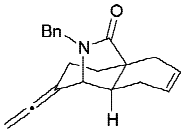
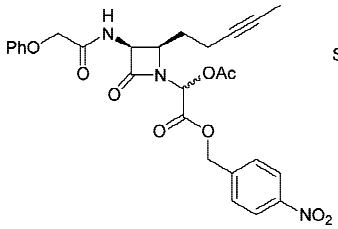
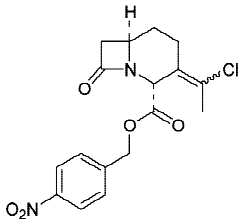
substrate	conditions	product(s) and yield(s) (%)	ref
	HCO_2H, rt, 1 h	 (50)	537
	$SnCl_4$, CH_2Cl_2, −23°, 1 h	 (80)	224
	BF_3•Et_2O, Et_2O, −78° to rt	 (62)	659
	BF_3•Et_2O, Et_2O, −78° to rt	 (53)	659
	BF_3•Et_2O, CH_2Cl_2	 (30)	428
	HCO_2H, rt, 65 h	 (87)	132
	$SnCl_4$, CH_2Cl_2, −23°, 1 h	 (98)	224
C_{23}			
	HCO_2H, rt, 0.5-1 h $SnCl_4$, CH_2Cl_2	 (<10) (81)	203
	HCO_2H	 (80)	395
	BF_3•Et_2O, Et_2O, −78° to rt	 (54)	659
C_{24}			
	$SnCl_4$, CH_2Cl_2, −78°, 1 h	 (87)	224

Table 6. (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
C_{25} 	HCO_2H, 0.5 h	 (97)	539
C_{27} 	$SnCl_4$, CH_2Cl_2, 0°-rt, 6 h	 (61)[d]	223

[a] Other isomers were detected by NMR. [b] The compound was a 13:5:1 mixture of diastereomers. [c] The compound was a 1.2:1 mixture of diastereomers. [d] The compound was a 5:1 mixture of diastereomers.

Table 7. Unimolecular Reactions with Miscellaneous Carbon Nucleophiles

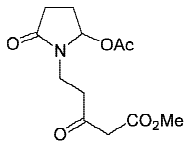
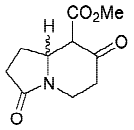
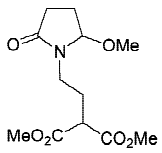
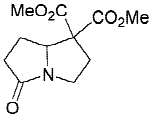
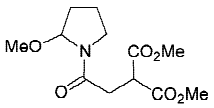
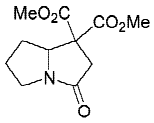
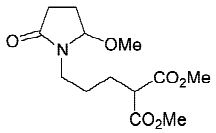
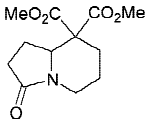
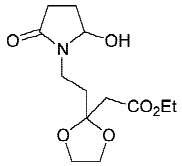
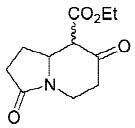
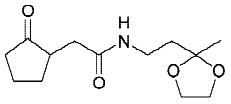
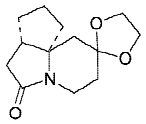
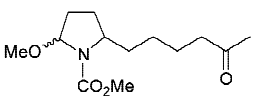
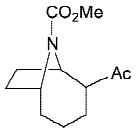
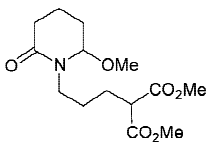
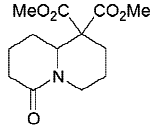
substrate	conditions	product(s) and yield(s) (%)	ref
C_{12} 	$TiCl_4$, CH_2Cl_2, rt, 3 h	 (71)	336
	$TiCl_4$, CH_2Cl_2, rt, 3 days	 (60)	535
	$AlCl_3$, CH_2Cl_2, 0°, 4 h	 (90)	532
C_{13} 	$TiCl_4$, CH_2Cl_2, rt, 3 days	 (76)	535
	HCO_2H, H_2O, rt, 18 h	 (97)	531
	TsOH, toluene, heat	 (83)	229
	HCl, MeOH, -45°, 5 h	 (93)	533
C_{14} 	$TiCl_4$, CH_2Cl_2, rt, 3 days	 (77)	535

Table 7. (Continued)

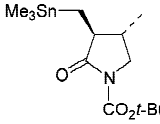
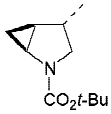
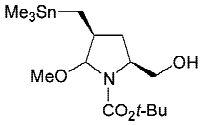
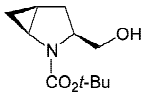
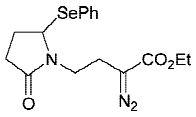
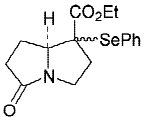
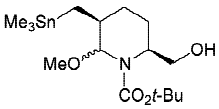
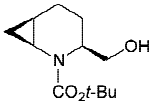
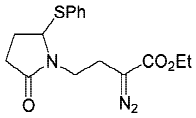
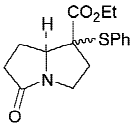
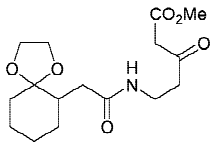
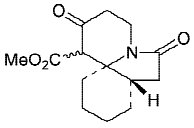
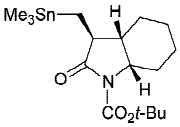
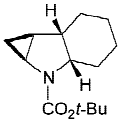
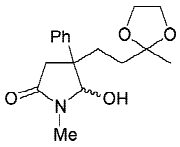
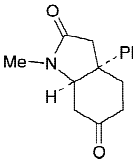
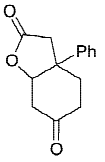
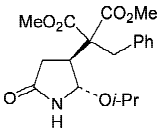
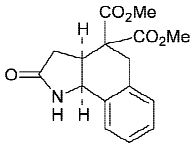
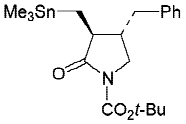
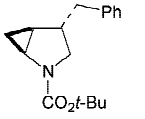
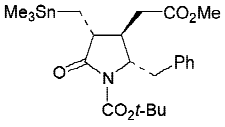
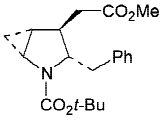
substrate	conditions	product(s) and yield(s) (%)	ref
	1. $LiEt_3BH$, THF, -78° 2. TFA, CH_2Cl_2, 0°	 (82)	540
C_{15}			
	TFA, CH_2Cl_2	 (79)	541
C_{16}			
	$Rh_2(OAc)_4$, C_6H_6, CH_2Cl_2, reflux, 10 min	 (36)	242
	TsOH, CH_2Cl_2, MeOH	 (42)	541
	$Rh_2(OAc)_4$, C_6H_6, heat, 15 min	 (55)	241
	BF_3•Et_2O, CH_2Cl_2, 50°, 2 h	 (82.5)	532
C_{17}			
	1. $LiEt_3BH$, THF, –78° 2. TFA, CH_2Cl_2, 0°	 (86)	540
		 + 	127 132
	H_2O, dioxane, H_2SO_4 HCl, MeOH, 21 h	(61) (17) (78) (0)	
C_{19}			
	$TiCl_4$	 (79)	395
C_{20}			
	1. $LiEt_3BH$, THF, –78° 2. TFA, CH_2Cl_2, 0°	 (81)	540
C_{23}			
	1. $LiEt_3BH$, THF, –78° 2. TFA, CH_2Cl_2, 0°	 (65)	540

Table 7. (Continued)

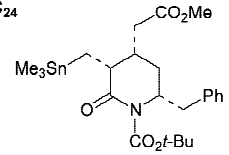
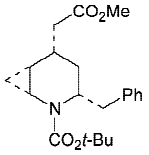
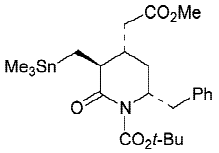
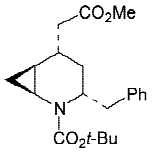
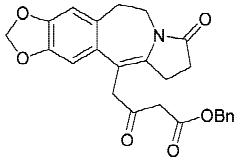
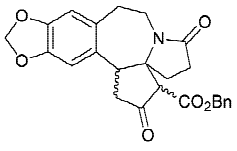
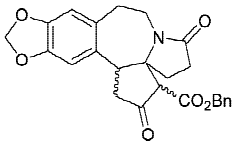
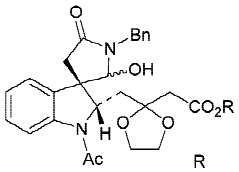
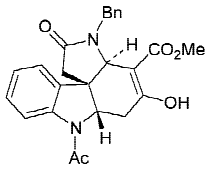
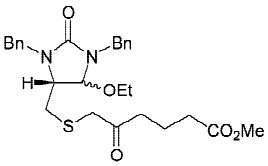
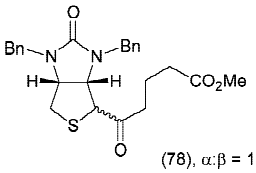
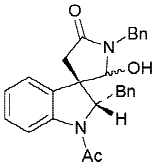
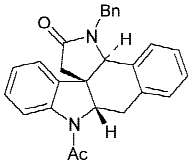
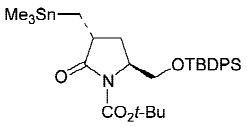
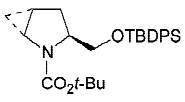
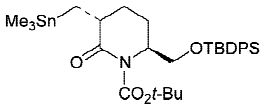
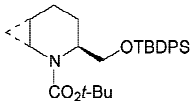
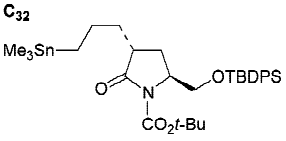
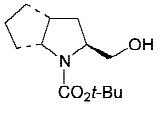
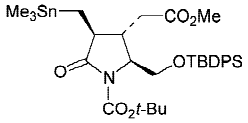
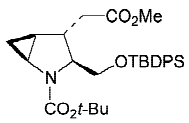
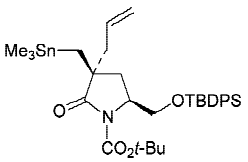
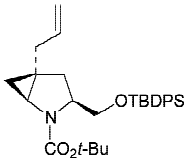
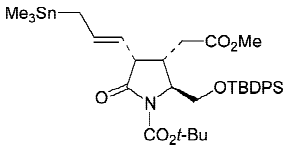
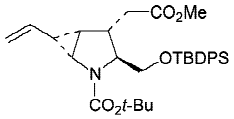
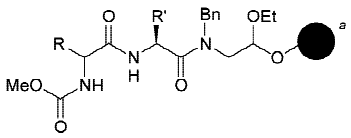
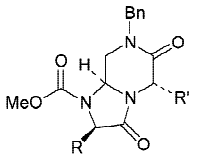
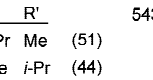
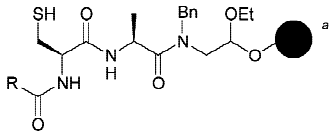
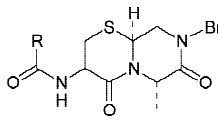
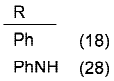
substrate	conditions	product(s) and yield(s) (%)	ref
C_{24} 	1. $LiEt_3BH$, THF, -78° 2. TsOH, CH_2Cl_2, MeOH, rt	 (63)	540
	1. $LiEt_3BH$, THF, -78° 2. TsOH, CH_2Cl_2, MeOH, rt	 (84)	540
C_{25} 	$TiCl_4$, AcOH, CH_2Cl_2, rt	 (97), *cis*:*trans* = 1:4.4	641
	NIS, $TiCl_4$, MeOH, rt	 (71)	641
C_{25-28}  R = Me, *t*-Bu	HCl, MeOH, reflux, 0.5 h	 (quant.) (70)	230
C_{27} 	1. $TMSCH_2CO_2Et$, Bu_4NF, THF, -78° to rt, 18 h 2. TMSOTf, CH_2Cl_2, -78°, 1 h	 (78), α:β = 1.5:1	237
	HCO_2H, rt, 18 h	 (quant.)	230
C_{30} 	1. $LiEt_3BH$, THF 2. TFA, CH_2Cl_2	 (66)	541
C_{31} 	1. $LiEt_3BH$, THF 2. TsOH, CH_2Cl_2, MeOH	 (90)	541
C_{32} 	1. $LiEt_3BH$, THF 2. TFA, CH_2Cl_2 3. Bu_4NF, THF	 (72)	541

Table 7. (Continued)

substrate	conditions	product(s) and yield(s) (%)	ref
C_{33}			
	1. $LiEt_3BH$, THF 2. TFA, CH_2Cl_2	 (67)	213
	1. $LiEt_3BH$, THF 2. TFA, CH_2Cl_2	 (62)	541
C_{35}			
	1. $LiEt_3BH$, THF 2. TFA, CH_2Cl_2	 (86)	213
	HCO_2H, rt-60°	 R R' 	543
	HCO_2H, rt-60°	 R 	543

[a] TentaGel-OH resin was used for the solid-phase reaction.

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