Cyclic Anhydrides in Formal Cycloadditions and Multicomponent Reactions

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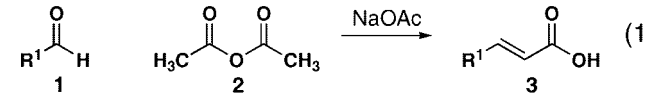
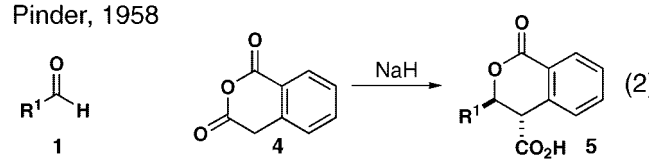
1. Introduction

The reactions of cyclic anhydrides acting dually as acylating agents and *C*-nucleophiles in stereoselective annulation reactions provide efficient one-step synthesis of polysubstituted heterocyclic and carbocyclic molecules. The reactivity of anhydrides is historically dominated by their ability to serve as mild acylating agents. An early example of anhydrides acting as *C*-nucleophiles is found in the Perkin reaction, in which aliphatic anhydrides undergo aldol condensation with aldehydes in the presence of a mild base (eq 1).[1,2] An early report of the reaction of homophthalic anhydride with an aldehyde (eq 2) using strong base demonstrated the ability for cyclic anhydrides to undergo annulation reactions.[3] Castagnoli observed in 1969 that cyclic anhydrides undergo formal cycloaddition reactions with imines (eq 3) under thermal conditions.[4] This discovery, paired with the observations of Cushman[5] and Haimova[6] (eq 4) in 1977 that homophthalic anhydride underwent a similar reaction at ambient temperature, formed the foundation for much of the subsequent work on this reaction. Finally, Tamura reported a related transformation in which homophthalic anhydride reacted with alkenes and alkynes to produce fused aromatic products (eq 5).[48]

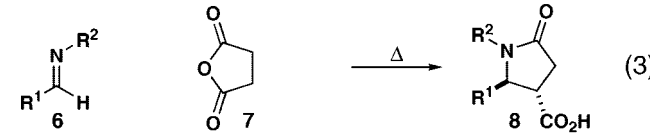
Perkin, 1868



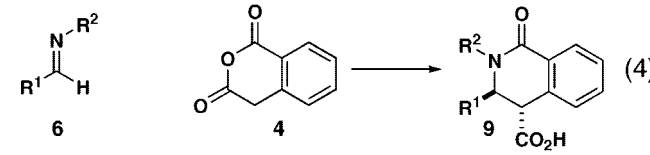
Pinder, 1958



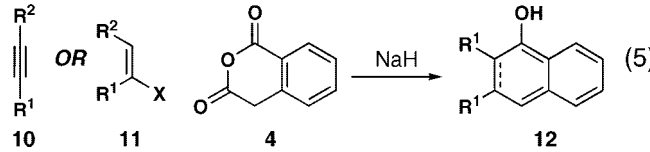
Castagnoli, 1969



Cushman, Haimova, 1977



Tamura, 1981



Each of these reactions proceeds with a varying degree of synchronicity. While the addition of homophthalic anhydride to aldehydes would appear to involve nucleophilic attack of the aldehyde carbonyl by an anhydride-derived enolate, the imine−anhydride reaction has been alternately proposed as a concerted cycloaddition and a stepwise annulation. Although the Tamura reaction is almost always depicted as a Diels−Alder-type cycloaddition, this reaction is probably asynchronous to a certain extent. For the purposes of this review, we will employ the term "cycloaddition" for all three reactions, mindful of Danishefsky's[7] choice to do so in the case of the Tamura reaction:

"We use the term cycloaddition in an empirical rather than mechanistic sense, thereby sidestepping difficultly resolvable issues related to the concerted nature of the reaction."

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Marcos González López was born in Madrid, Spain, in 1979. He received his B.S. in chemistry from Universidad Autónoma de Madrid in 2001. In 2006 he completed his Ph.D. at the same university under the guidance of Professors Carmen Carreño García and Antonio Urbano Pujol. Dr. González López is currently a Fundación Ramón Areces Postdoctoral Fellow with Professor Jared T. Shaw at the University of California, Davis, working on the total synthesis of complex natural products.

Jared Shaw was born in Fresno, California, and attended the University of California, Berkeley, where he conducted undergraduate research with Prof. Clayton Heathcock, receiving a B.S. in 1993. He worked at Gilead Sciences (Foster City, CA) for one year before attending the University of California, Irvine, where he received his Ph.D. under the guidance of Keith Woerpel in 1999. From 1999−2002, he was an NIH postdoctoral fellow with David Evans at Harvard University. Jared began his independent career in 2002 as an institute fellow at the Institute for Chemistry and Cell Biology (ICCB) at Harvard Medical School and helped found the Center for Chemical Methodology and Library Development (CMLD) in 2003. In 2005, the ICCB merged with several other research organizations to form the Broad Institute of Harvard and MIT, where Jared directed a research group through June of 2007. In July of 2007, Jared joined the faculty as an assistant professor of the University of California, Davis, where he currently works on the development of new synthetic methods for the synthesis of natural products and other complex molecules that modulate biological phenomena.

Cycloaddition reactions of cyclic anhydrides have seen wide application in the synthesis of natural products, medicinal lead compounds, and other molecules of biological interest. In addition, recent discoveries have revealed new three- and four-component reactions that greatly enhance the utility of cyclic anhydrides as useful reagents for preparing heterocyclic compounds. This review will describe the reactions of cyclic anhydrides as "extended dipoles" (eq 6) in the formation of polycyclic compounds, surveying literature after the initial discoveries made by Castagnoli, Cushman, Haimova, and Tamura. Although portions of the work of Cushman and Tamura have been discussed in recent

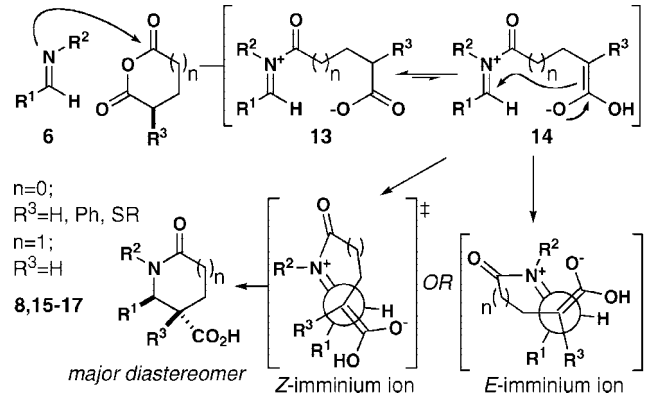
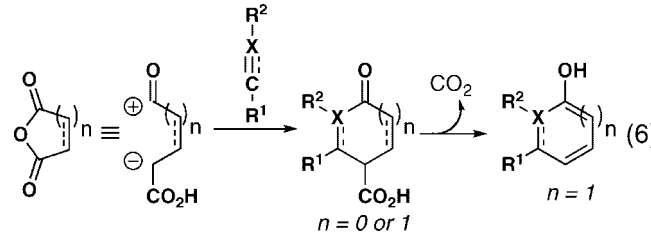


Figure 1. Mechanism of the imine−anhydride cycloaddition.

reviews on broader topics,[8,9] this is the first comprehensive review of the cycloaddition reactions of cyclic anhydrides.

2. Cycloaddition Reactions of Anhydrides

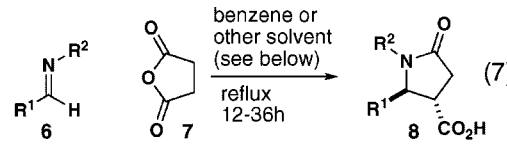


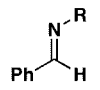
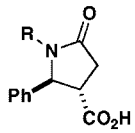
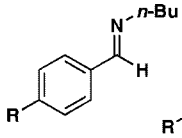
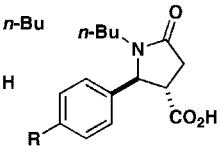
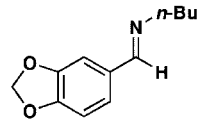
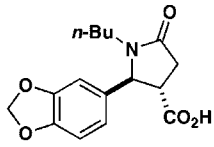
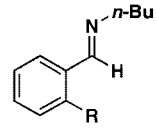
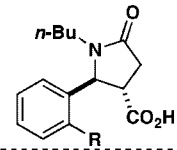
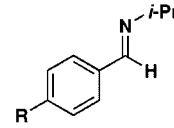
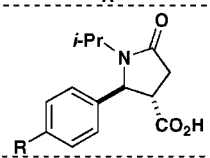
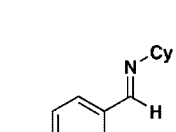
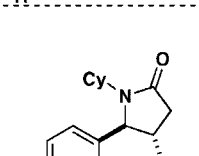
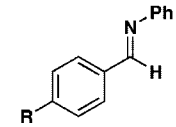
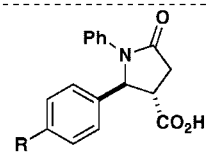
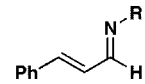
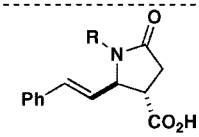
2.1. Imines

Imines react with cyclic anhydrides to form carboxy-substituted trisubstituted lactams. The first observation of this reaction involved succinic and glutaric anhydrides (Figure 1, $n = 1$ or 2, $R^3 = H$).[4,10−12] The mechanism of the reaction of imines with cyclic anhydrides is postulated to proceed in a stepwise fashion via zwitterionic intermediate **13** (Figure 1). This *N*-acyliminium carboxylate is in an unfavorable equilibrium with the corresponding enolate tautomer, which subsequently adds to the iminium ion to form the lactam ring. If $R^3$is an anion-stabilizing group (e.g., aromatic or thioalkyl), then the reaction proceeds at lower temperatures, which has been attributed to increased stabilization of the enolate tautomer. In all cases, the major diastereomer is anti with respect to the imine carbon substituent (R^2) and the carboxylic acid. An accurate assessment of the transition-state geometry is lacking, and no study yet has demonstrated that the anti-isomer is kinetically favored. That said, a transition state resulting from the *Z*-imine has been advanced to explain the stereochemical course of 3-thioaryl succinic anhydrides ($n = 0$, $R^3 = SR$).[14] An analogous transition state arising from the *E*-imine and *E*-enolate is also plausible. Kinetic selectivity as a result of anion−π repulsion between the carboxylate and the imine C-substituent has been proposed by Shaw[14] and is consistent with either transition state.

This mechanism was advanced by Cushman in a detailed study of imine substituent effects[15] and is supported by subsequent discoveries of multicomponent reactions by Yadav[68] (section 2.7) and Shaw (section 2.8).[16] Formation of the enolate is likely rate-limiting, as evidenced by the significant rate difference between homophthalic anhydride and glutaric anhydride. Formation of enolate **14** is favored by delocalization of negative charge into the electron-deficient aromatic ring if one is suitably positioned. A similar trend is observed in the direct comparison of phenylsuccinic

Table 1. Reactions of Imines with Succinic Anhydride



entry	substrate	product	yield
1			83% [R=CH_3][a]
2			45% [R=CH_3][b]
3			48% [R=*n*-Bu][b]
4			50% [R=*i*-Pr][b]
5			75%, dr 91:9 [R=Cy][c]
6			30% [R=Cl][b]
7			46% [R=CH_3][b]
8			50% [R=OH][b]
9			13% [R=NO_2][b]
10			97% [R=CH_3][d]
11			86% [R=Et][d]
12			81% [R=*n*-Pr][d]
13			67% [R=*i*-Pr][d]
14			61% [R=*n*-Bu][d]
15			87% [R=*s*-Bu][d]
16			43% [R=*n*-C_8H_{17}][d]
17			76% [R=Cy][d]
18			83% [R=Bn][d]
19			80% [R=OH][b]
20			76% [R=OCH_3][b]
21			0% [R=Cl][b]
22			46%, dr 93:7 [R=CH_3][b]
23			40%, dr 93:7 [R=$N(CH_3)$][c]
24			85%, dr 88:12 [R=OCH_3][c]
25			71%, dr 89:11 [R=Cl][c]
26			0% [R = NO_2][f]
27			72% [R=H][a]
28			50% [R=H][e]
29			45% [R=F][e]
30			40% [R=Cl][e]
31			6%[b]

[a] Reference 4. [b] Reference 19. [c] Reference 10. [d] Reference 20 (toluene). [e] Reference 23 (toluene). [f] Reference 4 (xylene).

anhydride and a related substrate appended with fluoro and nitro groups on the aromatic ring.[17]

An alternate mechanism involving a concerted cycloaddition between the imine and the enol tautomer of the anhydride has been advanced by Kaneti.[18] This reaction pathway is derived from calculations in the gas phase in which zwitterionic intermediate **13** was not observed as an energy minimum. The fact that ionic substrates rely on solvation to exist as reaction intermediates limits the extent to which Kaneti's calculations can be used to rule out a mechanism involving zwitterion **13**.

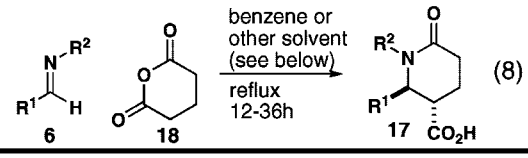
2.1.1. Succinic Ahydride

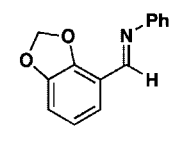
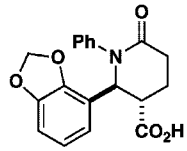
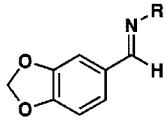
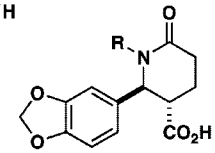
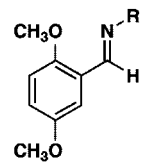
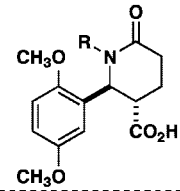
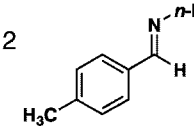
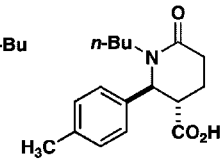
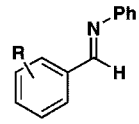
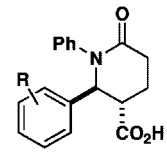
Castagnoli first observed that imines could be heated in the presence of succinic anhydride to produce γ-lactams (Table 1, eq 7).[4,10] The reaction requires forcing conditions, and although good diastereoselectivity is often observed, the yields vary significantly. Although Castagnoli often reports mixtures of diastereomers, Boucherle reported similar reactions that yield single diastereomers (Table 1, entries 2, 3, 6−9, 19−21) in all but one case (entry 22).[19] Because the products were purified by crystallization in both cases, and often without analyzing the crude mixtures, it is possible that substantial amounts of the syn-diastereomer were present and did not crystallize. A series of piperonal-derived lactams was prepared by Dallacker (Table 1, entries 10−18), and although the diastereoselectivity is not mentioned, spectroscopic data for a single isomer is reported that is assumed to be anti.[20] Use of *N*-phenyl imines has been reported by Castagnoli (entry 27) and others[21−23] (entries 28−30). Finally, Boucherle included a single example in which a cinnamic imine is used to form the corresponding lactams in poor yield (Table 1, entry 28). Although additional reaction products are not reported in this case, Haimova's study of the analogous reaction with homophthalic anhydride (section 2.6) demonstrated that multiple products arise from various modes of cycloaddition.[24] The high temperatures required for this reaction paired with the variable yields have limited its implementation. Furthermore, the use of 3-thioaryl substituted anhydrides[14] (section 2.1.4) and the advent of a four-component reaction[16] recently reported by Shaw give selective access to either the syn- or anti-diastereomers of the succinic anhydride products (section 2.8).

2.1.2. Glutaric Anhydrides

Glutaric anhydrides react with imines with similar scope and selectivity as is seen with succinic anhydrides (Table 2, eq 8). This reaction was first reported by Castagnoli in the context of preparing alkaloid analogues of tetrahydrocannabinol (section 3.1.2).[12,13] A solvent study of the Castagnoli reaction by Stanoeva,[25] wherein *p*-xylene outperformed lower boiling solvents (THF, benzene, and toluene), confirmed that high temperatures were required for this reaction. Boucherle,[26] Dallacker,[20] and Tabcheh each reported syntheses of a series of these compounds as potential medicinal leads. Although Boucherle only isolated the anti-diastereomer by crystallization, the low yields prevent definitive conclusions regarding the diastereoselectivity of this reaction. This author assigns the anti-stereochemistry of the product by ^{1}H NMR spectroscopy, which agrees with reported X-ray crystal structures.[25,27]

Table 2. Reactions of Imines with Glutaric Anhydride



entry	substrate	product	yield
1			20%[a]
2			86% [R=CH_3][b]
3			66% [R=Et][b]
4			37% [R=*n*-Pr][b]
5			86% [R=*i*-Pr][b]
6			86% [R=*n*-Bu][b]
7			76% [R=*s*-Bu][b]
8			29% [R=*n*-C_8H_{17}][b]
9			87% [R=Cy][b]
10			55% [R=Bn][b]
11			55% [R=Ph][a] 30% [R=PMP][a]
12			28% [R=CH_3][a]
13			30%,[a] 40% [R=H][c]
14			20% [R=*p*-F][c]
15			30% [R=*p*-Cl][c]
16			50% [R=*p*-CH_3][a]
17			60% [R=*o*-OCH_3][a]
18			10% [R=*o*-OH][a]
19			66% [R=*o*-OBn][a]

[a] Reference 26. [b] Reference 20 (toluene). [c] Reference 23 (toluene).

Dallacker's piperonal-derived δ-lactams are isolated in >86% yield in four out of nine cases, which suggests that the diastereoselectivity is reasonably high in most cases.

2.1.3. Homophthalic Anhydrides

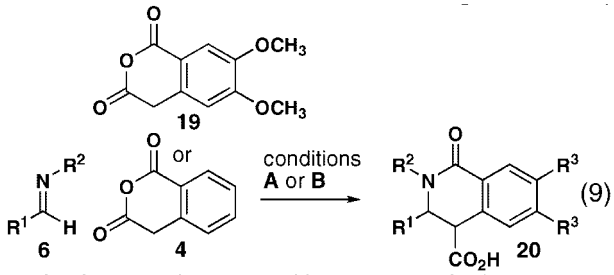
Cushman[5] and Haimova[6] published separate and nearly simultaneous reports on the reactions of homophthalic anhydrides with imines (Table 3, eq 9). Anhydrides possessing a functional group capable of facilitating enolate formation at one terminus are much more reactive toward imines than succinic or glutaric anhydride. This reactivity difference is most apparent with homophthalic anhydrides, which react readily with imines at ambient temperature. In addition, the reaction exhibits kinetic selectivity for the formation of the syn-diastereomer. Although the level of preference was just over 2:1 in Cushman's initial report, it was later demonstrated that the imine *N*-substituent has a large influence on selectivity, with methyl exhibiting the lowest preference.[15] In contrast to this result, Haimova observed high selectivity for the anti-diastereomer. A similar discrepancy was found in the reactions of dihydroisoquinolines wherein Cushman observed formation of the anti-diastereomer preferentially and Haimova reported syn-diastereoselectivity. Cushman demonstrated that the syn-isomer is kinetically favored and will epimerize to the trans-isomer either upon heating in xylene or acetic acid and, moreover, that the basic extraction used by Haimova also causes epimerization.[15] This kinetic preference for the syn-diastereomer with acyclic imines and the trans-diastereomer for tetrahydroisoquinolines has been confirmed in many subsequent reports of this reaction (section 3.1.1).

Cushman conducted a detailed study of substituent effects in the reactions of homophthalic anhydride with a series of imines (Table 4, eq 10).[15] Chloroform was the ideal solvent for the reactions, when compared to methanol and formamide. Higher diastereomer ratios, favoring the syn-product, were observed for imines derived from electron-deficient benzaldehydes and methylamine. Although methylamine gave variable diastereoselectivity, more substituted amines produced exclusively the syn-diastereomer **22**. In competition experiments, imines derived from methylamine reacted faster than more substituted imines. Haimova notes high anti-diastereoselectivity with a similar set of imines derived from various primary amines, which, presumably, results from epimerization during the basic workup.[6] In addition, Gesquiere has noted that the addition of a Lewis acid ($BF_3 \cdot OEt_2$) leads to the formation of the trans-isomer selectively.[28] The equilibration with acetic acid demonstrated by Cushman suggests that the effect of the Lewis acid might simply be to epimerize an initially formed cis-product. Addition of alum ($KAl(SO_4)_2 \cdot 12H_2O$) as a catalyst,[29] which may act as a mild Lewis acid, results in cis-selectivity and yields comparable to what is reported by Cushman.

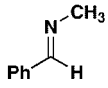
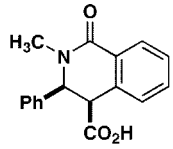
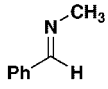
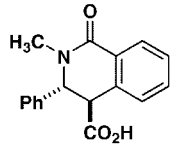
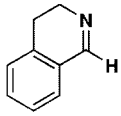
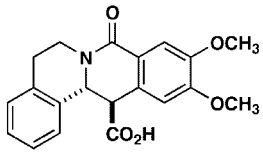
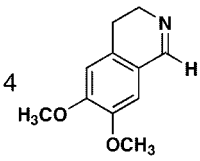
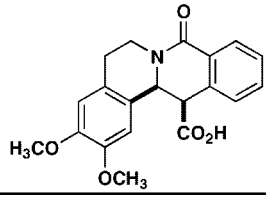
The reactions of homophthalic anhydrides with imines result in high kinetically controlled diastereoselectivity. The origin of this selectivity is unclear at this point because the imine can react through either the *E*- or *Z*-double-bond geometry. If the more thermodynamically stable *E*-isomer of imine is acylated, then antiperiplanar approach of the enolate is required to form the observed syn-diastereomer (Figure 2). This mode of reaction would be consistent with a smaller R^2 (i.e., methyl) producing lower syn/anti ratios. Furthermore, this transition geometry would adequately explain the kinetic anti-selectivity of dihydroisoquinolines, which are effectively *Z*-imines in which R^1 and H are interchanged when comparing **A** to **B**.

Gesquierre has reported conditions that enable the reactions of homophthalic anhydride with imines to be extended to aliphatic aldehydes (Scheme 1, eq 11). Trimethyl-*ortho*-formate is used to make imines in situ, which are then treated with homophthalic anhydride. Although the yields for **28** and **29** are modest, these are the only two reports to date where linear aliphatic aldehydes are used successfully in this reaction to provide the cis-diastereomer. Bigg has reported formation of the trans-diastereomers from the reaction of homophthalic anhydride and imines derived from *n*-butyral-

Table 3. Reactions of Imines with Homophthalic Anhydride



A: $CHCl_3$, 23 °C, 30min. (Cushman, ref. 3)
B: $ClCH_2CH_2Cl$, 10 min., reflux, 23 °C; 10% NaOH (aq), HCl (aq). (Haimova, ref 4,)

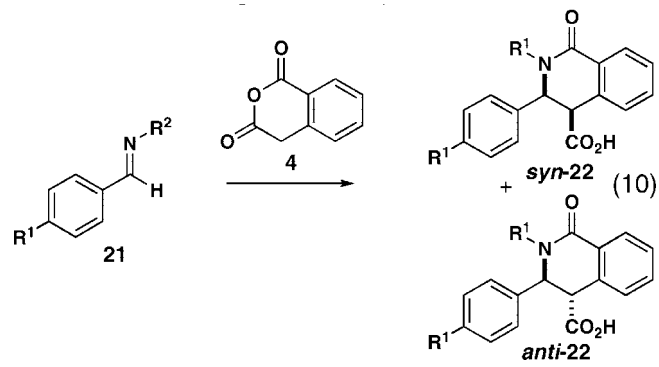
entry	substrate	product	yield, dr (**A** or **B**)
1			96%, 66:33 (**A**)
2			>95:5 (**B**)
3			90%, >90:10 (**A**)
4			50:50 (**B**)

dehyde and isobutyraldehyde in chloroform followed by isomerization in refluxing acetic acid.[30]

Kita reported both an efficient synthesis of heteroaromatic-fused glutaric anhydrides and several examples of their diastereoselective reactions with imines (Scheme 2, eq 12).[31] (Trimethylsilyl)ethoxyacetylene smoothly converts dicarboxylic acids into their corresponding anhydrides in yields that are quantitative in most cases.[32,33] The reactions of a subset of these anhydrides with dihydroisoquinoline show high diastereoselectivity. The formation of the anti-isomer in the case of **37** and **39** is likely consistent with isomerization of an initially formed syn-isomer, which is epimerized by the presence of the carboxylic acid in the product. Treatment of **43** with acetic acid under Cushman's conditions effects complete epimerization to the more thermodynamically favored anti-diastereomer. In the case of **37** and **39**, it is likely that the carboxylic acid in the product under these conditions is sufficient to effect epimerization.

Two interesting variants of the imine component have been reported. 2*H*-1,3-Benzothiazines used in place of dihydroisoquinolines react with similar efficiency and analogous diastereoselectivity (Scheme 3, eq 16). An additional methyl substituent was added to make a "ketimine" equivalent that also reacts with high selectivity (eq 17). Boronate ester-

Table 4. Solvent and Substituent Effects in the Reactions of Imines with Homophthalic Anhydride



entry	R^1	R^2	solvent	dr (syn/anti)
1	NO_2	CH_3	$CHCl_3$	97:3
2	Cl	CH_3	$CHCl_3$	82:18
3	H	CH_3	$CHCl_3$	83:17
4	CH_3	CH_3	$CHCl_3$	75:25
5	OCH_3	CH_3	$CHCl_3$	69:31
6	$N(CH_3)_2$	CH_3	$CHCl_3$	20:80
7	H	CH_3	CH_3OH	64:36
8	H	CH_3	$HCONH_2$	61:39
9	H	Cy	$CHCl_3$	>95:5
10	H	*t*-Bu	$CHCl_3$	>95:5
11	H	Ph	$CHCl_3$	>95:5
12	H	*i*-Bu	$CHCl_3$	>95:5

substituted benzaldehyde-derived imines **49a**−**58a** are also suitable substrates for this reaction, tolerating a wide range of *N*-substituents (eq 18). The increased acidity created in the reaction mixture by the presence of a carboxylic acid and a Lewis acid does not seem to affect the diastereomeric purity of the cycloaddition products.

One report of substrate control from an imine derived from a chiral aldehyde was reported in a study aimed at preparing the core structure of pancratistatin (Table 5, eq 19).[34] The lack of success with imines derived from enolizable aldehydes is often attributed to the potential formation of enamides after acylation. Clark and Souchet observed satisfactory reactivity and overall syn-diastereoselectivity in the absence of a Lewis acid additive (entry 1), but no influence of face selectivity on the chiral imine was observed. A survey of Lewis acid additives revealed that maximal selectivity was observed with trimethylaluminum, which the authors attribute to chelation control. This conclusion is at odds with the observations that neutral aluminum Lewis acids

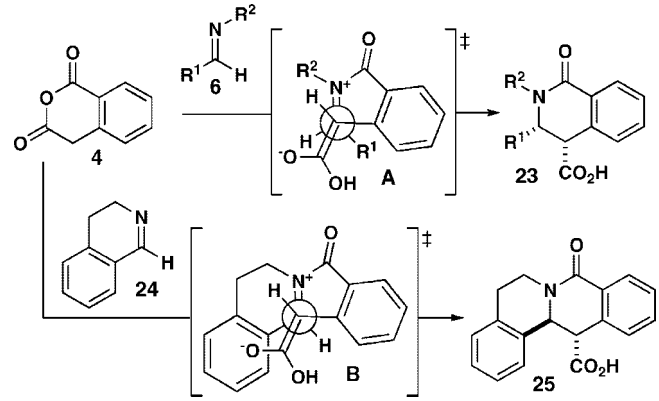
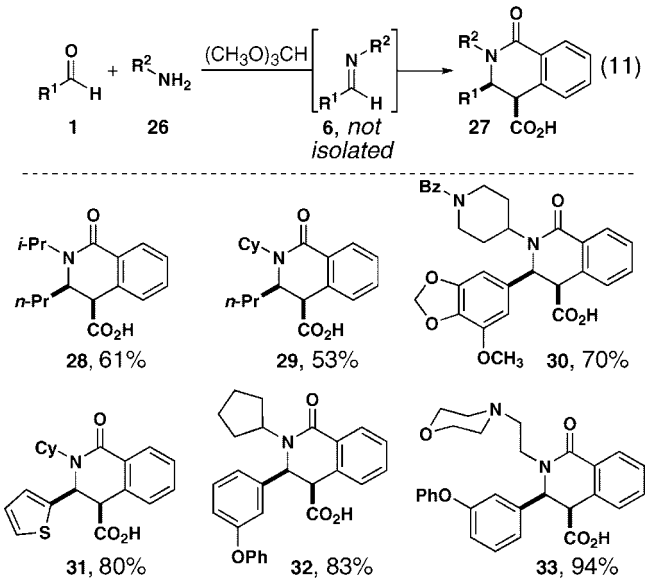
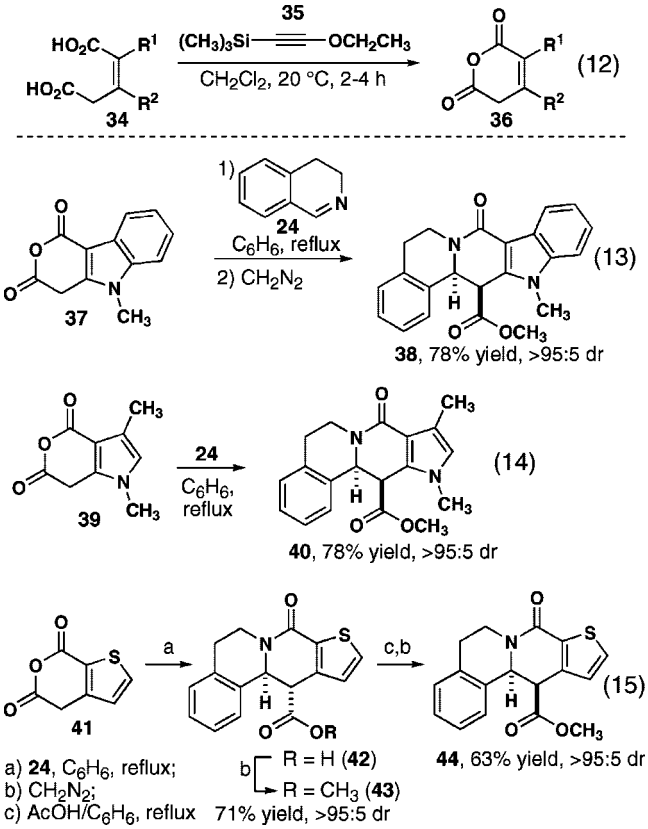


Figure 2. Transition-state geometries to explain the diastereoselectivity of the reactions of homophthalic anhydrides with imines and tetrahydroisoquinolines.

Scheme 1. One-Pot Imine Formation and Reaction with Homophthalic Anhydride



Scheme 2. Synthesis and Reactions of Heteroaromatic Analogues of Homophthalic Anhdyride with Imines



are not generally regarded as bidentate.[35] Although the impact of the Lewis acid on the mechanism and stereochemical outcome of this reaction is unclear, the high yields from an imine with α-protons and the significant asymmetric induction are noteworthy.

2.1.4. Substituted Succinic Anhydrides

Phenylsuccinic anhydride, which is capable of forming a much more stable enolate intermediate than succinic anhydride, exhibits much higher reactivity toward imines (Table 6, eq 20).[15]

Scheme 3. Imine−Anhydride Reactions of *N,S*-Acetals in Place of Imines and Boronate Ester-Substituted Imines

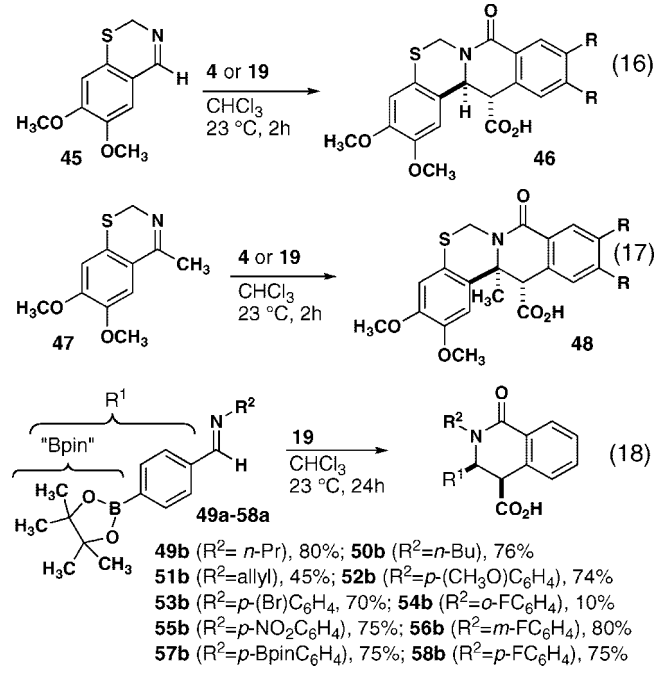
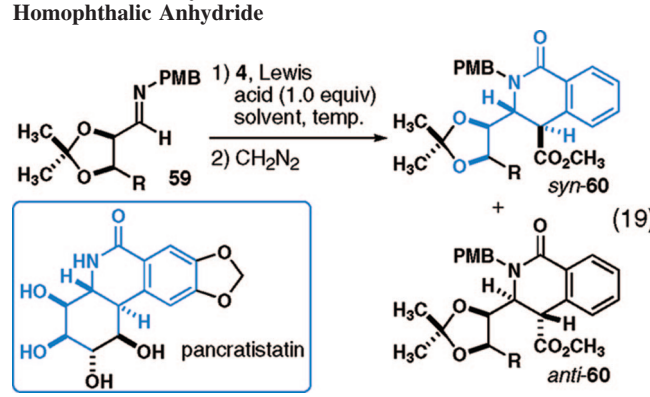


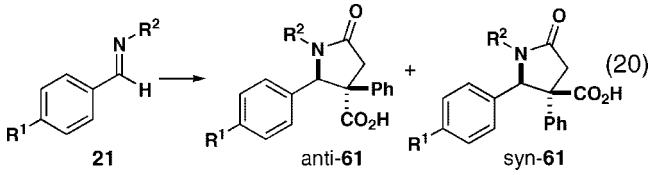
Table 5. Solvent and Lewis Acid Effects on Substrate-Induced Diastereoselectivity in the Reaction of Chiral Imine 59 with Homophthalic Anhydride



entry	Lewis acid	solvent	temp.	time	ratio syn/anti, yield
1		CH_2Cl_2	reflux	10 min	50:50
2	LiI	THF	reflux	10 min	60:40
3	$ZnCl_2$	CH_3CN	23 °C	2 h	82:18
4	MgI_2	THF	0 °C	2 h	70:30
5	MgI_2	THF	−50 to 0 °C	2 h	80:20
6	MgI_2	CH_3CN	0 °C	2 h	83:17
7	MgI_2	CH_3CN	−30 to 0 °C	24 h	93:7
8	$Al(CH_3)_3$	CH_2Cl_2	−78 to 0 °C	5 h	91:9, 60%
9	$Al(CH_3)_3$	CH_2Cl_2	−78 to 0 °C	5 h	>90:10, 50% (R = CH_2OBn)

N-substituted imines require 1−5 h at reflux, and in one case, (entry 2) the reaction is complete in 14 h at room temperature. The *N-tert*-butyl imine derived from benzaldehyde requires 48 h at reflux and poor conversion is observed, consistent with slow nucleophilic attack of the imine nitrogen on the anhydride carbonyl. Cushman's survey of the influence of imine structure on this reaction demonstrated that selectivity was lower than with homophthalic anhydride. In addition, the steric influence of the N-substituent is opposite, i.e., large substituents reduce the selectivity.

Table 6. Influence of Imine Substituents on Diastereomer Ratio (dr) in Reactions with Phenylsuccinic Anhydride



entry	R^1	R^2	solvent	dr (anti/syn)
1	Cl	CH_3	$CHCl_3$	77:23
2	H	CH_3	$CHCl_3$	82:18
3	CH_3	CH_3	$CHCl_3$	77:23
4	OCH_3	CH_3	$CHCl_3$	75:25
5	$N(CH_3)_2$	CH_3	$CHCl_3$	68:32
6	H	CH_2CH_3	$CHCl_3$	86:14
7	H	*i*-Pr	$CHCl_3$	60:40
8	H	*t*-Bu	$CHCl_3$	32:68

The addition of a thioether substituent to succinic anhydride has a similar influence on reactivity as the presence of an aromatic ring, which is likely derived from the comparable ability of a thioether to stabilize an adjacent carbanion when compared to a phenyl ring.[14] Shaw reported that 3-thiophenylsuccinic anhydride, which is easily prepared from maleic anhydride and a thiol, reacts readily with imines derived from substituted benzaldehydes to produce tetrasubstituted γ-lactams (Figure 3, eq 21). High selectivity for the isomer in which the carboxyl group is anti to the aromatic ring is observed, which is consistent with the major isomer produced by succinic, glutaric, and phenylsuccinic anhydride. These reactions show consistently high diastereoselectivity independent of the imine substituents.

The thioether substituent can be easily removed under radical conditions to provide access to the syn-diastereomer of the trisubstituted product, whereas unselective reduction with Raney nickel and epimerization provides the more thermodynamically stable anti-isomer (Scheme 4).[16] Thus, the use of thioether-substituted anhydrides gives access to the same products that result from the reactions of imines with succinic anhydride with high selectivity and the versatility of accessing either diastereomer selectively.

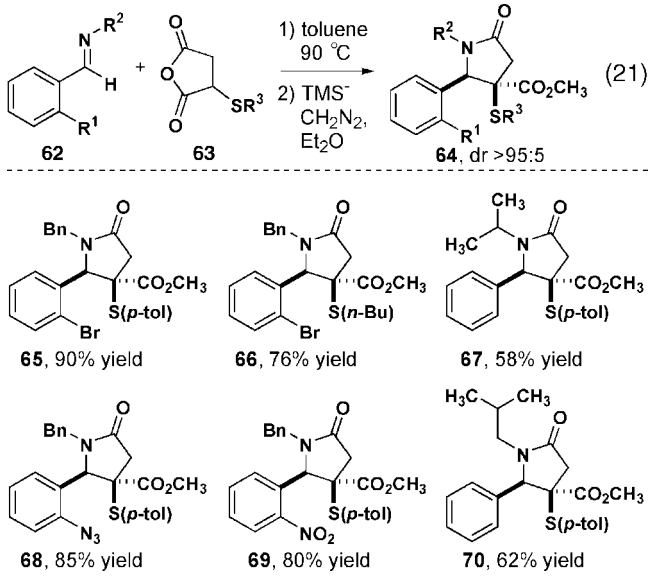
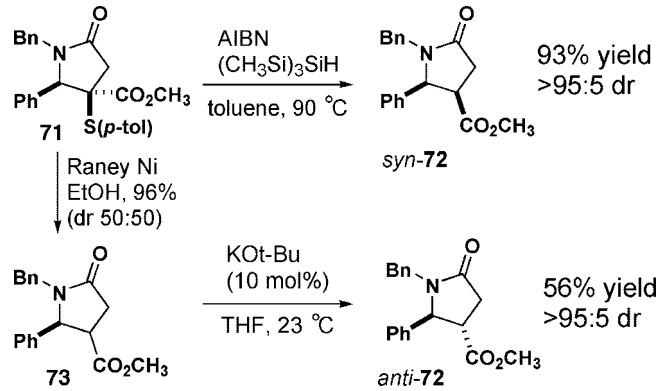


Figure 3. Reaction of imines with thioether-substituted succinic anhydrides.

Scheme 4. Diastereoselective Reduction of Lactam 71



2.2. Imines Derived from Ketones (Ketimines) with Homophthalic Anhydrides

Although the vast majority of the reactions of imines and cyclic anhydrides employ aldimines, several examples of ketimines have been reported.[5,30] The reduced reactivity results in longer reaction times at higher temperatures and reduced diastereoselectivity, as seen by the reaction of acetophenone methyl imine **74** with homophthalic anhydride (Figure 4, eq 22).[36] The high yields of densely substituted products **78** and **82** are notable. Ester **83** was obtained as a single diastereomer by converting an initially formed mixture of acids from the cycloaddition to the methyl ester and then effecting epimerization under basic conditions.[30]

Haimova demonstrated that α-chloroketimines can react with homophthalic anhydride and cyclize to form complex polycyclic lactones (Scheme 5).[37] The yields in this case are low, and the diastereoselectivity favoring the syn-isomers that spontaneously cyclize is variable. The reactivity of chloromethyl dihydroisoquinoline **87** is quite different, and in this case, high yields and superb diastereoselectivities are observed for the reactions of anhydrides **4** and **19**. Cyclization is induced with DMAP to provide the angularly fused polycyclic lactams **90** and **91**. The use of ketimines in cyclization reactions with anhydrides is quite rare, but it is

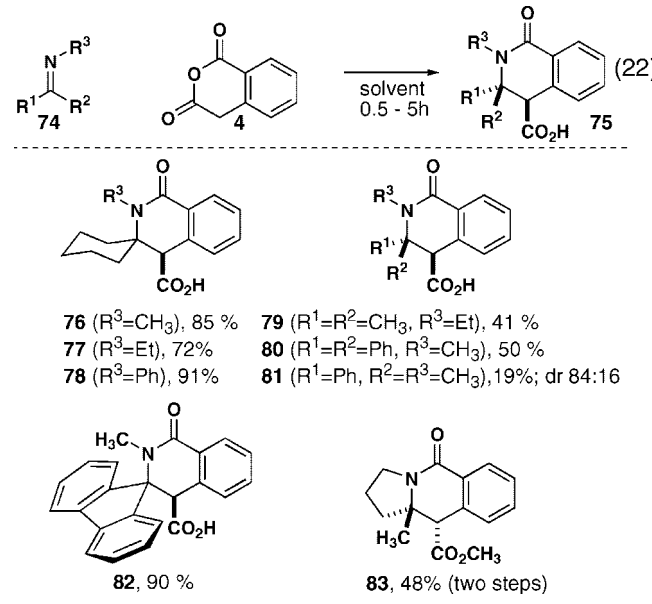
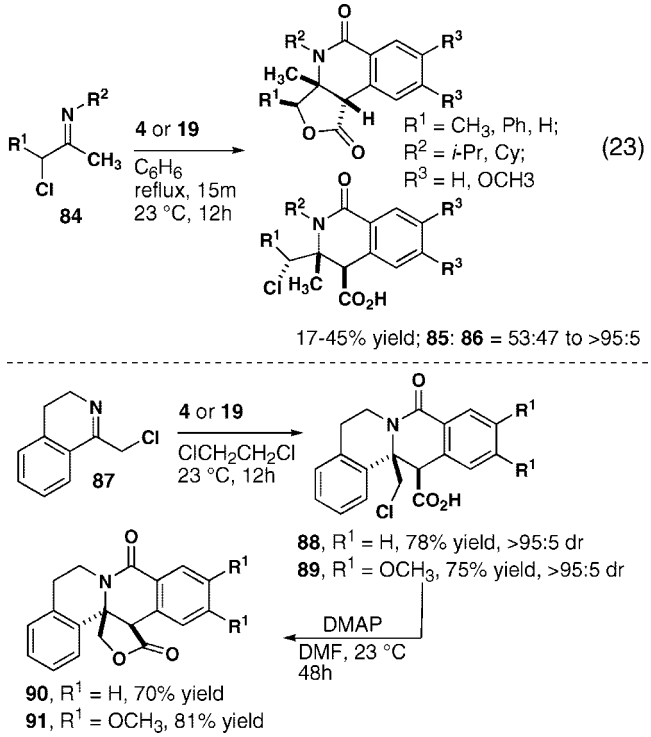


Figure 4. Cycloaddition of ketimines with homophthalic anhydride.

Scheme 5. Reactions of α-Chloroketimines with Homophthalic Anhydrides



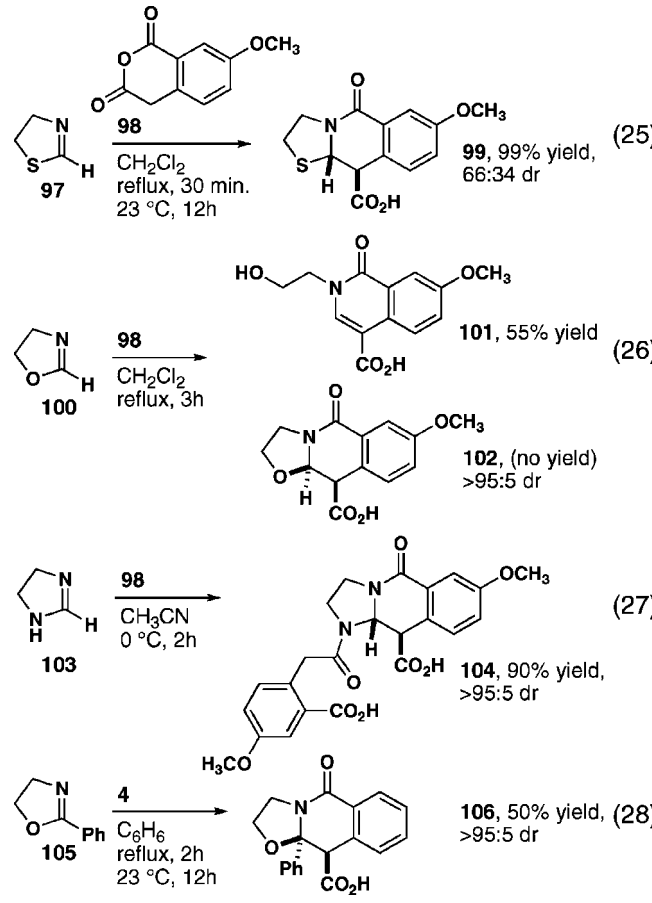
interesting to note that the presence of alpha protons is tolerated, which is not usually the case with aldimines.

2.3. Imidates and Imidoyl Chlorides

Chloroimine and alkyl imidates react readily with homophthalic anhydride and undergo spontaneous decarboxylative elimination to afford unsaturated lactams products (Figure 5). This reaction likely proceeds by the acylative mechanism implicated in the reactions of imines. An alternative mechanism involving deprotonation of the anhydride by the imidate to form an enolate that attacks the C=N double bond of the imidate has been proposed. Although it is difficult to discern the diastereoselectivity of the lactam intermediates, subsequent elimination can occur from the syn isomer by an E1-like mechanism via *N*-acyliminium ion **94** or by direct E2 elimination of the anti isomer. In some cases, mixtures of the formal cycloaddition products and the unsaturated lactams are observed, potentially indicating that one diastereomer of **93** might undergo elimination more readily.

The use of an imidoyl chloride or imidate substrate can lead to different levels of reaction efficiency (Table 7).[38−41] Although imidates are more synthetically tractable, imidoyl chlorides often result in higher yields when the two substrates are compared directly (entries 1, 2, 6−9). The reaction is versatile with respect to substrate structure and in most cases the products are crystalline and precipitate from the reaction mixture. The one example of an alkoxy oxazoline (entry 21) produced the expected product along with an anomalous product (not shown) that arises from the consumption of two equivalents of the starting material.[39] The author implies that this product is a single diastereomer and the relative stereochemistry was not determined. It is possible that this result is a manifestation of differing elimination rates of the proposed intermediates **93a** and **93b**.

Five-membered ring heterocyclic substrates react similarly to imidates and imidoyl chlorides with varying degrees of elimination observed depending on the leaving group.[42] 2-Thiazoline reacts with 7-methoxyhomophthalic anhydride to give exclusively the product of formal cycloaddition (eq 25). Under similar conditions, 2-oxazoline produces a mixture of products resulting from formal cycloaddition and elimination (eq 26). The observation of a single diastereomer of **102** suggests that the anti isomer eliminates more readily. These results emphasize the importance of conformation, and not necessarily leaving group ability, on the elimination reactions. 2-Imidazoline gives exclusively the product of formal cycloaddition in which the resultant basic nitrogen in the product is acylated by a second equivalent of the anhydride (eq 27). The implied reactivity of these three substrates suggests that the substrate with the most basic/nucleophilic nitrogen reacts fastest, consistent with the acylation mechanism proposed for imines. Finally, 2-phenyloxazoline **105** reacts with anhydride **4** to produce a single diastereomer of addition product **106** (eq 28).[43] The lack of elimination in this product is consistent with the lack of elimination of the syn diastereomer produced from 2-oxazoline (**102**, eq 26).



Aromatic heterocycles are less reactive in formal cycloaddition reactions with cyclic anhydrides because aromaticity is disrupted in the initial addition process.[41] 2-Chloroisoquinoline reacts with 3-methyl homophthalic anhydride (eq 29) or glutaconic anhydride (eq 30) to give products **109**

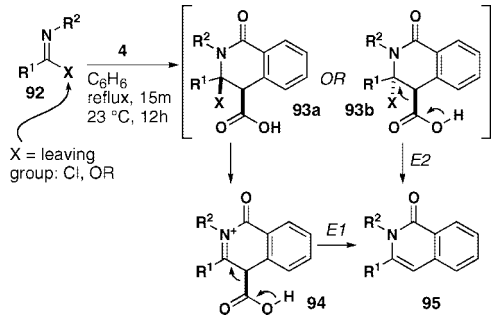


Figure 5. Reactions of imidates with homophthalic anhydride: Cycloaddition and decarboxylation.

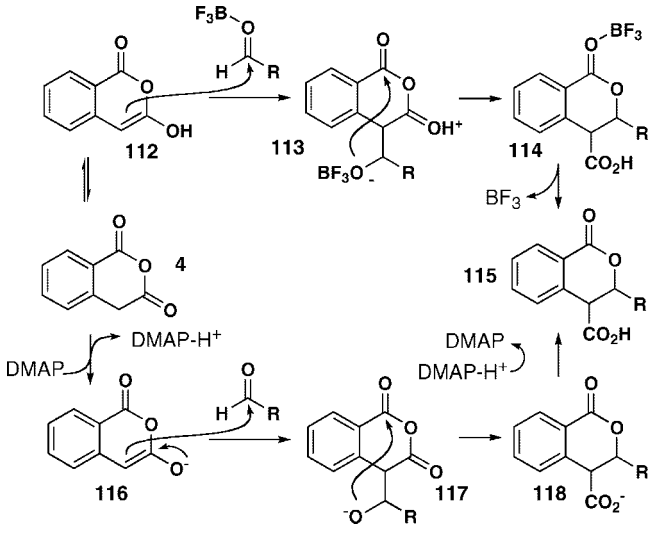
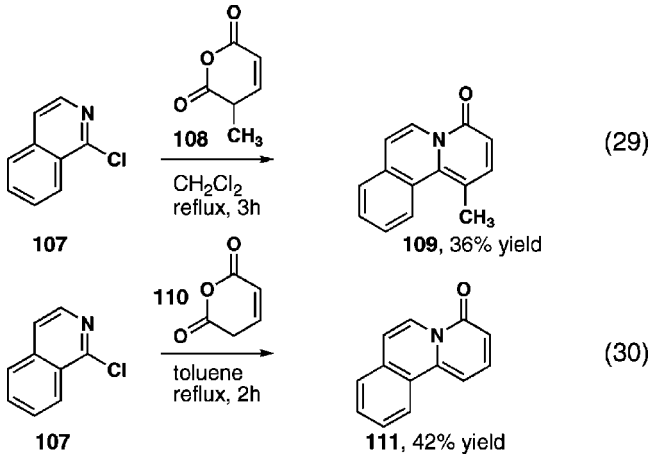


Figure 6. Mechanism of the cycloaddition reaction of aldehydes and ketones with homophthalic anhydrides.

and **111** in which aromaticity is restored in the final decarboxylation and elimination of chloride.

2.4. Carbonyl Compounds



Aromatic aldehydes and ketones have been demonstrated to react with homophthalic anhydrides under Lewis acid- or base-mediated conditions. In contrast to the reactions of imines, the mechanism of addition to aldehydes and ketones likely involves enolization of the homophthalic anhydride and addition to the aldehyde. BF_3-OEt_2 probably plays a dual role of activating the aldehyde for addition and inducing enolate formation on the anhydride (Figure 6). 4-Dimethylaminopyridine (DMAP) is commonly employed as a nucleophilic catalyst for acylation reactions of alcohols with anhydrides and acyl chlorides. It is possible that DMAP plays a similar role in this case by activating the anhydride carbonyl for attack by the oxygen of the aldehyde, in analogy to the acylative mechanism proposed for the reactions of imines. Given the low nucleophilicity of the aldehyde oxygen lone pair electrons, it is more likely that DMAP is serving as a base that deprotonates the anhydride.

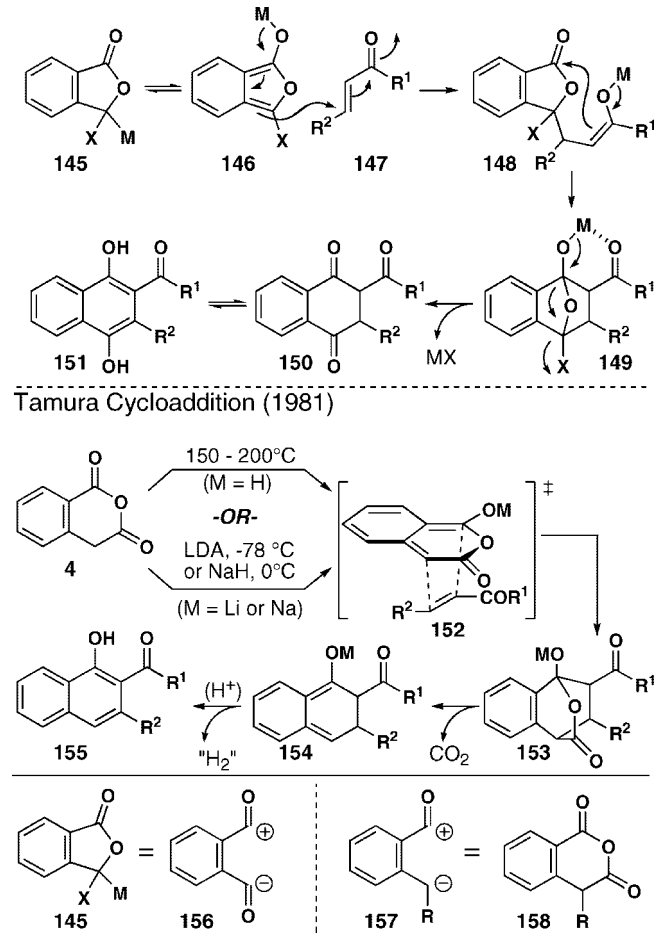
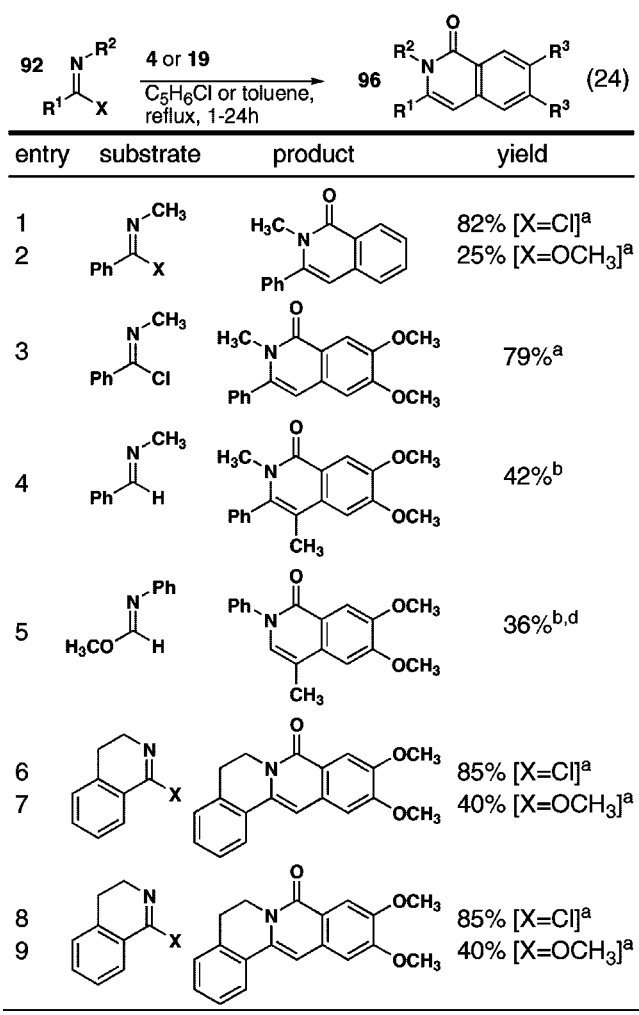


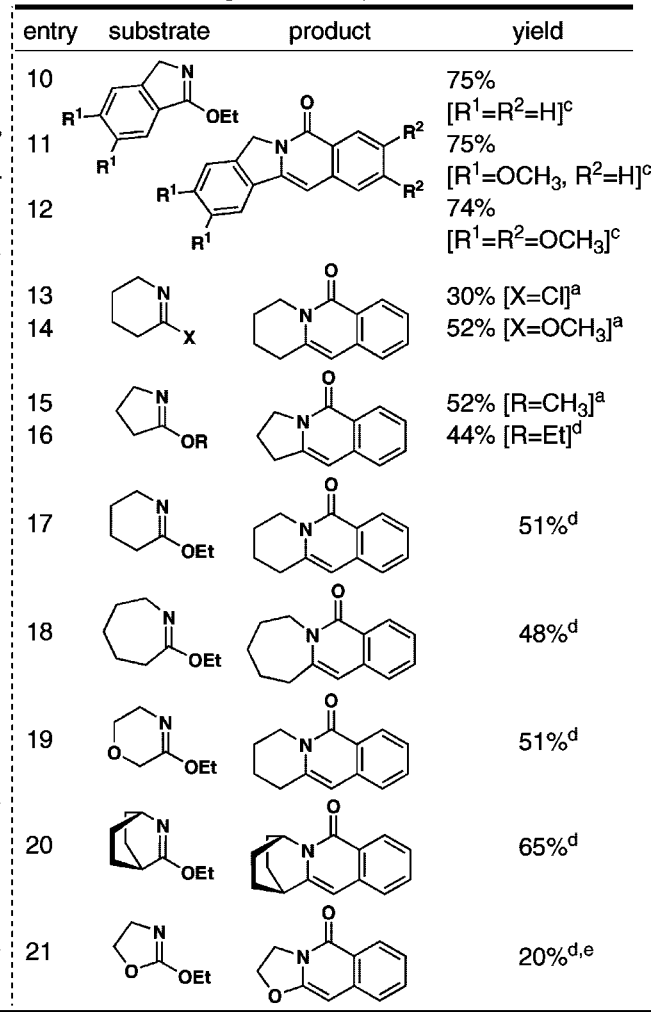
Figure 7. Cycloaddition reactions of alkenes with lactones and anhydrides.

Gesquiere demonstrated that stoichiometric quantities of BF_3-OEt_2 will mediate formal cycloadditions of aldehydes and ketones, albeit with variable yield and diastereoselectivity (Table 8, eq 31).[44] Although the diastereoselectivity appears to be very high (>95:5) in once case, the product was purified by crystallization without analysis of the crude mixture. The main advantage of employing the Lewis acid is to suppress the formation of aldol condensation products that dominate the product mixtures when the reaction is not conducted at low temperature. A related transformation was later reported by Palamavera in which DMAP catalyzes the addition reaction.[45] Formation of the trans-product is generally favored, and in some cases, aldol condensation products are also observed.

Carbonyl compounds with leaving groups, such as anhydrides and acyl chlorides, undergo reactions with homophthalic anhydride that ultimately result in decarboxylation and elimination, as was seen with imidates and imidoyl chlorides. Nadkarni and Usgaonkar developed a two-step synthesis of isoquinolones that probably proceeds via homophthalic anhydride, which is acylated under the reaction conditions to keto-anhydride **137** (Scheme 6).[46] In a second step, condensation with a primary

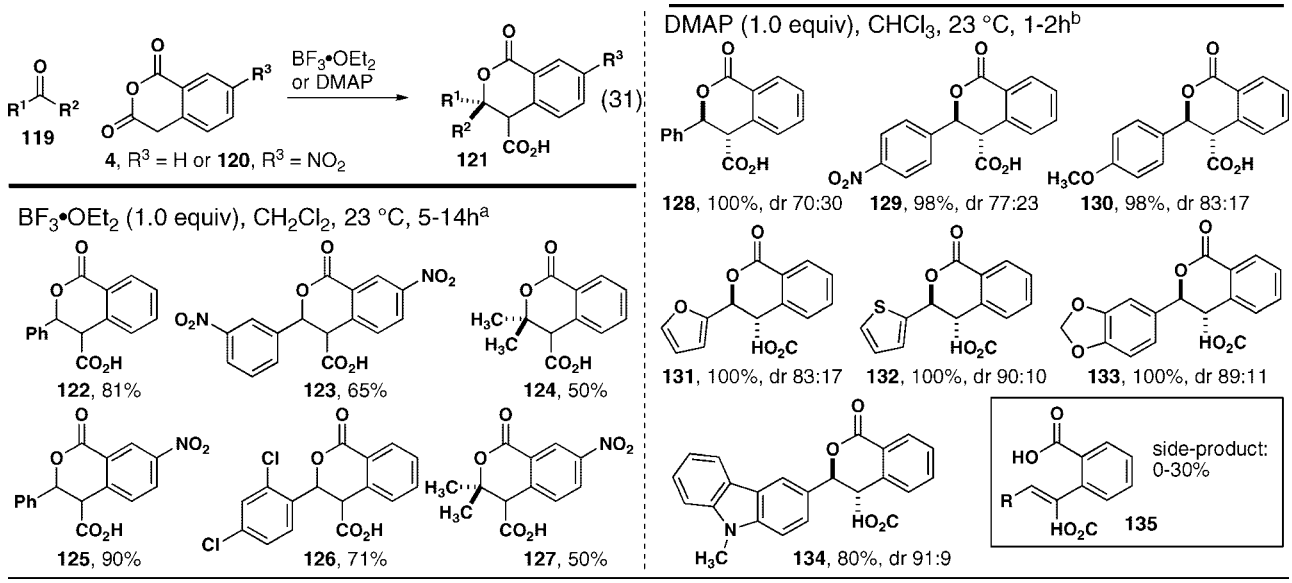
Table 7. Cycloaddition Reaction of Imidoyl Chlorides and Imidates with Homophthalic Anhydrides





[a] Reference 36. [b] Reference 39. [c] Reference 38. [d] Reference 37. [e] Reaction conducted in $ClCH_2CH_2Cl$ (reflux, 3 h).

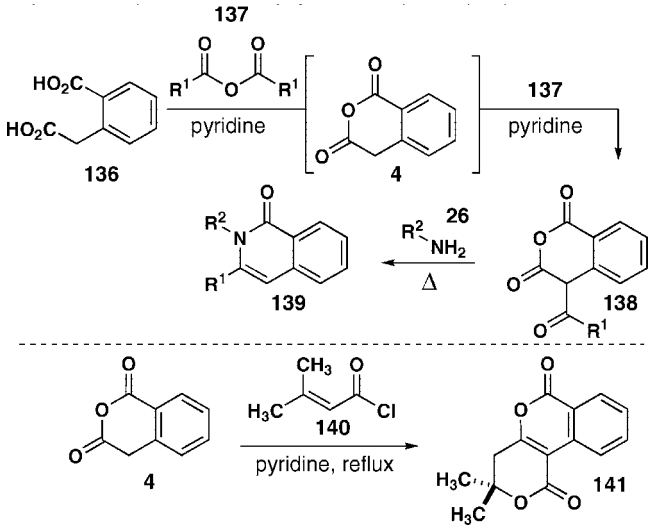
Table 8. Scope of the Cycloaddition Reaction of Aldehydes and Ketones with Homophthalic Anhydrides



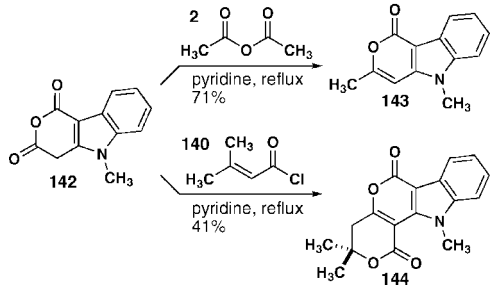
[a] Reference 36. [b] Reference 39.

amine is accompanied by decarboxylation to yield the corresponding isoquinolone. The same author later used homophthalic anhydride directly in a condensation with β,β-dimethyl acryloyl chloride (**140**) and observed cyclization of the intermediate carboxylic acid to polycyclic product **141**.[47] Using Usgaonkar's results as a starting point, Kita

Scheme 6. Reactions of Homophthalic Anhydride with Acyclic Anhydrides and β,β-Dimethyl Acryloyl Chloride



Scheme 7. Reactions of Indoloanhydride 142 with Acetic Anhydride and β,β-Dimethyl Acryloyl Chloride



employed anhydride **142** in reactions with acetic anhydride and β,β-dimethyl acryloyl chloride to form **143** and **144** in 71% and 41% yields, respectively (Scheme 7).[31]

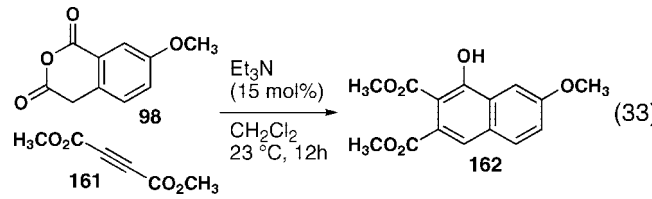
2.5. Alkenes/Alkynes

The reactions of homophthalic anhydrides with alkenes and alkynes produce carbocyclic compounds in reactions that parallel those observed for imines and carbonyl compounds. The synthesis of polycyclic aromatic compounds using annulation reactions was recently reviewed by Brimble.[9] The phthalide annulation was reported separately by Hauser[48] and Kraus[49] in 1978 (Figure 7) and has been applied extensively to the synthesis of natural products. Tamura initially reported the thermal reaction between homophthalic anhydrides and carbon−carbon multiple bonds[50,51] and later reported a base-mediated variant that was consistently higher yielding (Figure 7).[52] The Hauser−Kraus annulation and Tamura Diels−Alder reactions give similar products in different oxidation states unless the oxidation states of the starting materials are adjusted accordingly, i.e., by employing a 3-alkoxyhomophthalic anhydride with an alkyne or alkyne equivalent.

The Tamura cycloaddition proceeds in high yields with a variety of alkenes and alkynes (Table 9, eq 32).[53] In all cases, activation by an electron-withdrawing group at each terminus is required for high yields. When benzoquinone is employed in this reaction, loss of dihydrogen is presumably mediated by excess benzoquinone (Table 9, entry 1). Occasionally the reactions of acyclic alkenes result in products of breakdown of the tricyclic intermediate without decarboxylation (Table 9, entry 4). Although an alkoxy group in one of the ortho-positions of the phenyl ring of benzoquinone would be expected to direct the regiochemistry, halogenated substrates (entries 5 and 6) react exclusively by attack of the nucleophilic carbon of the anhydride opposite to the halogen. Assuming that the cycloaddition is somewhat asynchronous, carbon−carbon bond formation early in the transition state at the less-substituted carbon would be favored by steric considerations. A series of heterocyclic anhydrides were later reported to undergo cycloaddition to alkenes and alkynes (Table 9, entries 7−13).[31]

Intramolecular variants of the Tamura cycloaddition are observed with homophthalic anhydrides appended with electron-deficient alkynes (Table 10).[55,56] The reaction forms five- or six-membered rings in variable yield and tolerates alkynyl esters, ketones, and even aldehydes. The selectivity for alkyne cycloaddition in the intramolecular reaction is in contrast to the inherently greater propensity for reaction with the carbonyl group (Table 10, entry 7).

Base-catalyzed conditions for effecting the cycloaddition reaction between a homophthalic anhydride and dimethyl acetylene dicarboxylate (DMAD) have been reported. Smith reported that triethylamine (15 mol %) was sufficient to induce the reaction, observing a yield that was comparable to those reported by Tamura for the same alkyne (eq 33).[42] Although sodium hydride, or another comparably strong base, seems to be the reagent of choice for most total syntheses reported to date (section 3.1.4), Smiths's conditions would likely be a useful alternative in some cases.

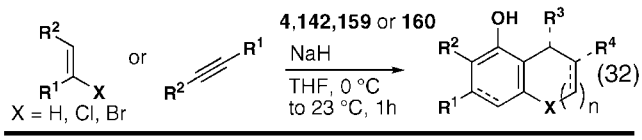


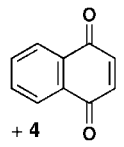
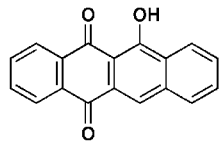
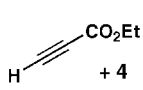
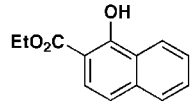
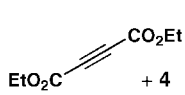
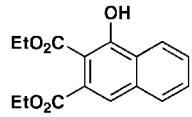
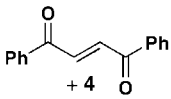
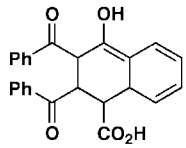
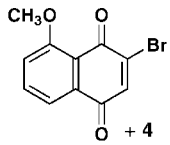
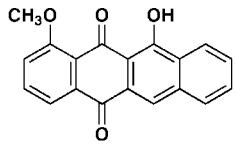
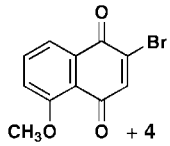
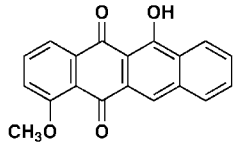
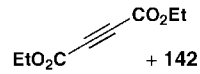
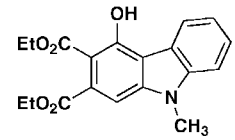
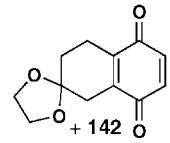
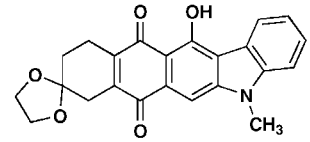
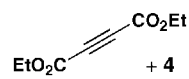
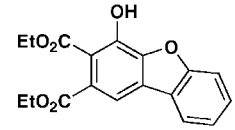
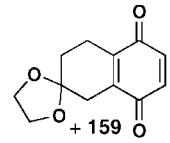
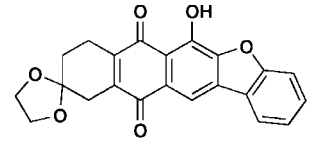
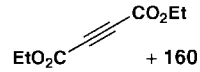
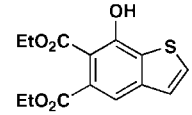
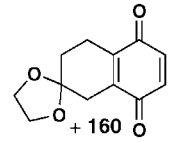
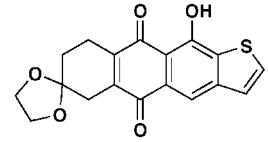
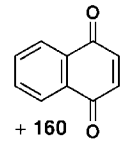
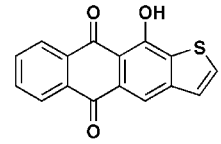
2.6. Other Substrates and Reactions

Several reactions have been discovered in the course of attempting cycloaddition reactions with certain imines and anhydrides. Imines derived from *ortho*-hydroxy benzaldehydes and anilines form dehydrogenated cycloadducts, or pyridones, when allowed to react with homophthalic or 3-arylpentenedioc anhydrides (Figure 8, eq 34).[57] The requirement of 2 equiv of the imine paired with the isolation of the analogous benzylic aniline provides good evidence that the second imine equivalent mediates dehydrogenation of a presumed imine−anhydride product. Although related products have been previously observed, analogous imines do not appear to have been employed in reactions with homophthalic anhydride previous to this report. Haimova noted that the use of *N*-alkyl imines derived from salicylaldehydes provide the expected cycloaddition products with no dehydrogenation.[58]

Imines derived from unsaturated aldehydes provide carbocycles when allowed to react with homophthalic anhydrides **4** or **174** (Table 11).[24,59] The reaction appears to proceed through a Tamura-like cycloaddition with no loss of CO_2 in the final product, which is surprising given the greatly reduced electrophilicity of the unsaturated imines when compared to electron-deficient alkynes and the lack

Table 9. Scope of the Cycloaddition Reaction of Alkenes and Alkynes



entry	substrates	product	yield
1			88%
2			50%
3			96%
4			83%
5			90%
6			73%
7			45%
8			27%
9			76%[a]
10			31%[a]
11			67%
12			28%
13			60%

[a] Anhydride #, the benzofuran analogue of homophthalic anhydride, was prepared from the diacid with acetyl chloride.[54]

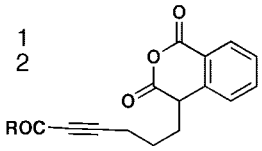
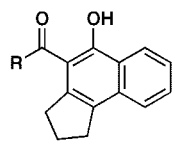
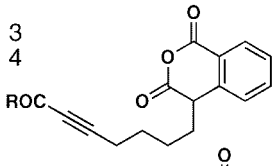
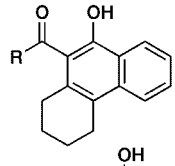
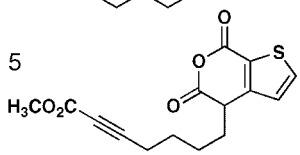
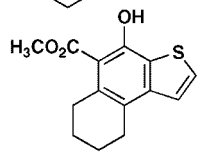
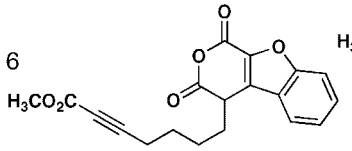
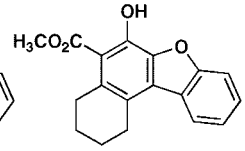
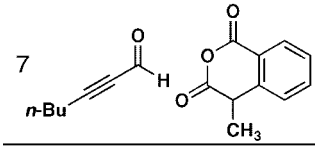
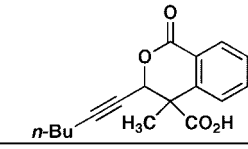
of base in the reaction. In the case of α-methacrolein, the major product is the *β*-iminoketone, whereas substrates lacking alpha substitution tautomerize to the corresponding enaminoketones. Cinnamaldehyde-derived imines react to form predominantly the syn- or anti-diastereomer depending on the N-substituent, and in each case, 15−17% of the corresponding Perkin condensation product is observed. In the case of the *N*-isopropyl imine of cinnamaldehyde, five products are isolated: two diastereomers of the expected carbocycle (8% and 21% yield, respectively), the anticonfigured lactam product of imine−anhydride cycloaddition (15%), Perkin condensation product (not shown), and an isomeric lactam that presumably arises from an acylative mechanism wherein the enolate undergoes conjugate (Michael) addition to the iminium ion intermediate (3%). Although this reaction is of limited synthetic utility, this result highlights the different modes of reactivity that are enabled by the unsaturated imine.

Homophthalic anhydride undergoes an interesting annulation reaction with *o*-cyanobenzyl bromides in the presence of triethylamine.[60] Jagtap and co-workers found that fused tetracycles were produced in modest yield upon refluxing the two reagents in acetonitrile (Scheme 8). The mechanism for the formation of **178**−**181** probably involved base-mediated alkylation of the benzylic position of homophthalic anhydride followed by base-catalyzed cyclization and decarboxylation. These compounds represent reduced forms of the indanone compounds that Cushman has explored for topoisomerase I inhibitory activity (section 3.2.1).

Derivatives of homophthalic and succinic anhydride have been reported to participate with aldehydes and imines. Acyl imidates derived from homophthalic and succinic anhydrides have been used in cycloaddition reactions with aldehydes and imines (Figure 9). These reactions produce the same products that might result from the cycloaddition reactions wherein the resultant acid has been converted to the amide. The diastereoselectivity was generally low, and in the cases were it was determined, it did not exceed 70:30 in favor of either possible stereoisomer. The Lewis acid-catalyzed reaction of 2,5-bis(trimethylsilyloxy)furan, which can be viewed as the silylketene acetal of succinic anhydride, to imines proceeds in good yield and diastereoselectivities that are >90:10 in 9 out of 12 examples (Figure 9). Each of these reactions provides an alternate pathway for producing structures typically prepared by the cycloaddition reactions of anhydrides.

Another interesting variant of the imide−anhydride cycloaddition has been reported for isatoic anhydride.[61,62] Although this reaction may not involve a mechanism that is directly related to the analogous reaction of homophthalic

Table 10. Intramolecular Cycloaddition of Alkenes with Cyclic Anhydrides

entry	substrate(s)	product	yield
1 2			24% (R=OCH$_3$) 36% (R=H)
3 4			54% (R=OCH$_3$) 36% (R=CH$_3$)
5			67%
6			41%
7			62%

anhydride, the structural complementarity is notable. A comprehensive account of this reaction is outside the scope of this review. One example from Bose is illustrative of how this reaction can create substrates suitable for subsequent cyclization reactions (Scheme 9).[63] The authors subsequently use AIBN and tributyltin hydride to effect radical cyclization followed by oxidation with $KMnO_4$ to convert the mixture of products to quinazolone **203**. Several variants, including one-pot/3CR procedures,[64−66] and applications[67−69] have been reported.

2.7. Three-Component Reactions of Homophthalic Anhydrides, Amines, and Aldehydes

Yadav and co-workers observed that the lactam products of the imine−anhydride reaction can arise from a three-component condensation reaction.[70] When an amine, aromatic aldehyde, and homophthalic anhydride are combined in an ionic liquid, the isoquinolinic carboxylic acid is formed in high yield with high syn-diastereoselectivity (Table 12). A subsequent paper by Azizian, which uses alum ($KAl(SO_4)_2 \cdot 12H_2O$) as a catalyst in organic solvent, followed the process by ^{1}H NMR spectroscopy and demonstrated that the amide forms quickly and is slowly converted to the lactam product.[71] In the first step, the amine reacts regioselectively with homophthalic anhydride to provide the hemiamide shown in Table 12. In the presence of an aldehyde, condensation to form an iminium ion takes place, yielding the presumed intermediate of the imine−anhydride reaction. Although the authors depict a reaction via iminium ion **206** derived from a *Z*-configuration of R^1 and R^2, the production of the syn-diastereomer as the major product suggests a reaction with these substituents in the *E*-configuration (Figure 2, **A**, vide supra). In addition to alum, several additional

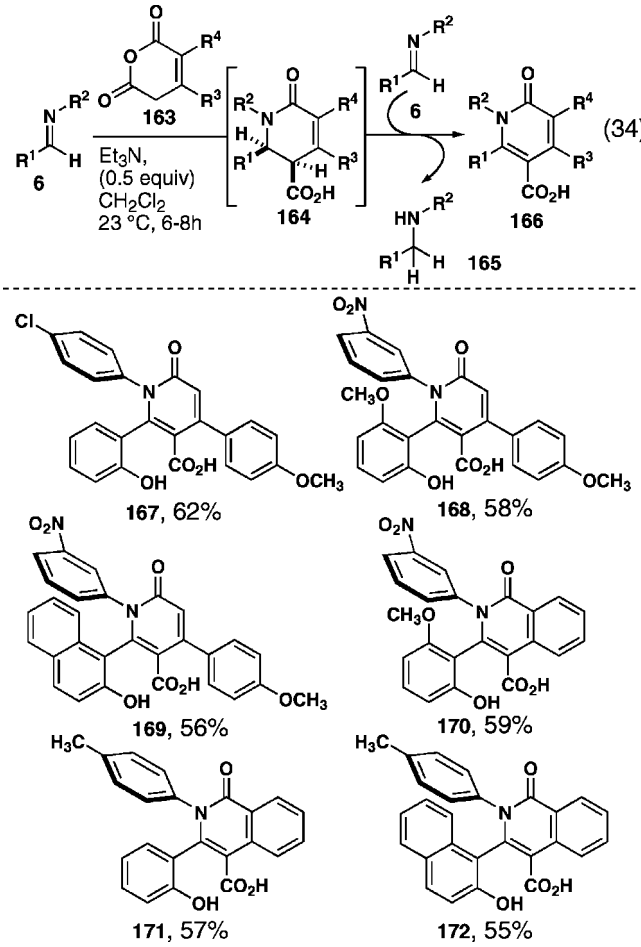


Figure 8. Reactions of salicyl imines with cyclic anhydrides.

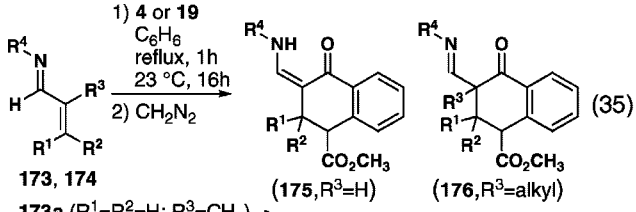
catalysts ($InCl_3$,[70] H_2SO_4/silica gel,[72] $Yb(OTf)_3$,[73] and iodine[74]) have been reported. This necessarily stepwise mechanism supports the idea of a polar mechanism for the imine anhydride reaction by establishing **204** as an intermediate that can also arise from nucleophilic attack of the anhydride by the imine.

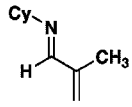
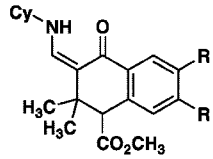
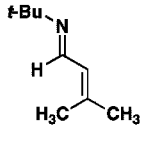
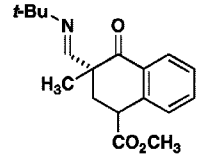
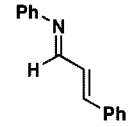
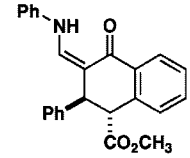
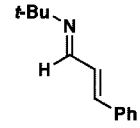
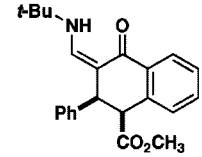
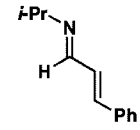
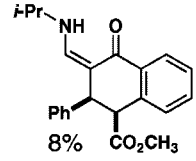
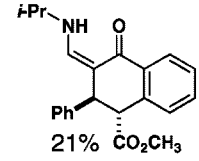
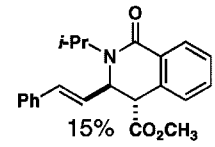
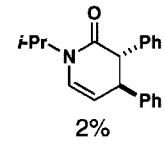
2.8. Four-Component Reactions of Maleic Anhydrides, Thiols, Amines, and Aldehydes

The Shaw group disclosed a remarkable four-component reaction (4CR) that forms tetra- and pentasubstituted γ-lactams with high levels of diastereoselectivity (Scheme 10).[16] The reaction involves a final ring-closure step similar to what is observed by Yadav. In this case, the intermediate iminium ion can undergo a "deacylation" step that yields the imine and the anhydride. This crucial equilibrium allows the two possible regioisomers of the amide intermediate (**214** and **217**) to interconvert, allowing isomer **214** to form stabilized enolate intermediate **216** that goes on to product.

The Shaw 4CR is highly selective for many different amines and aromatic aldehydes (Figure 10). Although cyclopropane carboxaldehyde is viable because of its reduced propensity for enolate formation, most enolizable aldehydes do not function in this reaction. Thiol components give the best diastereoselectivity when they are bulky. This reaction forms the same products as the imine−anhydride cycloaddition using thioether-substituted anhydrides in a single step, i.e., synthesis of the imine and anhydride in separate steps is avoided.

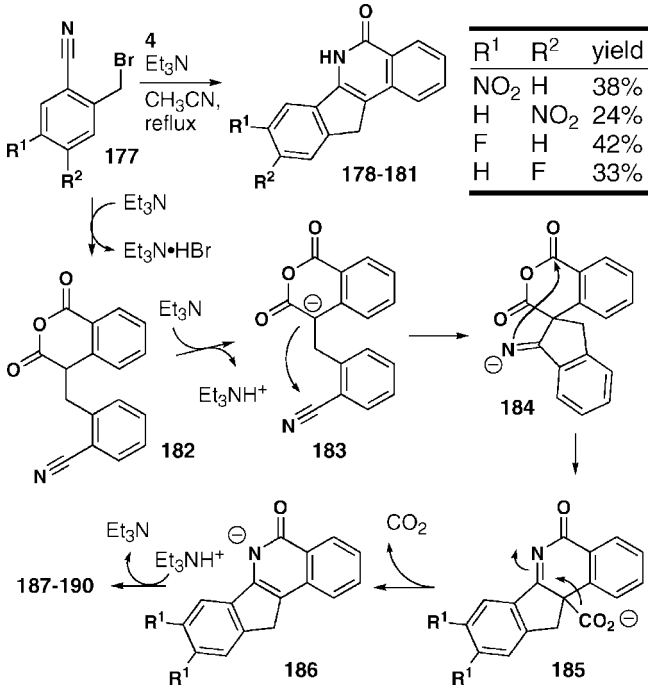
Table 11. Cycloaddition of α,β-Unsaturated Imines with Homophthalic Anhydrides



entry	substrate	product	yield
1			45% (R=OCH3)
2			70% (R=H)
3			45%
4			49%
5			20%
6			8%
			21%
			15%
			2%

Pentasubstituted γ-lactams with three contiguous stereogenic centers are prepared from 3-alkyl maleic anhydrides in a single operation (Table 13). Formation of the major diastereomer occurs with 83−85% selectivity in yields that are comparable to the reactions with maleic anhydride. This reaction compares favorably to the Ugi 4CR in efficiency and is one of the few 4CRs to date that creates a product with three stereogenic centers in which each of the four inputs can be varied independently.

Scheme 8. Tandem Alkylation/Cyclization Reaction between Homophthalic Anhydride and *o*-Cyanobenzyl Bromides



R1	R2	yield
NO2	H	38%
H	NO2	24%
F	H	42%
H	F	33%

3. Applications

3.1. Natural Products and Analogues

3.1.1. Protoberberine Alkaloids and Related Natural Products

The 13-methyltetrahydroprotoberberine alkaloids constitute a small family of fused polycyclic alkaloids isolated from various species of the herb Corydalis.[75−77] The cycloaddition reactions of suitably substituted homophthalic anhydrides with the appropriate dihydroisoquinolines provide an efficient synthetic route to many alkaloids in this family. The

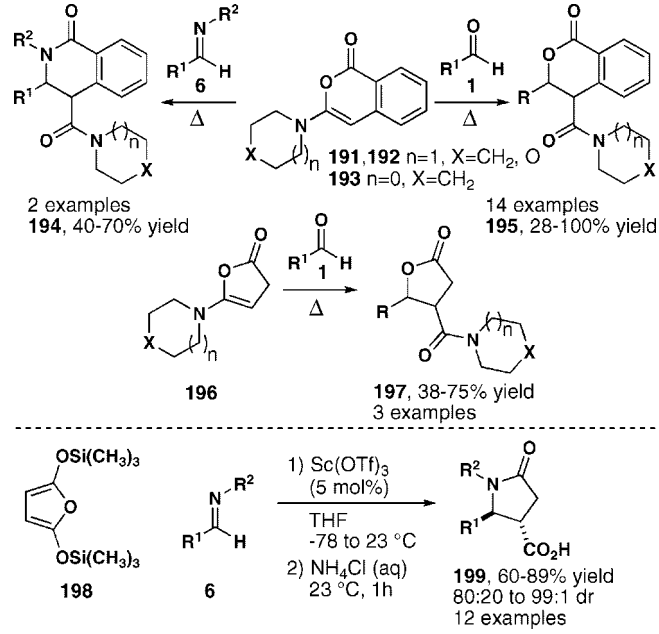


Figure 9. Addition of anhydride derivatives to imines and aldehydes.

Scheme 9. Annulation Reaction of an Imine with Isatoic Anhydride

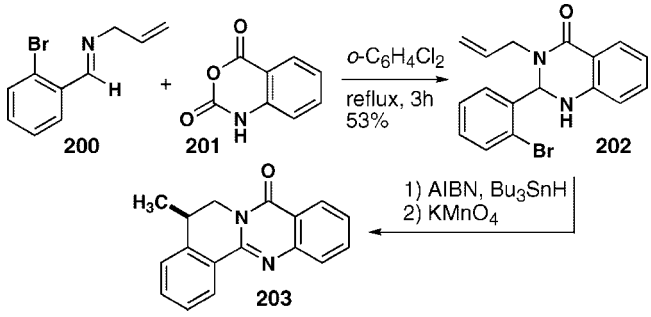
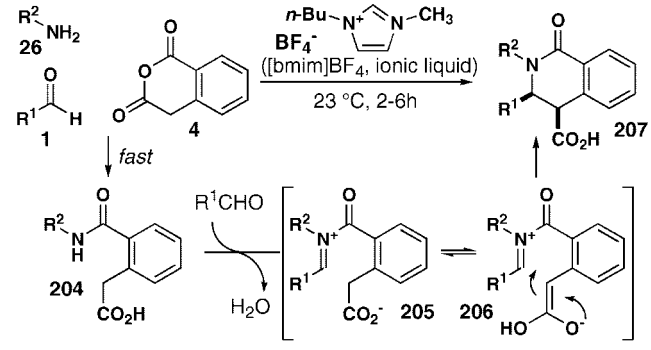
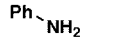
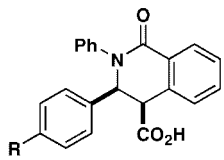
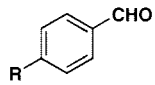
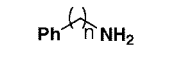
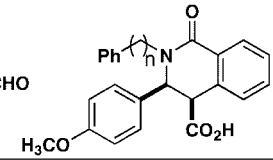
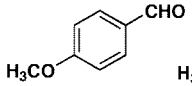


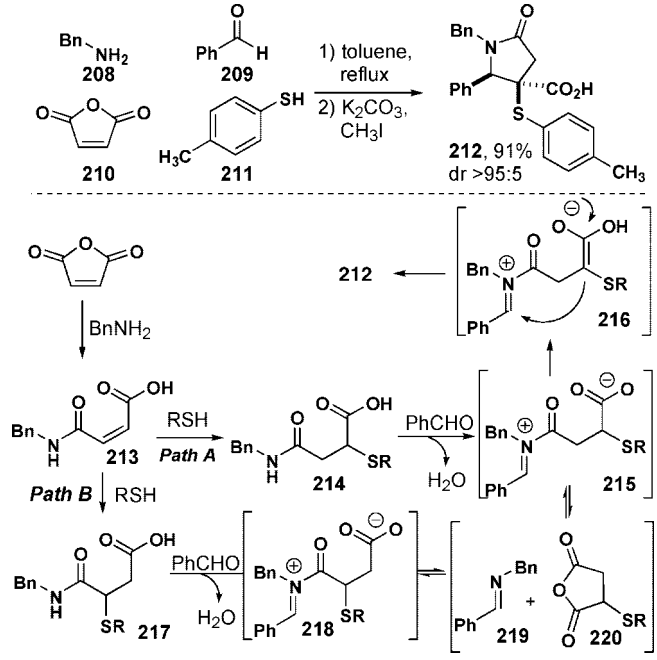
Table 12. Three-Component Reactions with Homophthalic Anhydride



entry	substrates	product	yield
1			90% (R=H)
2			89% (R=OCH_3)
3			90% (R=$NCH_3)_2$)
4			80% (R=CN)
5			89% (n=1)
6			78% (R=2)

cycloaddition of norhydrastinine (**237**) with 4,5-dimethoxyhomophtalic anhydride (**19**), carried out by Cushman and co-workers in 1977,[5] has emerged as a general method toward both syn- and anti-diastereomers of 13-methyltetrahydroprotoberberine alkaloids from a common anticarboxytetrahydroprotoberberine intermediate **238** (Scheme 10). This cycloaddition reaction was carried out at room temperature in chloroform to yield a mixture of *anti*- and *syn*-carboxytetrahydroprotoberberines. The anticarboxytetrahydroprotoberberine diastereomer **238**, represented in Scheme 11, could be isolated pure in 90% yield after crystallization in acetic acid. Carboxylic acid **238** was converted to the methyl ester with diazomethane and then carried on to the final product by converting the carboxylate carbon to a methyl group in three steps (77% yield). The thermodynamically more stable syn-diastereomer could be accessed in >95:5 diastereoselectivity (90% yield) by refluxing the anti-diastereomer in acetic acid to effect epimerization. This intermediate was converted to the corresponding *syn*-13-methyltetrahydroprotoberberine (**241**) in the same four-step sequence used to produce **240**.

Scheme 10. Four-Component Reactions of Maleic Anhydrides



In the racemic total synthesis of a series of hexahydrobenzo[*c*]phenanthridine alkaloids reported by Cushman,[78−80] the cycloaddition of 7-methyl homophthalic anhydride was employed to produce a quaternary stereogenic center. Initially, the reaction exhibited modest diastereoselectivity

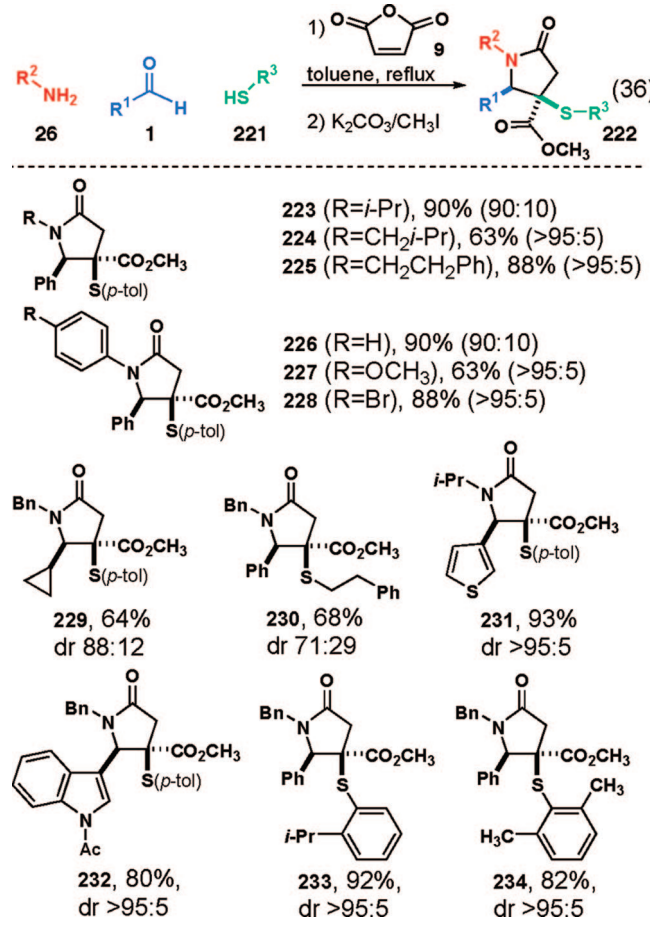
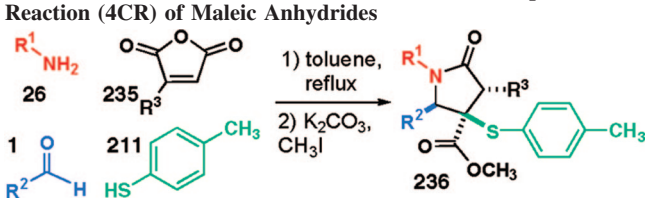


Figure 10. Scope of amine, aldehyde, and thiol performance in the Shaw 4CR.

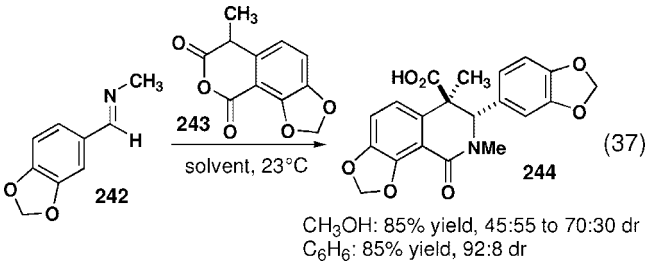
Table 13. Effect of the Substitution in the Four-Component Reaction (4CR) of Maleic Anhydrides



entry	R^1	R^2	R^3	yield	dr[a]
1	*i*-Pr	Ph	CH_3	70%	86%
2	Bn	Ph	CH_3	65%	83%
3	*o*-BrC_6H_5	*o*-BrC_6H_5	*i*-Bu	49%	*b*
4	*i*-Pr	Ph	*i*-Bu	68%	83%
5	Bn	Ph	*i*-Bu	62%	*b*

[a] Determined by GC. [b] Baseline resolution of the four isomers was not possible with GC or HPLC.

(45:55[78] to 70:30[80]) in the cycloaddition reaction between homophthalic anhydride **243** and piperonylidenemethylamine (**242**) in methanol (eq 37). The syn- and anti-diastereomers of isoquinoline **244** were readily separable by chromatography in 29% and 66% yield, respectively. Unlike the analogous reaction of unsubstituted homophthalic anhydrides, epimerization is not possible using base or acid. Cushman demonstrated a significant impact of solvent on the diastereoselectivity of this reaction,[78] confirming that benzene, which was used in the initial report on the synthesis of isocorynoline, was the most effective at forming the syn-diastereomer selectively (92:8).[79] The efficiency and selectivity with which this generates the quaternary stereogenic center present in the isoquinoline **244** is noteworthy.[81−86]

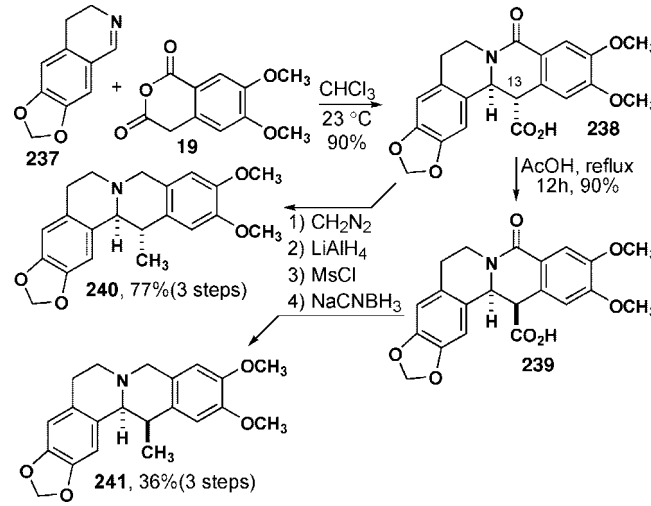


(37)

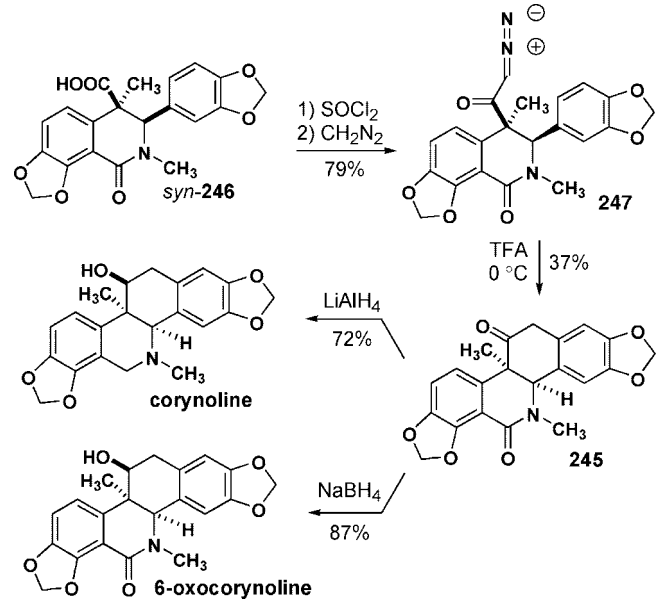
cis-Fused 13-methylbenzophenantridine alkaloids corynoline and 6-oxocorynoline were prepared in a straightforward sequence from **245** (Scheme 12). The last ring was formed from *syn*-**246** through a modest yielding (37%) cyclization reaction of the α-diazoketone **247**. This α-diazoketone **247** was generated in 79% yield by reaction of the corresponding acid chloride with diazomethane. Reduction of the two carbonyl groups present in **245** with $LiAlH_4$ in refluxing tetrahydrofuran yielded the tricyclic alkaloid corynoline in 72% yield. Diastereoselective reduction of ketone **245** with $NaBH_4$ yielded the natural alkaloid 6-oxocorynoline in 87% yield.

trans-Fused 13-methylbenzophenantridine isocorynoline was synthesized in seven steps from *anti*-**246** (Scheme 13). The final ring of this natural product was, in this case, assembled by a Friedel−Crafts reaction performed with the carboxylic acid that resulted from the homologation of compound *anti*-**246**. The reduction of the resulting ketone with $NaBH_4$, followed by elimination of the resulting carbinol, under acidic conditions, installed the olefin present in compound **249**. The epoxidation of **249** with *m*-CPBA (77% yield) followed by epoxide opening with $LiAlH_4$ as

Scheme 11. Synthesis of 13-Methyltetrahydroprotoberberine Alkaloids



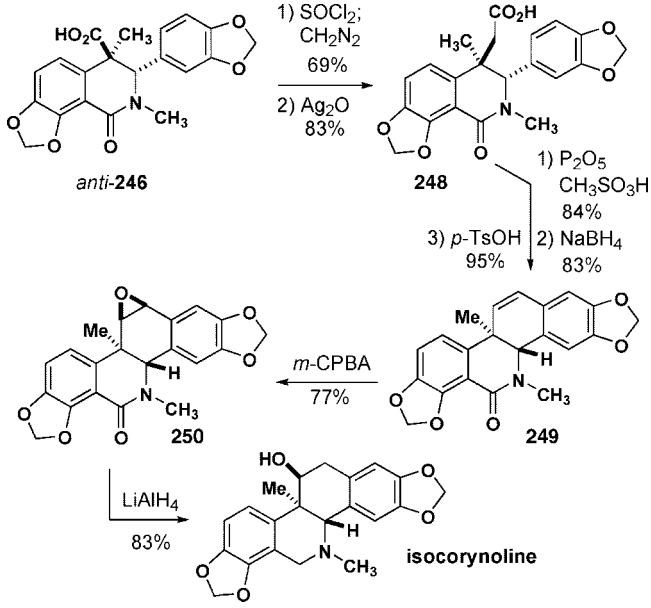
Scheme 12. Synthesis of Corynoline and 6-Oxocorynoline



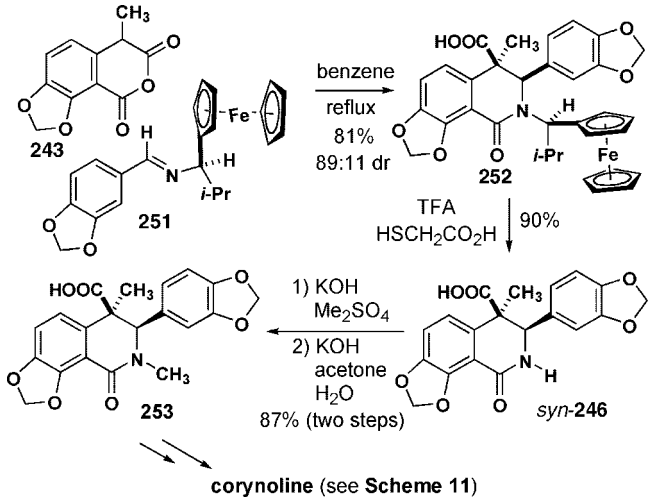
the hydride source gave access to the final product 14-epicorynoline in 83% yield.

Three years after the publication of the total synthesis of corynoline by Cushman and co-workers, the author reported an enantioselective approach to this target based on the stereoselective cycloaddition of chiral imine **251** and racemic homophthalic anhydride **243** in refluxing benzene (Scheme 14).[87] This approach is noteworthy in that it is the sole example of any imine−anhydride reaction controlled by a chiral auxiliary. The use of the ferrocenyl chiral auxiliary group present in the imine proved to be effective, allowing the formation of the two contiguous stereogenic centers, one of which is quaternary, in an 89:11 diastereomer ratio. Optically pure compound **252** was obtained in 81% yield after crystallization of the crude reaction mixture. The removal of the ferrocenyl chiral auxiliary with mercaptoacetic acid in trifluoroacetic acid yielded *syn*-**246** in 90% yield. Methylation of the lactam and the carboxylic acid in **246**, followed by the hydrolysis of the resulting ester group, gave rise to the carboxylic acid **253**, an advanced intermediate in the previously commented racemic total synthesis of corynoline.[78]

Scheme 13. Synthesis of Isocorynoline



Scheme 14. Asymmetric Formal Synthesis of Corynoline



In addition to the illustrative examples above, the reaction of substituted homophthalic anhydrides with isoquinolines has been used extensively in the preparation of related alkaloids by Cushman[88−97] and others.[98,99] These syntheses and their corresponding key cycloaddition steps are summarized in Table 14. Although the imine−anhydride cycloaddition is by no means a biomimetic process, the striking efficiency and versatility with which members of this class of natural product can be prepared clearly distinguishes this reaction as a privileged transformation for the assembly of these compounds.

Haimova and co-workers reported the total synthesis of the alkaloid xylopinine through the use of an imidoyl chloride in a cycloaddition reaction with homophthalic anhydride **19** (Scheme 15).[38] Imidoyl chloride **261** was prepared by treating isoquinolinone **260** with phosphoryl chloride and pyridine in chlorobenzene at room temperature. This compound was not isolated but was allowed to react in situ with homophthalic anhydride **19** to give compound **262** in 87% yield. This product was transformed into xylopinine by application of a previously reported sequence reported by Kametani and co-workers in their total synthesis of the same natural product.[100]

3.1.2. Tetrahydrocannabinol and Nicotine Analogues

The cycloaddition of glutaric anhydride with different imines has been successfully employed by Castagnoli and co-workers in the preparation of pharmacologically active nitrogen analogues of tetrahydrocannabinol (THC).[12,13] The cycloaddition of *o*-anisylidenemethylamine and glutaric anhydride in refluxing xylene as a model system afforded the *anti*-piperidone 83% yield and with 88:12 diastereoselectivity (not shown). For the synthesis of a THC analogue, *anti*-**264** was isolated in 48% yield by fractional crystallization. Although the yield and dr were not reported for the crude reaction mixture, it is probably comparable to the model system. Acid **264** was converted to alkene **265** by the four-step sequence shown in Scheme 16. The synthesis of the B ring of the final product was achieved by cyclization of olefin **265** in $BF_3 \cdot OEt_2$ as solvent. The transformation of lactam **266** to the final enamine **267** proceeded in good yield (63%) with an excess of CH_3MgBr.

In 1972, Cushman and Castagnoli devised a straightforward route toward *anti*-3′-methylnicotine, allowing the authors to establish the relative stereochemistry of this biosynthetic product of a feeding experiment.[11] Thus, the cycloaddition of *N*-3-pyridylidenemethylamine (**268**) with succinic anhydride furnished *anti*-1-methyl-5-(3-pyridil)-2-pyrrolidinone (**269**), which possesses all of the carbon atoms present in the final target (Scheme 17). The anti-stereochemistry of this product was established on the basis of the coupling constant value (5 Hz) observed between protons attached to C-3 and C-4. The final product *anti*-3′-methylnicotine (**271**) was obtained in good yield after a four-step sequence.

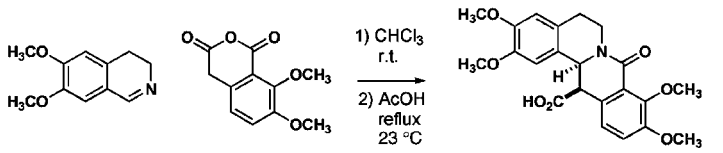
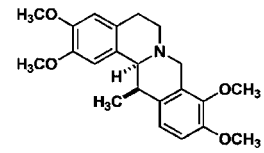
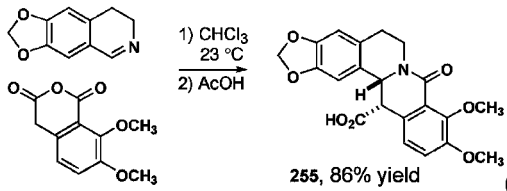
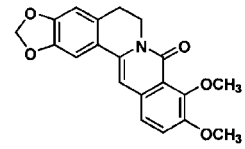
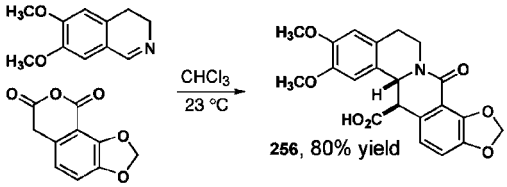
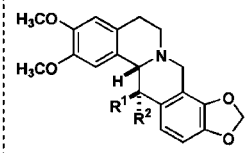
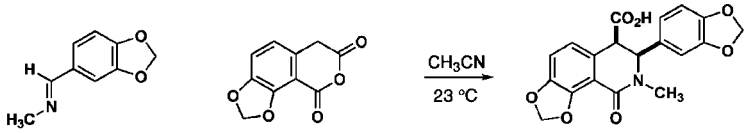
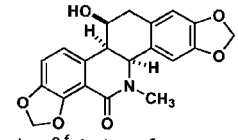
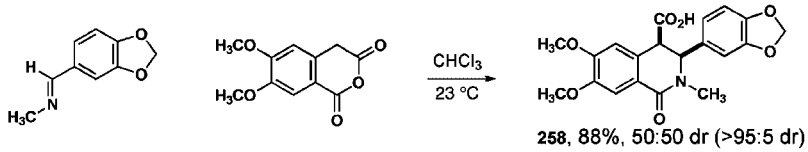
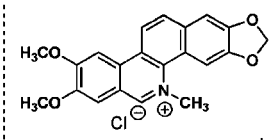
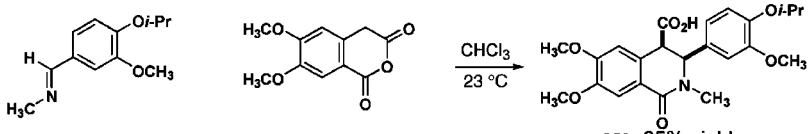
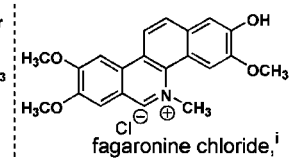
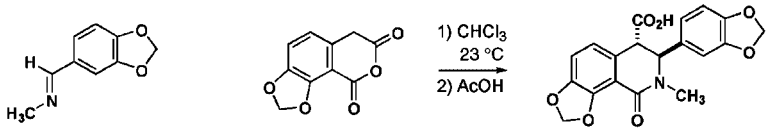
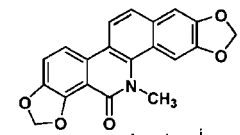
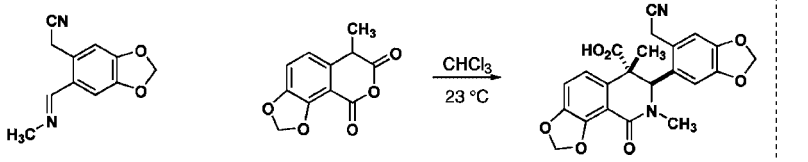
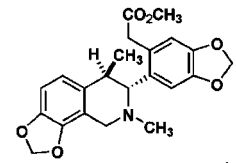
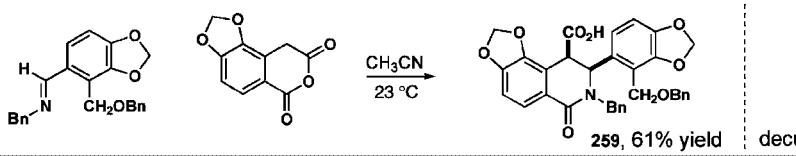
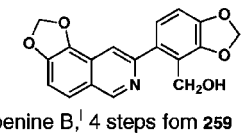
3.1.3. Martinellic Acid Core

The imine−anhydride reaction developed by the Shaw group has been applied in a formal synthesis of the alkaloid martinellic acid (Scheme 18).[14] The key γ-lactam **274** was synthesized by the three-component reaction between commercially available aldehyde **272**, benzylamine, and anhydride **273**. This reaction took place in a diastereocontrolled fashion, obtaining the corresponding γ-lactam as a >95:5 mixture in favor of the syn-diastereomer. The analogous 4CR is not suitable for this particular substrate because of the reactivity of nitro groups toward thiols. Methylation of the pendant carboxylic acid with trimethylsilyldiazomethane afforded ester **274** in 61% yield (two steps). Reductive cleavage of the arylthio group, as well as reduction of the nitro group employing Raney nickel in the presence of DBU, gave access to the corresponding aniline that underwent a cyclization with the ester group to yield tricyclic lactam **275** in 41% yield. The cis-ring fusion present in tricyclic compound **275** was assigned by X-ray diffraction studies of a closely related tricyclic compound obtained by the same synthetic route. Introduction of the allyl group present in compound **276** was performed in three steps by BOC protection of the amide group, *N*,*O*-acetal formation with $LiHBEt_3$, and nucleophilic attack of allyltrimethylsilane to the *N*-acyliminium ion generated by reaction with scandium triflate.

3.1.4. Anthracyclinones

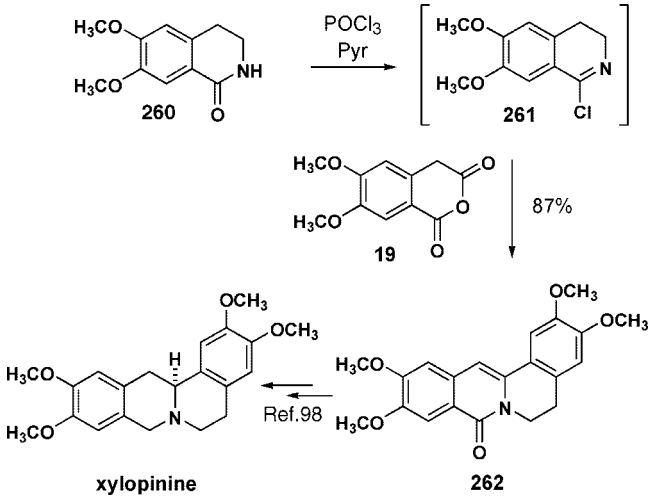
The cycloaddition of quinones and homophthalic anhydrides has given access in one step to the ABCD tetracyclic core of several members of the anthracyclinone family of

Table 14. Synthesis of Protoberberine Alkaloids and Related Natural Products

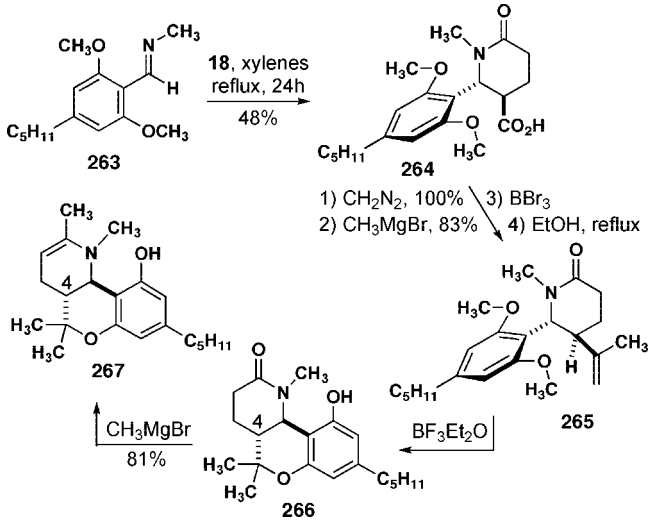
Entry	Imine-anhydride reaction	target
1		
	254, 81%, 75:25 dr (>95:5 dr)	(±)-corydaline,[a] 4 steps from **254**
2		
	255, 86% yield	(+)-canadine (R^1=R^2=H),[b,c] 3 steps from **255** (+)-thalictricavine (R^1=CH_3, R^2=H),[b,c] 5 steps from **255**
		berlambine,[c] 1 step from **255**
3		
	256, 80% yield	(+)-cavidine (R^1=H, R^2=CH_3),[b] 6 steps from **256** (+)-thalictrifoline (R^1=CH_3, R^2=H),[d] 5 steps from (+)-**256**
4		
	syn-**257**, 62%, 66:33 dr	(±)-chelidonine,[e,f] 4 steps from *syn*-**257**
5		
	258, 88%, 50:50 dr (>95:5 dr)	(±)-nitidine chloride,[g,h] 4 steps from **258**
6		
	259, 65% yield	fagaronine chloride,[i] 4 steps from **259**
7		
	anti-**257**, 95% yield	oxysanguinarine,[j] 7 steps from *anti*-**257**
8		
	258, 94%, 66:33 dr	corydalic acid methyl ester,[k] 4 steps from **258**
9		
	259, 61% yield	decumbenine B,[l] 4 steps fom **259**

[a] Reference 89. [b] Reference 94. [c] Reference 90. [d] Reference 93. [e] Reference 92. [f] Reference 91. [g] Reference 95. [h] Reference 88. [i] Reference 97. [j] Reference 98. [k] Reference 96. [l] Reference 99.

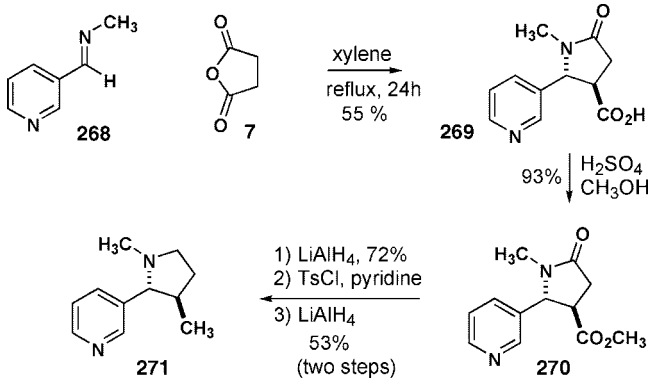
Scheme 15. Synthesis of Xylopinine



Scheme 16. Synthesis of Nitrogen Analogues of Tetrahydrocannabinols

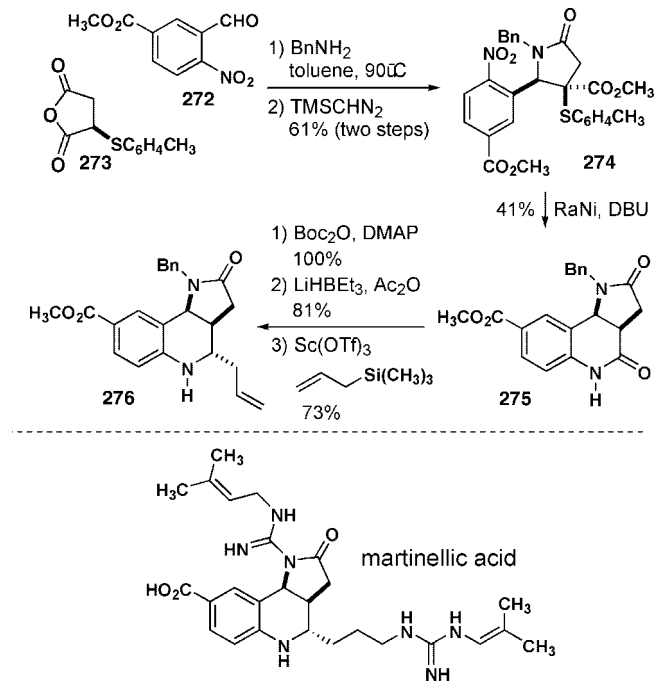


Scheme 17. Synthesis of *anti*-3′-Methylnicotine

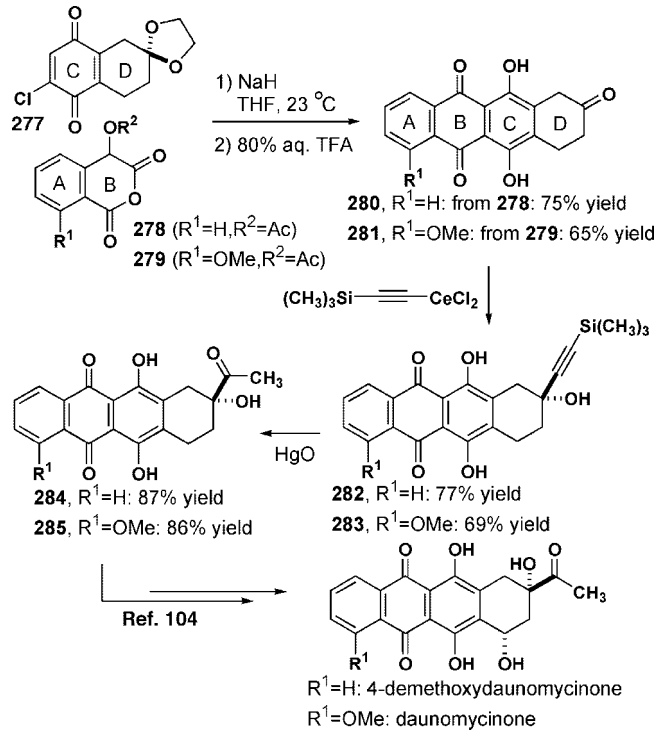


antibiotics, which are clinically useful drugs for the treatment of a broad spectrum of human cancers.[101−103] The key steps in Tamura's total syntheses of 4-demethoxydaunomycinone and daunomycinone[104,105] involve the cycloaddition of chloroquinone **277** (C and D rings in the final product) and homophthalic anhydrides **278** and **279** (A and B rings in the final product) as shown in Scheme 19. The reactions take place with sodium hydride as base in THF at room temperature, followed by aqueous trifluoroacetic cleavage of the acetal protecting group present in the quinone counterpart.[52]

Scheme 18. Assembly of the Core Structure of Martinellic Acid

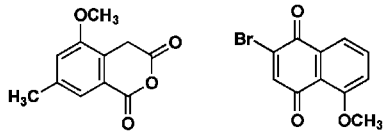
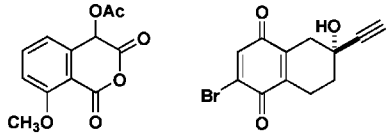
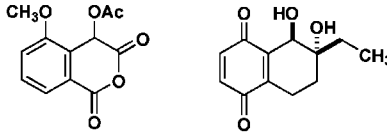
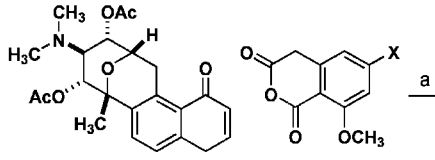
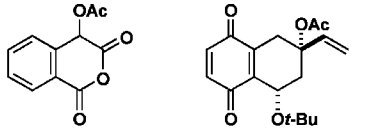
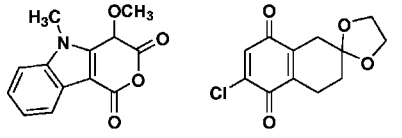
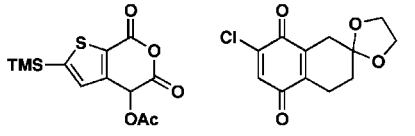


Scheme 19. Synthesis of 4-Methoxydaunomycinone and Daunomycinone



This cycloaddition reaction takes place via a [4 + 2]-cycloaddition between the enolate generated from homophthalic anhydride (diene) and the highly reactive chloroquinone **277** as the dienophile counterpart, followed by extrusion of carbon dioxide and hydrogen chloride.[53] The presence of a chlorine atom at C-2 of the quinone plays a double role in this reaction. This atom controls the regiochemistry of the cycloaddition reaction and facilitates aromatization of the cycloadduct formed via elimination of HCl. As a result of this process, tetracyclic compounds **280** and **281** were obtained with 75% and 65% yield, respectively. The addition

Table 15. Synthesis of Anthracyclinone Natural Products

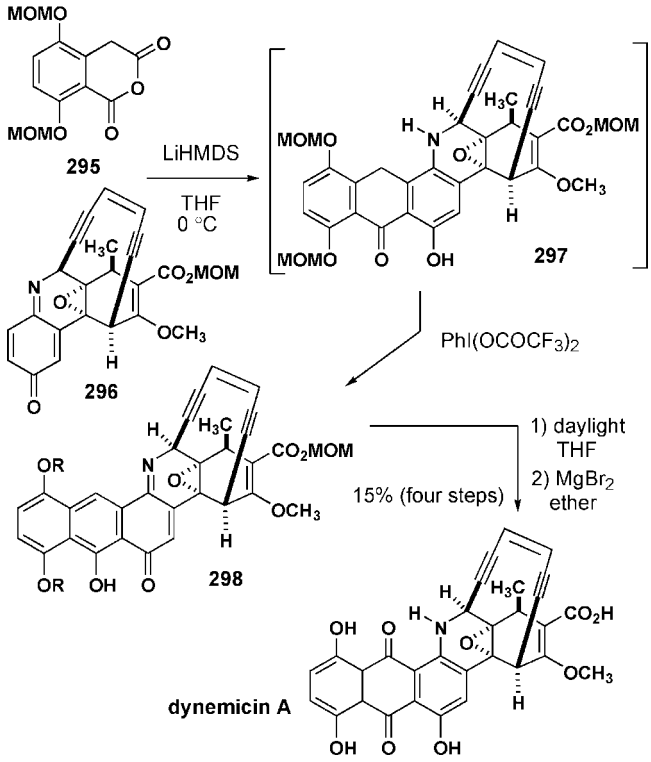
Entry	Anhydride-quinone reaction	product	target
1		**286**, 78% yield	SS-228R,[b] 1 step from **286**
2		**287**, 70% yield	(-)-7-deoxydaunomycinone,[c] 1 step from **287**
3		**288**, 55% yield	(-)-γ-rhodomycinone,[d] 2 steps from **288**
4	 **215**a, X=H; **215**b, X=CH_3 **215**c, X=OCH_3; **215**d, X=OBn	**289**, 62-100% yield	(+)-7-methoxynogarene[e]
5		**290**, 70% yield	(±)-4-demethoxyadriamycinone,[f] 3 steps from **290**
6		**291**, 57% yield	daunomycin analogue **292**,[g] 7 steps from **291**
7		**293**, 51% yield	daunomycin analogue **294**,[h] 11 steps from **293**

[a] Experimental conditions: NaH, THF, 23 °C. [b] Reference 105. [c] References 107 and 108. [d] References 109 and 110. [e] References 111−113. [f] Reference 114. [g] Reference 117. [h] Reference 118.

of trimethylsilylethynylcerium(III) to ketones **280** and **281** resulted, after oxidation with mercuric oxide, in the formation of the C-9 α-hydroxyketone portion present in the final products. Two additional transformations, previously reported by Kende and co-workers,[106] carried out over these two advanced intermediates completed the total synthesis of 4-methoxydaunomycinone and daunomycinone.

The versatility of this cycloaddition reaction has been exploited by Tamura[105,107] and others[108−118] in the synthesis of various anthracyclinones by modification of the architecture of the quinone and the homophthalic anhydride involved in this key step. Anthracyclinones synthesized by application of this methodology have been summarized in Table 15. In the first two cases (entries 1 and 2), regiochemistry is determined by a halogen substituent on the electrophilic alkene. A notable exception to this trend is found in Fujoika's synthesis of rhodomycinone (entry 3)[109,110] wherein high regioselectivity is realized without halogen substitution. Regiocontrol in this case is attributed to hydrogen-bond activation from the unprotected hydroxy group on the

Scheme 20. Total Synthesis of Dynemicin A



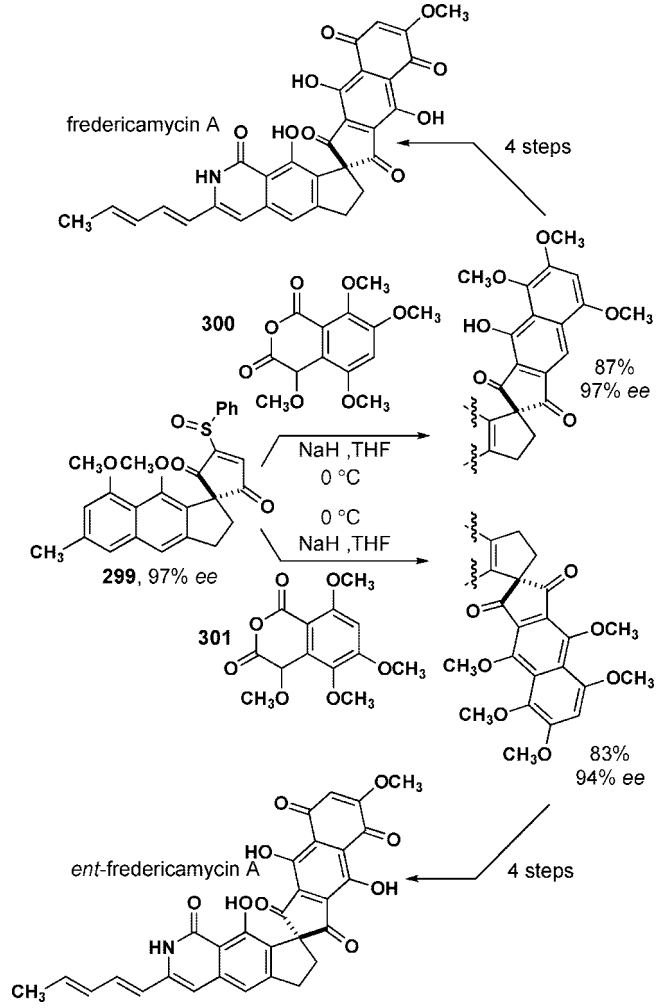
quinone. Although this explanation is intriguing, and later was invoked by Danishefsky,[7,119] high regiocontrol in the cycloadditions leading to the syntheses of 7-methoxynogarene[111−113] (entry 4) and 4-demethoxyadriamycinone[114] (entry 5) suggests that other factors contribute to the observed selectivity.

The anthracyclinone fragment present in dynemicin A was assembled by Danishefsky and co-workers by employing the cycloaddition of homophthalic anhydride **295** with quinone imine **296** (Scheme 20).[120−123] The reaction of the enolate resulting from the deprotonation of **295** with 0.98 equiv of LiHMDS and quinone imine **296** yielded anthrone **297**. This intermediate was not isolated, due to its lability, but oxidized in situ by addition of 7.5 equiv of $PhI(OCOCF_3)_2$. The spontaneous oxidation of compound **298**, followed by removal of the three MOM protecting groups, yielded the final target dynemicin A with a 15% yield for these four steps.

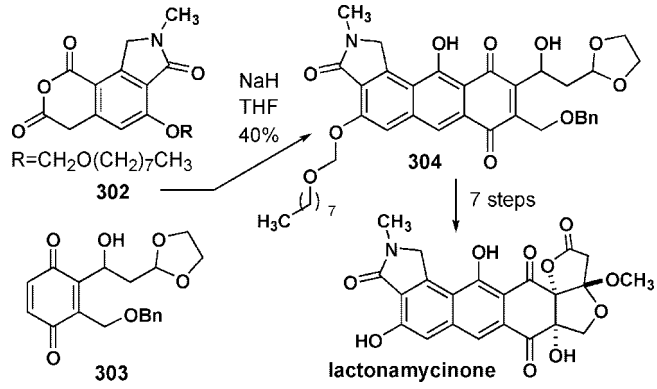
An efficient and divergent approach to both enantiomers of fredericamycin A by Kita and co-workers made use of the cycloaddition reaction of enantiomerically pure sulfoxide **299** and homophthalic anhydrides **300** and **301** (Scheme 21).[124−128] This cycloaddition takes place by addition of the appropriate sulfoxide to the enolate derived from the deprotonation with sodium hydride in THF of homophthalic anhydride **300**, yielding after four steps the natural enantiomer of fredericamycin A, or **301**, which in that case leads to the opposite enantiomer. The pendant sulfoxide present in the starting material plays a double role in this reaction by dictating the regiochemical outcome of the key cycloaddition reaction and also facilitating the aromatization step by spontaneous sulfoxide elimination.

The Tamura cycloaddition has proved to be a suitable reaction for the construction of highly functionalized aromatic systems. This methodology has been successfully applied by Danishefsky and co-workers in the construction of the

Scheme 21. Total Synthesis of Fredericamycin A

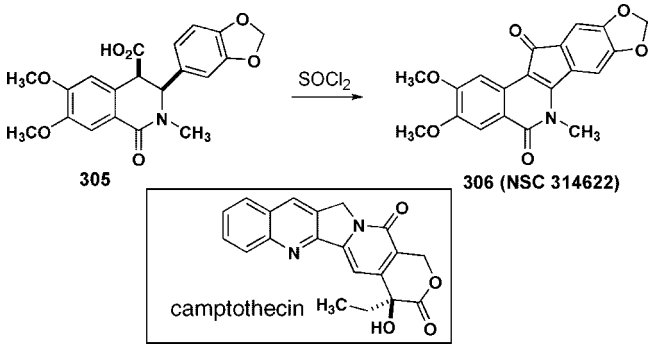


Scheme 22. Total Synthesis of Lactonamycinone



C-ring of the natural product lactonamycin (Scheme 22).[7,119,129] The reaction of homophthalic anhydride **302** with 2 equiv of quinone **303**, in the presence of 2 equiv of sodium hydride, afforded the tetracyclic intermediate **304** in 40% yield with complete control of the regiochemistry. This step has been studied in some detail by the authors, highlighting the importance that the unprotected hydroxyl group present in the side chain of quinone **303** has on the regiochemistry outcome of this step, consistent with the findings of Fujioka.[109,110] The role of quinone **303** in this reaction is not solely limited to act as the electrophilic counterpart in the key cycloaddition reaction, but it also behaves as an oxidant carrying out the in situ aromatization of the cycloadduct.

Scheme 23. Synthesis of NSC 314622



3.2. Drug Leads

3.2.1. Topoisomerase I Inhibitors and Other Potential Anticancer Compounds

The topoisomerases are enzymes that modify and regulate the topological state of DNA and thus play an important role in processes such as DNA replication and packaging. These enzymes are further classified according to their activity, wherein type I enzymes cut and reanneal single strands of DNA and type II enzymes act similarly on both strands. Since their discovery by Wang in 1971,[130] topoisomerases I have been found in both prokaryotes and eukaryotes. Because of their function in gene expression, high levels of topoisomerases are typically encountered in tumor cells, resulting in the emergence of topoisomerase inhibitors as anticancer drugs.

Indenoisoquinoline **306** (later known as NSC 314622)[131] was initially prepared in the context of Cushman's study of the total synthesis of nitidine chloride[88] through an unexpected cyclization (Scheme 23). Subsequent in vitro studies demonstrated that NSC 314622 exhibited a cytotoxicity profile similar to that of camptothecin (CPT), a well-known topoisomerase I inhibitor.[132]

Several important features of NSC-314622 distinguish this compound from camptochecin:

(i) It has complementary DNA cleavage patterns.

(ii) The cleavage complexes induced by NSC 314622 were more persistent than the cleavage complexes induced by CPT.

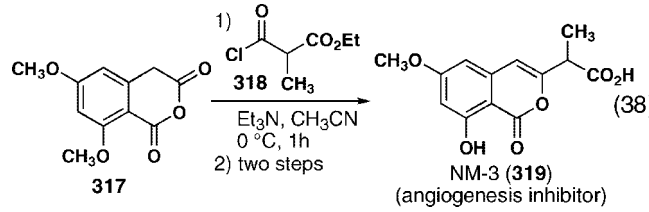
(iii) NSC 314622 presented a higher chemical stability than CPT.

(iv) Unlike most non-CPT topoisomerase inhibitors, NSC 314622 did not intercalate into DNA.

Motivated by this finding, the Cushman group has pursued the development of new topoisomerase I inhibitors based on NSC 314622 using the cycloaddition reaction of imines and homophthalic anydrides.[133−143] Table 16 highlights a subset of these compounds from the many candidates synthesized and tested by Cushman and co-workers that demonstrated superior anticancer activity. A related series of compounds was recently reported by Ryckebusch.[144]

Smith and co-workers reported the synthesis of a duocarmycin-inspired compound with the aim of capturing the key structural elements of the natural product in a potential drug lead (Scheme 24).[145] The duocarmycins and related natural products have shown high levels of cytotoxicity, and their resultant anticancer activity has prompted considerable effort toward their synthesis. These compounds display sequence-specific alkylation within the minor groove of DNA. Anhydride **311** was allowed to react with 1-pyrroline trimer (**312**) to yield isoquinoline **314** in quantitative yield as a 50:50 mixture of syn- and anti-diastereomers.[146] The reduction of the pendant carboxylic acid was achieved in two steps to afford the corresponding terminal alcohol that was mesylated, at which point the syn- and anti-diastereomers were separated. Hydrogenolysis of the benzyl group present in the phenolic hydroxyl group of *syn*-**314** set up the ensuing formation of the cyclopropyl ring, which was effected with a slight excess of sodium hydride. This reaction took place in THF at room temperature to afford the final product **316** in 92% yield.

The addition of a homophthalic anhydride to an acid chloride has been employed in the preparation of NM-3, an angiogenesis inhibitor that was advanced to clinical trials (eq 38).[147]



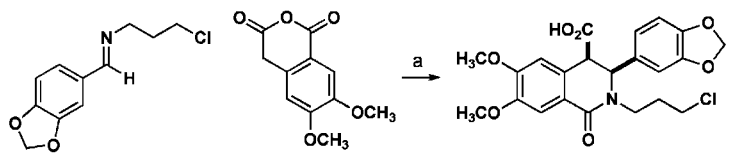
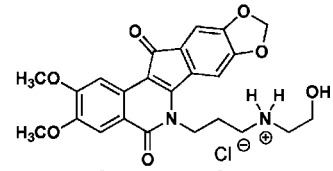
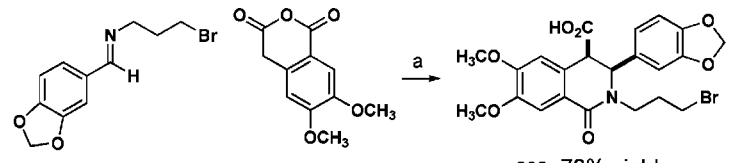
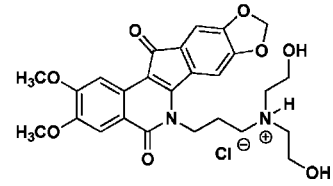
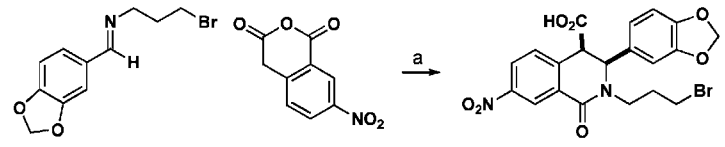
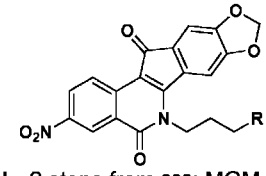
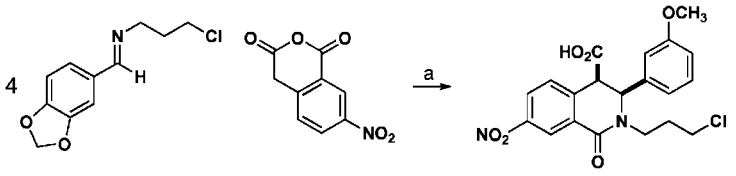
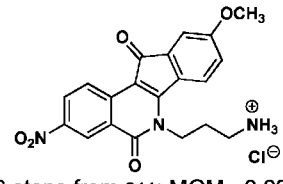
Careful optimization was required to prevent the reaction of homophthalic anhydride **317** with itself. The optimized conditions involved adding the acid chloride to a solution of the anhydride, tetramethylguanidine (TMG), and triethylamine, and it proceeded in 86% yield. Two steps for conversion of the initial condensation product into NM-3 had been previously described in the patent literature.

3.2.2. DOS and Library Synthesis

The reactions of imines with anhydrides has been employed in the preparation of libraries of diverse compounds for use in high-throughput screening. The imine−anhydride cycloaddition is an ideal starting point for diversity-oriented synthesis (DOS),[148] which has as its aim the rapid assembly of complex molecules for high-throughput screening (HTS) experiments in chemical biology or drug discovery. Griffith and co-workers initially explored the possibility of developing reactions with homophthalic anhydrides using resin-bounded imines in 1996, leading to the combinatorial synthesis of a large number (43 000) of dihydroisoquinolines.[149,150] Three years later, Lebl and co-workers made use of the same reaction, developing the so-called "surface suction" method.[151−153] This method presented the advantage of not requiring a porous material for carrying out the separation of liquid and solid phases. The application of this novel improvement afforded a library of 30 816 compounds following the synthetic sequence shown in Scheme 25. Lebl also reported that the use of 4-nitrohomophthalic anhydride resulted in decarboxylation during the cycloaddition step.[151]

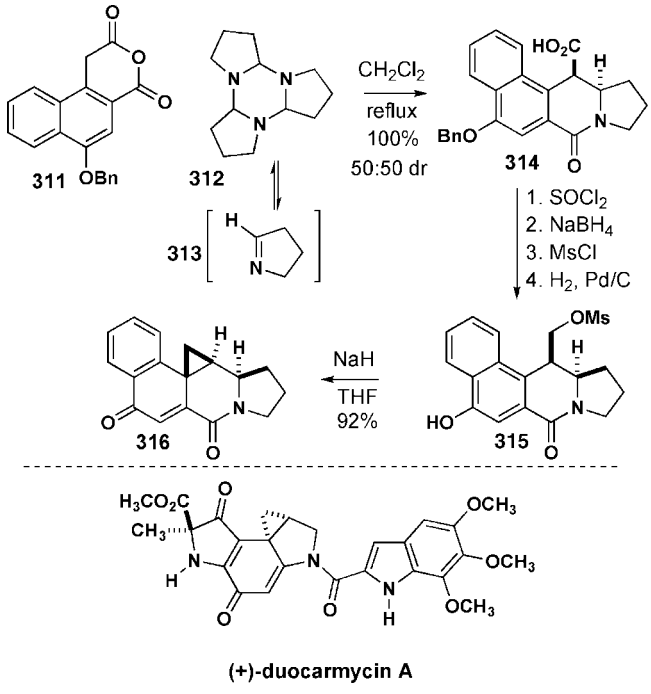
The Shaw group has demonstrated that different cyclization pathways accessible from the reactions of imines with phenylsuccinic anhydrides can lead to either fused or spirocyclic products.[17] The cycloaddition reactions of various para-substituted phenylsuccinic anhydrides was examined using a silicon-based linker to tether *ortho*-iodo-*para*-hydroxymethylbenzaldehyde imine to polystyrene resin (Scheme 26). The combined effect of solid-phase attachment and an ortho-substituent on the imine required higher reaction temperatures, which were achieved using a microwave reactor, to achieve full conversion. High conversion and moderate-to-high diastereoselectivity was observed in all cases except *para*-methoxyphenylsuccinic anhydride, for

Table 16. Synthesis of Topoisomerase I Inhibitors

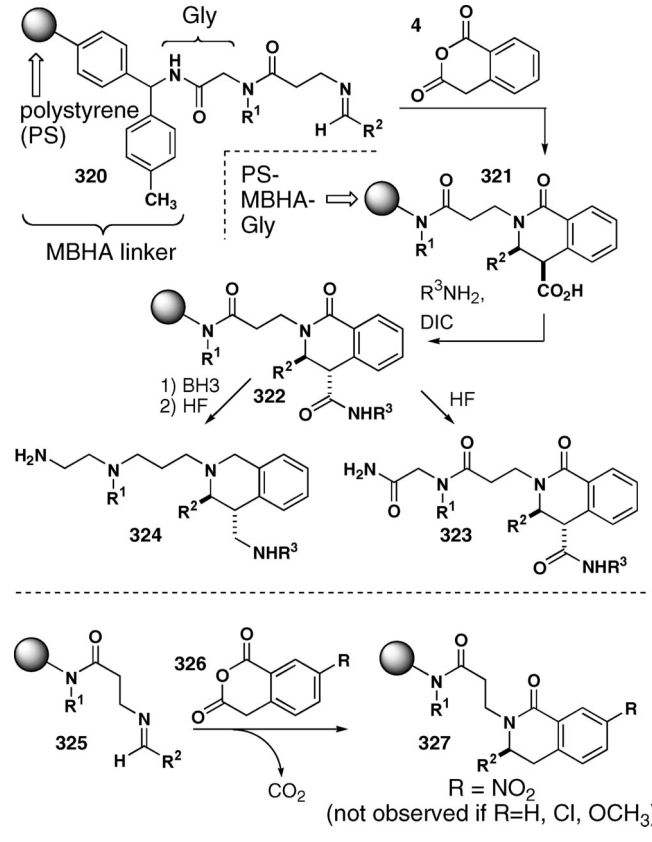
Entry	Imine-anhydride reaction	Topoisomerase I inhibitor
1		
	307, 89% yield	5 steps from **307**; MGM= 0.11 μM[b]
2		
	308, 78% yield	2 steps from **308**; MGM= 0.07 μM[c]
3		
	309, yield not given	R=N_3, 2 steps from **309**; MGM= 0.098 μM[d] R=NH_2HCl, 3 steps from **309**; MGM= 0.090 μM[d]
4		
	311, 76% yield	3 steps from **311**; MGM= 0.027 μM[e]

[a] Experimental conditions: $CHCl_3$, 25 °C. [b] Reference 140. [c] Reference 138. [d] Reference 133. [e] Reference 137.

Scheme 24. Synthesis of Compound 316

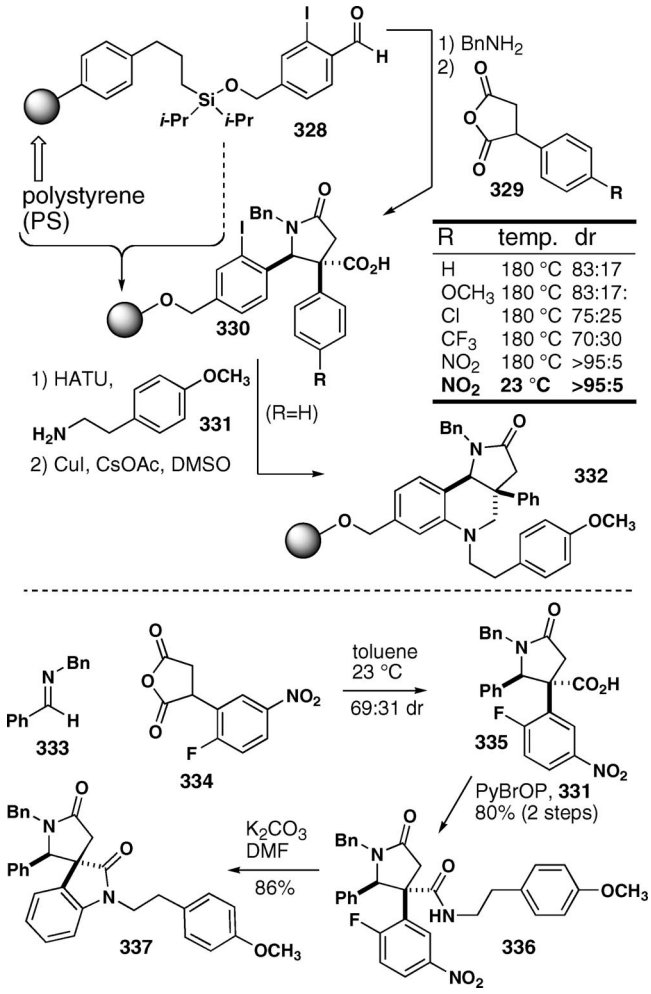


Scheme 25. Solid-Phase Cycloaddition of Imines and Homophthalic Anhydrides



which low (80%) conversion was observed. Nitro substitution on the anhydride resulted in a much faster reaction that could reach full conversion at room temperature due to the increased stability of the proposed enolate intermediate. The cycloadduct derived from phenylsuccinic anhydride was

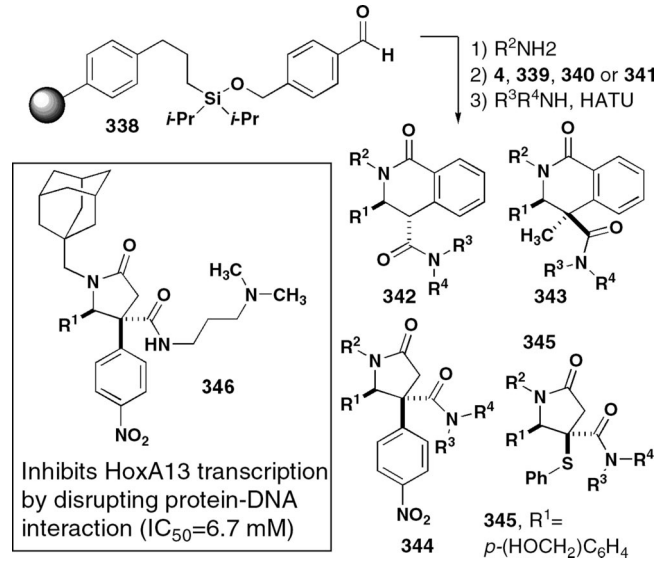
Scheme 26. Solid- and Solution-Phase Reactions of Phenylsuccinic Anhydrides to Prepare Fused and Sprirocyclic Structures



converted to an amide with 4-methoxyphenethylamine and subsequently cyclized using aryl amidation conditions reported by Tokuyama. The authors attempted to employ the same reaction sequence to prepare spirobicyclic products, but no cycloaddition was observed when an ortho-iodo-susbtituted phenyl succinic anhydride was employed. The spirocyclization pathway was demonstrated in solution using nitrofluoro-substituted anhydride **334**, which was later cyclized under traditional S_NAr conditions.

The Shaw group later prepared a library of lactam carboxamides on solid phase using Irori Kans (Scheme 27).[154] This library used a tethered benzaldehyde that was condensed with a series of primary amines (R^2NH_2) and allowed to react with one of four different anhydrides (**4**, **339**, **340**, or **341**). The cycloadducts were then converted to amides in a final pool/split step to ultimately produce 400 distinct products. These compounds were arrayed, cleaved from resin, and used to prepare DMSO stock solutions that were employed in a variety of high-throughput screening experiments at the NCI-funded Initiative for Chemical Genomics (NCI-ICG) screening center. One screen used fluorescence polarization to detect disruption of a transcription factor (HoxA13) with its DNA target. Compound **346** was discovered as a potent inhibitor of this protein−DNA interaction and was subsequently demonstrated to be effective in cells in a reporter gene assay.

Scheme 27. Solid-Phase Split-Pool Synthesis of a Screening Library Using Imines with Different Anhydrides and Structure of 346, a Transcription Factor Inhibitor Discovered in a Screen of This Library



4. Conclusions

The reactions of cyclic anhydrides in C−C bond-forming processes give rapid access to a diverse array of structures. The reactions of imines to form lactams have been used for the synthesis of a wide variety of heterocycles, including many alkaloid natural products. Although this reaction is highly efficient and diastereoselective in many different settings, induction of asymmetry represents an area for significant new development. The recent advent of three- and four-component reactions employing cyclic anhydrides has set the stage for new reactions in this area as well. The reactions of aldehydes and other carbonyl compounds with cyclic anhydrides are less well-developed than the imine counterparts, partly based on the propensity for Perkin condensation to dominate the reaction mixture. Finally, the condensation reactions between homophthalic anhydrides and C−C multiple bonds have been largely directed at the synthesis of anthracyclines and related natural products, offering a complement to the Hauser−Kraus annulation. It is clear that cyclic anhydrides exhibit rich and varied chemistry that goes far beyond the traditional use of these reagents in acylation reactions.

5. Acknowledgments

The authors thank Profs. Mark Cushman (Purdue University) and Dean Tantillo (University of California, Davis) for helpful discussions. J.T.S. thanks the University of California, Davis, for financial support, and M.G.L. acknowledges the Fundación Ramón Areces for a postdoctoral fellowship.

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