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PERSPECTIVE

Intramolecular catalytic asymmetric carbon–hydrogen insertion reactions. Synthetic advantages in total synthesis in comparison with alternative approaches

Michael P. Doyle,* Maxim Ratnikov and Yu Liu

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The synthetic potential of highly directional formal insertion of a carbene between carbon and hydrogen of a carbon–hydrogen bond has recently been developed for intramolecular reactions that lead to compounds of biological and medicinal interest. Stereoselective and regiocontrolled intramolecular processes from diazoacetate reactants, catalyzed by dirhodium(II) compounds with chiral carboxamidate ligands, provide efficient and selective access to compounds as diverse as enterolactone, baclofen, imperanene, xylolactone, and rolipram. A comparison of the C–H insertion methodology with alternative approaches is presented.

Introduction

Asymmetric intramolecular carbon–hydrogen insertion reactions provide a methodology for asymmetric induction and cyclization to occur in the same transformation. As an approach to the synthesis of lactones and lactams this methodology is competitive with a diverse set of synthetic approaches that target the same compounds. Because experimental and conceptional plans for the synthesis of complex molecules have considerable breadth, this perspective will be focused on well-defined targeted molecules for which there have been multiple examples of their synthesis. In these cases, and with few exceptions, the alternate approaches

Department of Chemistry and Biochemistry, 0107 Chemistry Building, University of Maryland 20742-4454, College Park, Maryland, USA. E-mail: mdoyle3@umd.edu; Fax: +1 (301) 314-2779

Michael P. Doyle

Michael P. Doyle was born in Minneapolis, MN, received his B.S. degree from the College of St. Thomas in St. Paul, MN, and obtained his Ph.D. degree from Iowa State University. Following a brief postdoctoral engagement at the University of Illinois at Chicago Circle, he joined the faculty at Hope College in 1968 where he became full professor in 1974 and was appointed as the first Kenneth Herrick Professor in 1982. In 1984, he moved to Trinity University in San Antonio, TX, as the first Dr D. R. Semmes Distinguished Professor of Chemistry, and in 1997 he came to Tucson, AZ, as Vice President, then President, of Research Corporation and Professor of Chemistry at the University of Arizona. In 2003 he accepted the position of Professor and Chair of the Department of Chemistry and Biochemistry at the University of Maryland, College Park. His research interests include catalysis, especially reactions catalyzed by paddlewheeled dirhodium compounds, and the diverse chemistries that surround the dirhodium framework.

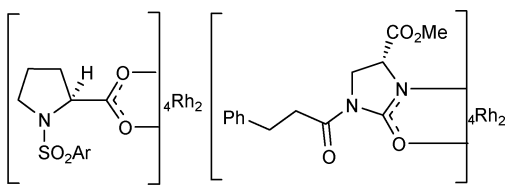
Maxim O. Ratnikov

Maxim O. Ratnikov was born in Moscow, Russia, in 1984. In 2007, he received his M.S. degree from the Higher Chemical College, Moscow, Russia. There Mr. Ratnikov conducted research under the supervision of Dr William Smit and Dr Alexander Churakov. After receiving his degree, he moved to University of Kentucky where he worked under the guidance of Dr Marc Knecht. In 2008, he joined Professor Michael Doyle's research group at the University of Maryland where he is currently working towards his doctoral degree. His research interests are in the development of novel oxidative methods and their applications in synthesis. Mr. Ratnikov is the recipient of a 2009 Department of Chemistry & Biochemistry Summer Fellowship for excellent academic performance and is a 2010 recipient of the Graduate Assistance in Areas of National Need (GAANN) Fellowship.

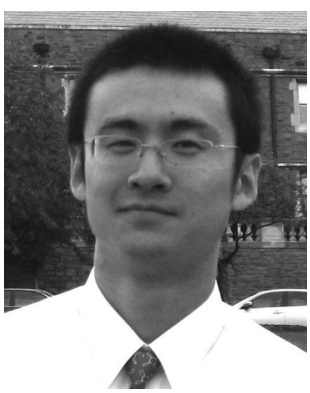
to carbon–hydrogen insertion provide molecular asymmetry with enantiocontrol prior to cyclization rather than enantioselective cyclization that occurs in intramolecular asymmetric C–H insertion reactions.

Carbon–hydrogen insertion transformations from reactions of carbenes have been known for over a century,[1] but only in recent years has control of selectivity in these transformations been achieved[2] and synthetic applications been realized. The cause of this change is primarily due to advanced understanding of the synthesis and properties of diazocarbonyl compounds[3] and the introduction of dirhodium(II) catalysts.[4] Diazocarbonyl compounds, and specifically diazoacetates, are the optimum substrates for catalytic reactions that proceed through metal carbene intermediates, and these are the intermediates that provide control of chemoselectivity and regioselectivity in carbon–hydrogen insertion reactions.[5] The introduction of dirhodium(II) catalysts have made possible selective insertion reactions that have occurred in high yield, realization of the high preference for cyclization to form five-membered ring products in intramolecular reactions, and the discovery that these reactions occur with high diastereocontrol.[4]

Asymmetric catalytic carbon–hydrogen insertion reactions are optimally achieved with chiral dirhodium(II) catalysts. For intermolecular asymmetric reactions of aryl- and styryldiazoacetates chiral dirhodium(II) carboxylate catalysts that include the DOSP-ligated catalysts (**1**) of Davies are most suitable.[6] For intramolecular carbon–hydrogen insertion reactions of diazoacetates and diazoacetamides chiral dirhodium carboxamidate catalysts that include the MPPIM-ligated catalysts (**2**) of Doyle give the highest selectivities.[7]



1 Ar = *p*-(^{n}C$_{12}$H$_{25}$)C$_6$H$_4$ Rh$_2$(*S*-DOSP)$_4$ **2** Rh$_2$(4*R*-MPPIM)$_4$

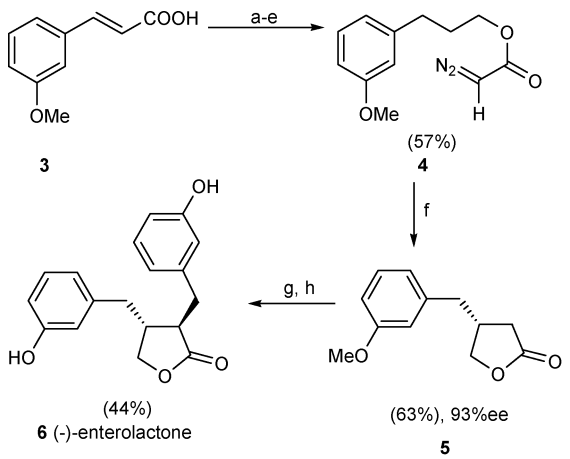


Yu Liu

Yu Liu was born in Xi'an, China. As an undergraduate student, he studied in Peking University and worked on the development of new methodologies applying α-diazo carbonyl compounds under the direction of Professor Jianbo Wang. He received his B.S. degree in chemistry in 2006 and joined the research group of Professor Michael Doyle at University of Maryland the same year. He is currently working towards his doctoral degree and his research interest includes novel transformations of diazo compounds and rhodium catalyzed diazo decomposition reactions.

Synthesis of lignan lactones

Lignan natural products are widespread in plants and have diverse biological activities and some medicinal uses.[8] The most commonly prepared lignan lactone has been enterolactone (**6**) which exhibits, among other biological roles, antiestrogenic and anticarcinogenic activities.[9] Access to this lignan from common reactants (*e.g.*, **3**) *via* asymmetric catalytic C–H insertion (**4** → **5**) has been described,[10] and Scheme 1 outlines the overall approach (16% overall yield). Ring formation and asymmetric induction are introduced in the same step. Among the chiral catalysts that have been reported for this transformation, the Rh$_2$(MPPIM)$_4$ catalysts provide the highest level of enantiocontrol. Alkylation of the lactone at the position alpha to the carbonyl group occurs with complete selectivity. The advantages of this synthesis are the limited number of synthetic steps from relatively inexpensive commercially available reactants, the high enantiocontrol achieved, and the ease in isolation/purification of insertion product. Disadvantages include the cost of the catalyst and the isolated yield of C–H insertion product in the key asymmetric induction step that rarely exceeds 70%.

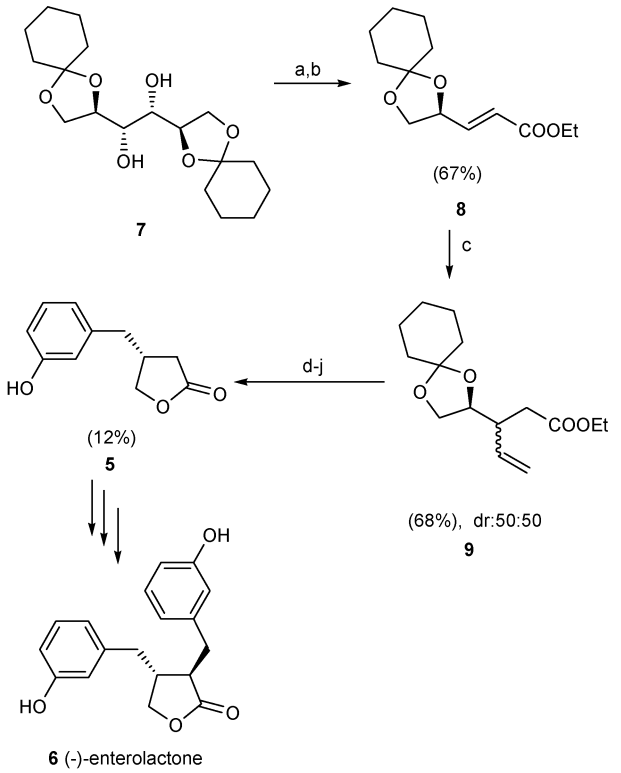


(a) H_2, 5% Pd/C, 1:1 MeOH/EtOH; (b) $LiAlH_4$, THF, reflux; (c) cat. NaOAc, diketene, THF; (d) $MeSO_2N_3/Et_3N$, MeCN; (e) LiOH, H_2O/MeCN; (f) 2.0 mol% Rh_2(4*R*-MPPIM)$_4$ (**2**) CH_2Cl_2, reflux; (g) LDA, THF/HMPA, -78°C, then 3-$MeOC_6H_4CH_2Br$; (h) BBr_3, CH_2Cl_2, -18°C.

Scheme 1

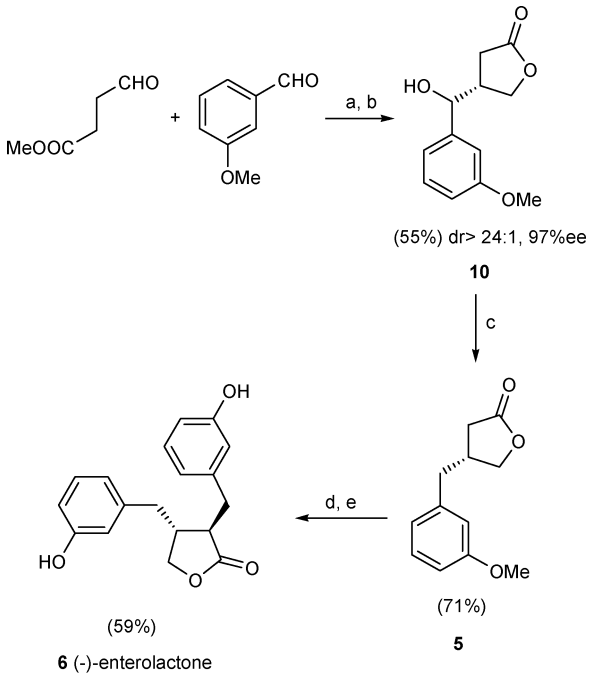
Chiral, non-racemic enterolactone has been prepared by diastereomeric resolution of a hydroxycarboxylic acid with D-amphetamine,[11] by chemoenzymatic synthesis (7 steps, 34% overall yield) that involves asymmetric acetylation of a substituted 1,3-diol catalyzed by *Pseudomonas cepacia* lipase (94% ee, 99% yield),[12] by bacterial conversions (*e.g.*, from plant enterodiol or from plant lignins in sesame seed),[13] and by synthesis (4 steps, 47% yield) from isolated natural non-racemic hydroxymatairesinol (from Norway spruce).[14] There have been two reported syntheses that use reagents from the chiral pool,[15] the latest of which from the protected D-mannitol derivative **7** is outlined in Scheme 2 (9 steps, 2% overall yield).[15a]

A seven-step chiral auxiliary (4-diphenylmethyl-2-oxazolininone) directed synthesis of enterolactone from



(a) $NaIO_4$, $MeCN/H_2O$; (b) $(EtO)_2P(O)CH_2COOEt$; (c): $MeC(OEt)_3$,CH_3CH_2COOH,140°C; (d) LDA, THF/HMPA, -78°C, then 3-$MeOC_6H_4CH_2Br$; (e) $LiAlH_4$, THF, rt; (f) HOAc, H_2O, rt; (g) $NaIO_4$ $MeCN/H_2O$; (h) CrO_3, acetone; (i) $RuCl_3(xH_2O)$, $NaIO_4$, $MeCN/H_2O$ then Jones reagent; (j) $PhCH_3$, reflux

Scheme 2



(a) 20 mol% L-proline, DMF, 4°C; (b) $NaBH_4$, MeOH, 40°C; (c) 10% Pd/C $Cl(CH_2)_2Cl$, 50-60°C; (d) LDA, THF/HMPA, -78°C, then 3-$MeOC_6H_4CH_2Br$; (e) BBr_3, CH_2Cl_2, -18°C.

Scheme 3

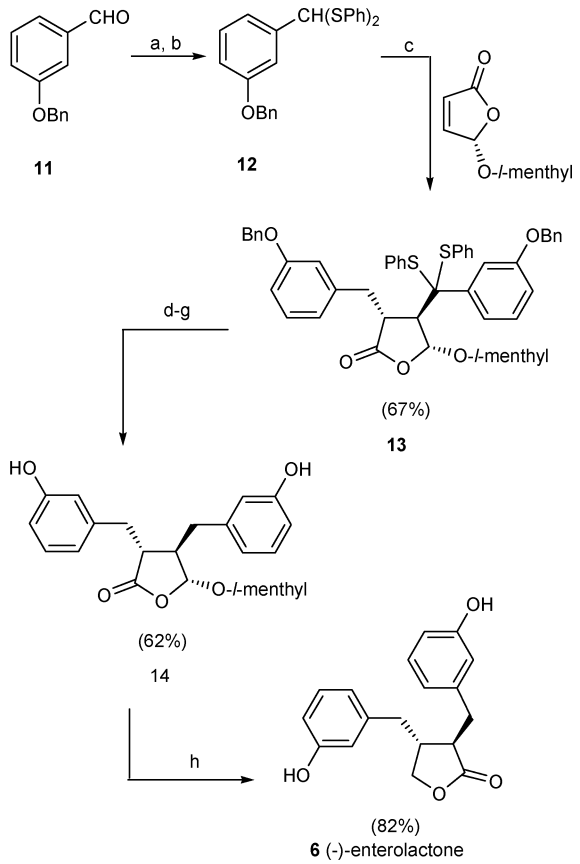
3-hydroxyhydrocinnamoyl chloride with high stereocontrol has also been reported (19% and 27% overall yields for the two enantiomers).[16] Organocatalyzed mixed aldol condensation with L-proline to produce **10** which is a precursor to **5** (Scheme 3, 23% overall yield) offers an alternative approach to metal catalyzed C–H insertion.[17] Alkylation of the lactone and demethylation is common to the syntheses described in Schemes 1–3.

Conjugate addition is an alternative approach[18] that takes advantage of butenolides as reactants but uses chiral auxiliaries in its applications. The success of the key conjugate addition step in this approach (**12** → **13**) rests upon the availability of enantiomerically pure butenolides[19] that direct conjugate addition as exemplified in Scheme 4 (8 steps, 27% overall yield).[18a] An alternative samarium(III) triflate promoted free radical conjugate addition process with a chiral oxazolidinone-bound substrate followed by a second alkylation, cyclization, and demethylation has been reported (6 steps from oxazolidinone-functionalized compound, 21% yield).[20] Additional steps for preparation of the chiral auxiliary, the use of 5-fold excess tri-n-butylstannane, and a 10-fold excess of 3-methoxybenzyl bromide on a key step are major disadvantages of this methodology. A combination of cross-metathesis and conjugate addition using a vinyl phosphonate has also been used for a formal synthesis of enterolactone.[21]

The apparent symmetry in lignan lactones prompted studies of access to them through oxidative homocouplings of (4*S*)-3-(3-arylpropanoyl)-4-isopropyl-2-oxazolidinones and similar chiral imidazolidinones;[22] using a chiral oxazolidinone auxiliary for 3-methoxyphenylpropanoic acid, addition of LDA followed by metal oxidant effects dimerization at the alpha position in moderate yields with up to a 92 : 8 diastereomer ratio [27% yield from the 3-(*m*-methoxyphenyl)propanoylimidazolidinone reactant to the methyl ether precursor of enterolactone. (Scheme 5)]. An enzymatic lipase desymmetrization approach to the synthesis of lignans (**19** → **20** in Scheme 6 for hinokinin using 0.1 g lipase per mmole of **19**) provides a general route to β-substituted-γ-butyrolactones.[23]

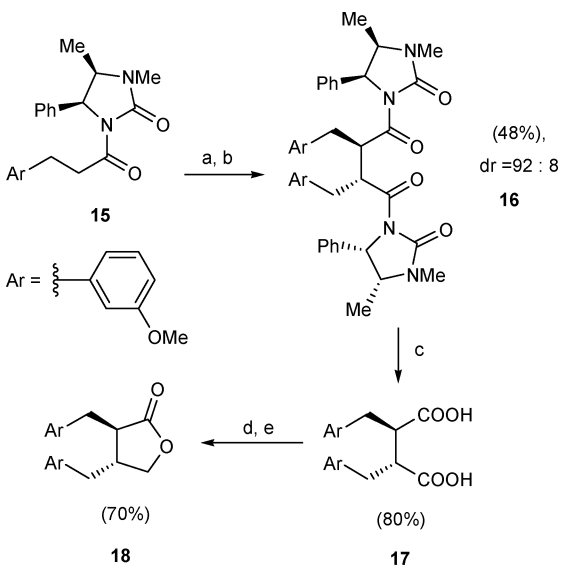
Synthesis of *R*-baclofen

There are few compounds for which there are as many diverse synthetic approaches as those for *R*-(−)-baclofen (**27**), which as the hydrochloride salt is a therapeutically effective $GABA_B$ receptor agonist.[24] The approach using C–H insertion begins with 2-(4-chlorophenyl)ethanol (**24**) and introduces high enantiocontrol (95% ee) in catalytic diazo decomposition to the β-substituted-γ-butyrolactone intermediate **26** using the $Rh_2(4S\text{-MPPIM})_4$ catalyst (Scheme 7, 40% overall yield in seven steps).[25] This methodology provides excellent enantioselectivity in the key insertion step. Among the older methodologies that have been reported for the enantioselective synthesis of *R*-baclofen key steps include enantioselective deprotonation of 3-(*p*-chlorophenyl)cyclobutanone with a chiral lithium amide (6 steps, 41% overall yield, 97% ee)[26a] and asymmetric methanolysis of an acid anhydride catalyzed by modified cinchona alkaloids (33% and 35% yields for 4 steps and 95% and 75% ee for *S*- and *R*-isomers, respectively, seven steps),[26b] enzymatic Baeyer–Villiger oxidation (from



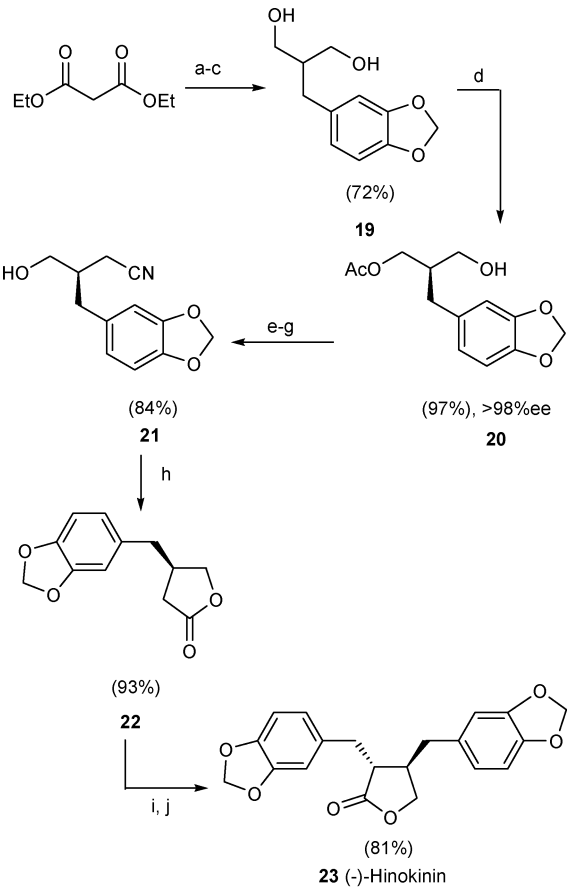
(a) PhSH, CH_2Cl_2, $AlCl_3$; (b) BuLi/hexane, THF, -20°C; (c) LDA, TMEDA, THF, -80°C, then 3-$BnOC_6H_4CH_2Br$; (d) $NiCl_2(6H_2O)$, MeOH/THF; (e) $NaBH_4$; (f) KOH(aq), $NaBH_4$; (g) HCl(aq); (h) 5% H_2, Pd/C, EtOAc

Scheme 4



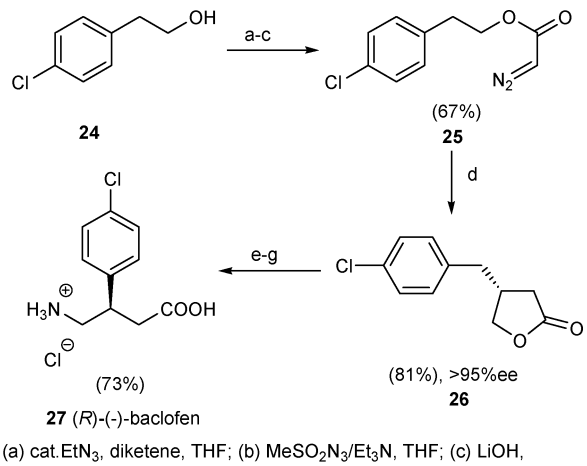
(a) LDA, THF, -78°C; (b)$TiCl_4$; (c) LiOH,THF/H_2O; (d)Ac_2O; (e) $NaBH_4$.

Scheme 5



(a) NaH, THF; (b) piperonyl chloride, THF; (c)$LiAlH_4$, THF; (d) lipase PS, vinyl-OAc_2,6-di-*t*-Bu-4-MeC_6H_2OH H_2O/*i*-Pr_2O, rt; (e) TsCl, C_6H_5N, CH_2Cl_2, rt; (f) KCN, DMSO, 90°C; (g)KOH(aq), THF/H_2O; (h) 2M NaOH, reflux; (i) LDA, THF,-70°C: (j) piperonyl bromide, HMPA, -50°C

Scheme 6

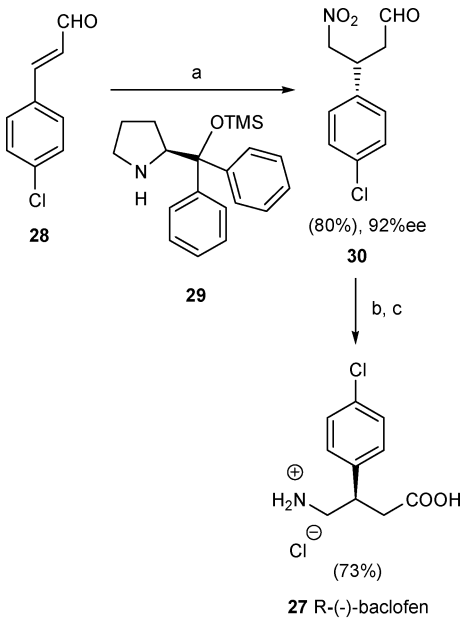


(a) cat.EtN_3, diketene, THF; (b) $MeSO_2N_3/Et_3N$, THF; (c) LiOH, H_2O/THF; (d) 0.5 mol% Rh_2(4*S*-MPPIM)$_4$,CH_2Cl_2, reflux; (e) TMSI, CH_2Cl_2/EtOH; (f) NaN_3, DMF, 50°C; (g) 2 M NaOH, 50°C, then HCl

Scheme 7

3-(*p*-chlorophenyl)cyclobutanone in 30% yield),[27] and less efficient syntheses from reactants formed by enzymatic resolution (14% yield for five steps, >99% ee)[28] or from L-aspartic acid (34% yield in seven steps, >99% ee).[29]

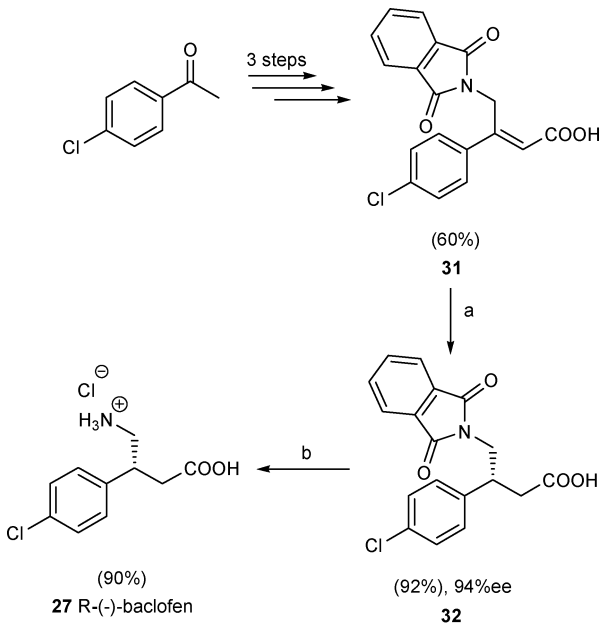
A popular approach for the introduction of the amino group has been organocatalytic enantioselective Michael addition of nitromethane to α,β-unsaturated aldehydes (Scheme 8)[30] or α,β-unsaturated ketones (from a *p*-chlorochalcone using 10 mol% of a cinchoninium salt; 52% yield for 4 steps, 70% ee),[31] and Michael addition of 1,3-dicarbonyl compounds to nitroolefins using 10 mol% of a bifunctional urea organocatalyst (38% overall yield in six steps).[32] Similarly constructed GABA derivatives have been prepared by this methodology.[30a] Analogous Michael addition processes that employ chiral auxiliaries (*e.g.*, *N*-phenylpantolactone) have also been reported,[33] as has a chemoenzymatic method involving α-chymotrypsin mediated kinetic resolution of a 3-(4-chlorophenyl)-4-nitrobutyric acid methyl ester precursor (91% ee for product acid and 73% ee for reactant ester at 45% conversion).[34]



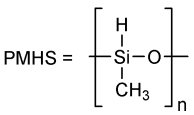
(a) CH_3NO_2, 2 mol% catalyst **25,** 20 mol% PhCOOH, MeOH, rt; (b) $NaClO_2$, NaH_2PO_3, $Me_2C{=}CHMe$, *t*-BuOH/H_2O; (c) 5 atm H_2, Ra-Ni, MeOH

Scheme 8

The Heck–Matsuda arylation of 3-pyrroline with arenediazonium salts has also been employed to form racemic β-aryl-γ-butyrolactams (54–67% overall yields),[35] and a similar process has been reported using arylboronic acids.[36] Other approaches include enantioselective reductions with $Cu(OAc)_2$/(*S*)-BINAP/polymethylhydrosiloxane (PMHS) of γ-phthalidimido-substituted α,β-unsaturated carboxylic acid esters (Scheme 9: 60% yield overall from *p*-chloroacetophenone in five steps, 94% ee),[37] molybdenum carbonyl-catalyzed asymmetric allylic alkylation with the sodium salt of the diethyl malonate anion 14% overall yield for 6 steps from an allylic carbonate intermediate, 96% ee),[38] cobalt-catalyzed reductive cyclization of azido-substituted unsaturated esters with borohydride using a structurally complex (+)-phenyl-α-[(4*S*)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile ligand (45% yield for four steps, 89% ee),[39] asymmetric Ru/(*S*)-BINAP/H_2 reduction of ethyl 4-chlorophenylbenzoyl acetate (23% yield for four steps, 96% ee),[40] enantioselective microbial conversion of nitriles to amides ((*R*)-2-(4-chlorophenyl)-4-pentenamide) in 44% isolated yield,[41] and a complex sequence of transition metal catalyzed processes including Pd-catalyzed asymmetric allylic alkylation using a chiral diaminophosphine oxide ligand followed by ring-closing metathesis (46% yield for seven steps from a functionalized allylic carbonate to Boc-protected *R*-baclofen, 97% ee).[42]



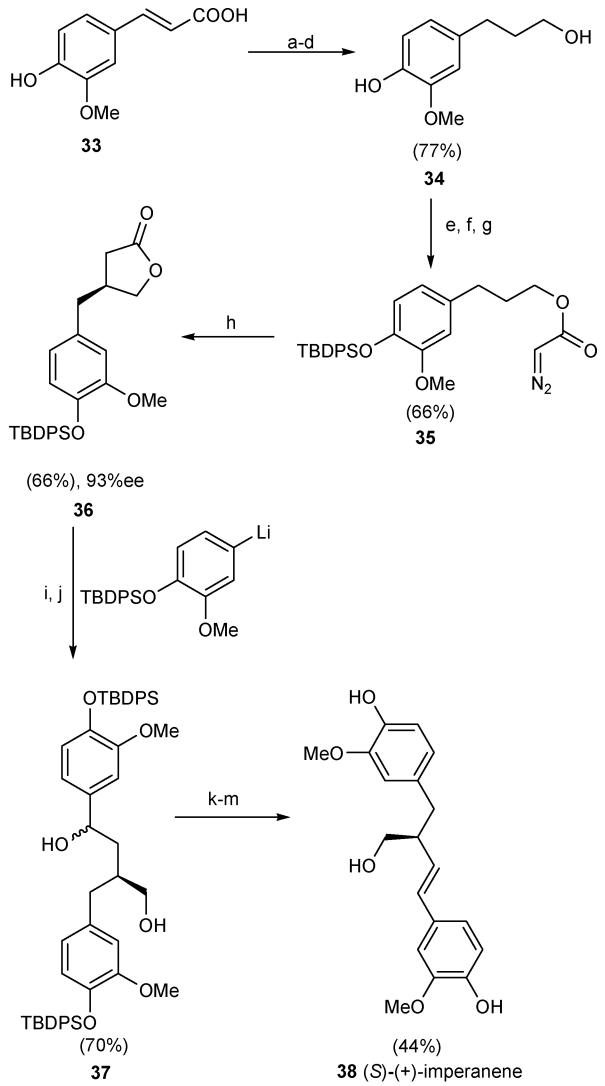
(a) 5 mol% $Cu(OAc)_2H_2O$, 5 mol% (R)-BINAP, PMHS, *t*-BuOH, toluene, rt; (b) 6N HCl, reflux



Scheme 9

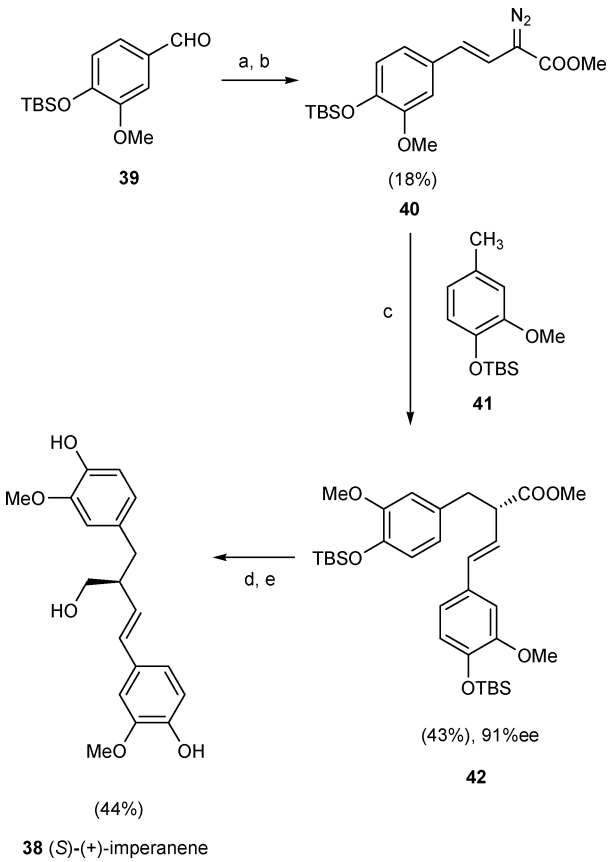
Synthesis of *S*-imperanine

The γ-lactone structure that is the common product of intramolecular C–H insertion processes can be the precursor to acyclic products, and with the use of chiral catalysts these compounds can be formed with a high degree of enantiocontrol. The synthesis of (*S*)-(+)-imperanene (**38**), a natural product in Chinese medicine used as a diuretic and anti-inflammatory agent and known to have platelet aggregation activity,[43] provides an illustrative example of this methodology. The approach using C–H insertion begins with 3-(3,4-disubstitutedphenyl)-1-propanol (**34**) from whose diazoacetate the highly enantioenriched β-substituted-γ- butyrolactone intermediate **36** is formed using the Rh_2(4*S*-MPPIM)$_4$ catalyst (Scheme 10);[44] subsequent reduction to the hemiacetal, organolithium addition, and elimination results in the formation of (*S*)-(+)-imperanene. Because the absolute configuration of the C–H insertion product is predictable in reactions with alkyl



(a) H_2, 10% Pd/C; (b) MeOH, H_2SO_4; (c) TBDPSCl, DMF, imidazole; (d) $LiAlH_4$, THF; (e) diketene, cat. EtN_3, CH_2Cl_2; (f) MsN_3, Et_3N, CH_2Cl_2; (g) LiOH, H_2O/THF; (h) 1.0 mol% Rh_2(4*S*-MPPIM)$_4$; (i) DIBAL-H; (j) THF, -78°C-rt (k) TBDPSCl, TMF, imidazole; (l) MsCl/DBU, PhCl, reflux; (m) TBAF

Scheme 10



(a) (Ph_3P-CH_2CH_2COOMe)Cl, THF, *t*-BuOK, 0°C; (b) $MeCONHC_6H_4SO_2N_3$/DBU, MeOH; (c) 1 mol% Rh_2(*S*-DOSP)$_4$ $Me_2CHCHMe_2$, reflux; (d) $LiAlH_4$, THF,-40°C; (e) TBAF

Scheme 11

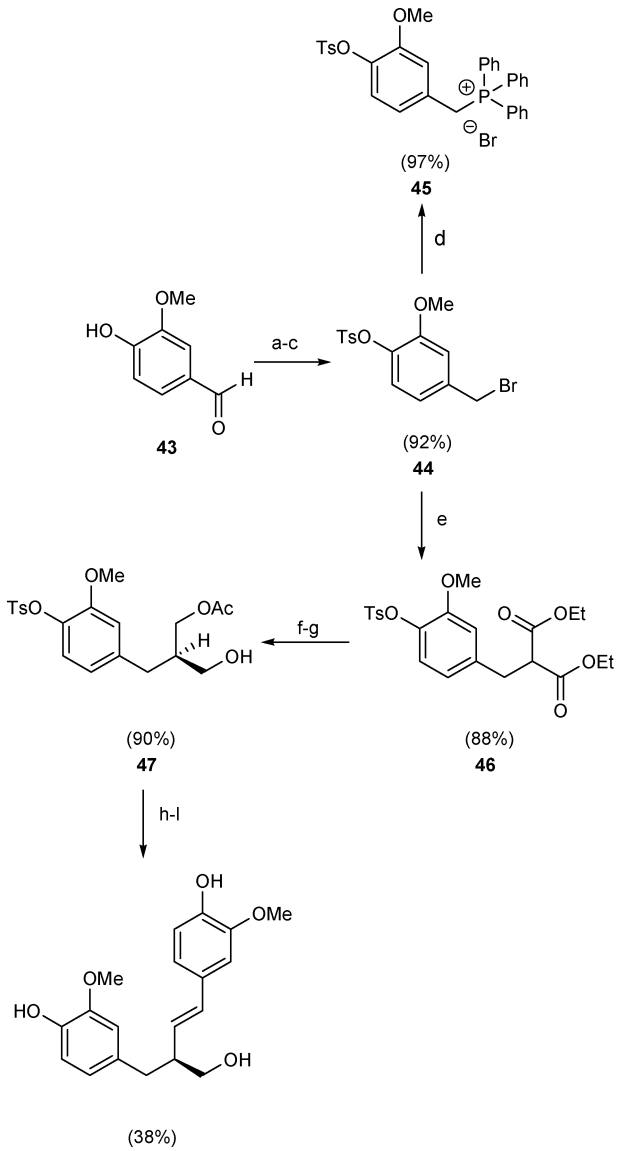
diazoacetates,[10a] the previously unknown configuration of (+)-imperanene could be established using this catalytic methodology. In an overall twelve-step synthesis from ferulic acid (**33**), (*S*)-imperanene was produced in 16% overall yield.

An alternate approach of enantioselective intermolecular C–H insertion using a vinyldiazoacetate (**40**) has been reported by Davies and Jin (Scheme 11) that in comparison with that of Scheme 8 offers a more direct approach to (*S*)-imperanene (5 steps).[45] However, access to the vinyldiazoacetate is problematic, and insertion into the benzyl position of **41** occurs in relatively low reported yield (less than 4% overall). This is one of the few examples in which optimum catalysts for intermolecular and intramolecular C–H insertion have been compared.

A synthesis of (*S*)-imperanene using a chiral auxiliary suffering from very low overall yield (9% and 5% yields for nine step syntheses of the two enantiomers from eugenol)[46] and one using allylic substitution that begins with the chiral allyl acetate (ArCH=CHC*H(OAc)CH_2Ar) (16% yield for the twelve step synthesis from the TBDMS ether of vanillin)[47] have been reported. A *Pseudomonas cepacia* lipase induced symmetrical diol desymmetrization process has been employed in a nine step synthesis of both imperanene enantiomers from vanillin in 19% and 24% yields, respectively (Scheme 12).[48]

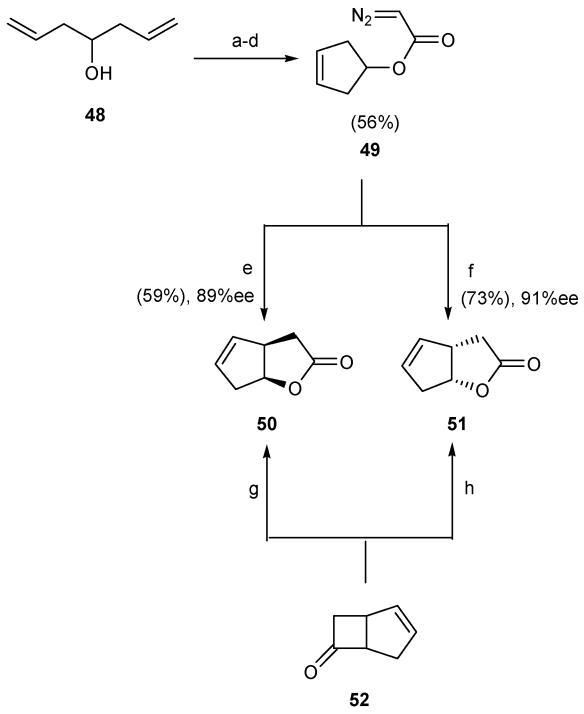
Miscellaneous methods

Bicyclic lactones **50** and **51** have proven to be useful for the synthesis of prostaglandins and monoterpenes. The racemic mixture is readily available in multigram quantities from cyclopentadiene,[49] and access to individual enantiomers is possible through either recrystallization of diastereomeric salts from (+)-α-methylbenzylamine[50] or enzymatic differentiation of a diol precursor,[51] but highly enantioselective methods (Scheme 13) have been limited to microbial/enzymatic Baeyer–Villiger oxidations of racemic **52** that generally require expensive NADH or NADPH[52–54] and catalytic asymmetric C–H insertion of **49**.[55] Chemical methods to achieve enantioselective Baeyer–Villiger oxidations of **52** have also been attempted, but high selectivities have not been reported.[56]



(a) TsCl, K_2CO_3, acetone, reflux; (b) $NaBH_4$, MeOH, 0°C; (c) PBr_3, ether, rt ; (d) Ph_3P, toluene, reflux; (e) diethylmalonate, NaH, 0°C; (f) $NaBH_4$, LiCl, MeOH/ether, 0°C; (g) vinyl acetate, Pseudomonas cepacia lipase, 40°C; (h) TsCl, Et_3N, DMAP, CH_2Cl_2, 0°C; (i) K_2CO_3, MeOH, 0°C; (j) Dess-Martin periodane, CH_2Cl_2, rt; (k) **45**, *n*-butyllithium, THF, 0°C; (l) KOH, ethanol, reflux.

Scheme 12



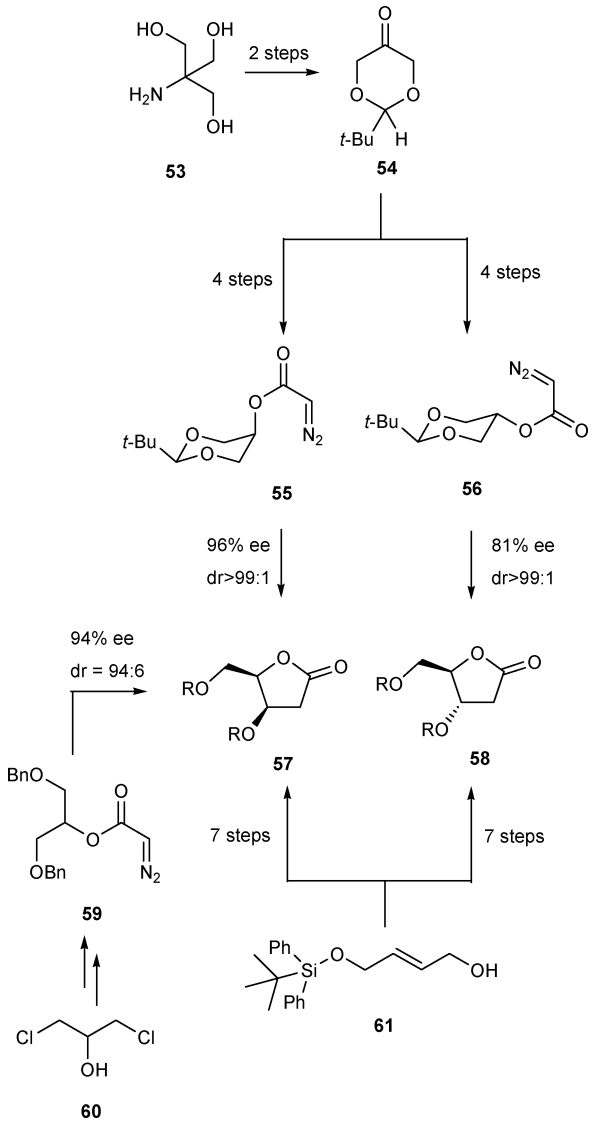
(a) diketene, THF, cat.Et_3N/DMAP; (b) 1 mol% $(Cy_3P)_2RuCl_2(CHPh)$, CH_2Cl_2; (c) MsN_3/Et_3N; (d) LiOH, H_2O/THF; (e) 1 mol% Rh_2(4R-MPPIM)$_4$, CH_2Cl_2, reflux; (f) 1 mol%Rh_2(4*S*-MPPIM)$_4$,CH_2Cl_2, reflux; (g) Pseudomonas putida NCIB 10007; (h) Acinetobacter sp.NCIB 9872

Scheme 13

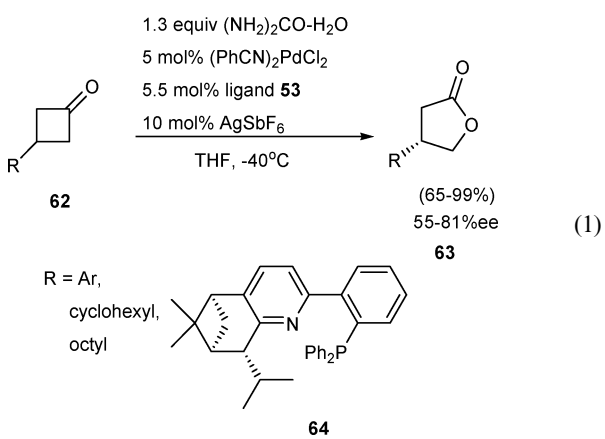
The synthesis of (3*S*,4*R*)- (**57**) and (3*S*,4*S*)-3-hydroxy-4-hydroxymethyl-4-butanolides (**58**) and (2-deoxyxylono-1,4-lactone and 2-deoxyribono-1,4-lactone, respectively), as well as their enantiomers, also provides a comparison of methodologies. Two versatile methodologies utilizing catalytic asymmetric intramolecular C–H insertion have been reported (Scheme 14: 31% overall yield for **57** and 18% overall yield for **58**),[57] and one has been described that employs asymmetric Sharpless epoxidation (7% yield for an eleven-step synthesis of **58**) and asymmetric dihydroxylation (14% yield for an eleven-step synthesis of **46**) as key steps[58] These methods of lactone formation provide more opportunities for additional functionalization, while several short syntheses of 2-deoxy-L-ribonolactone that have been reported[59] are limited by carbohydrate availability. Efficient alternative syntheses of 2-deoxy-L-xylolactone are nonexistent.

The Baeyer–Villiger oxidation of 3-substituted cyclobutanones is a general route to β-substituted-γ-butyrolactones, and various oxidants and catalysts have been used for this transformation.[60] In addition to the uses of enzymes (*e.g.*, Scheme 10),[61,62] asymmetric transition metal catalyzed Baeyer–Villiger oxidations have also been employed but with limited success.[63] A recent example of this approach (eqn (1)) shows some of its limitations.[64] Other approaches to β-substituted-γ-butyrolactones include copper-catalyzed PMHS enantioselective (*p*-tol-BINAP ligand) conjugate reduction of lactones,[65] and enantioselective additions of *n*-alkyl Grignard reagents or diethylzinc to pentenolides using catalytic amounts of chiral copper complexes. Syntheses of β-substituted γ-butyrolactones based on the asymmetric intramolecular C–H insertion methodology are generally more efficient and versatile due to very high asymmetric induction and easy access to the alcohol precursors.[10a,67]

The catalytic asymmetric synthesis of β- and γ-lactams is a continuing area of intense inquiry.[68] The C–H insertion route to γ-lactams (*e.g.*, synthesis of (*R*)-(–)-rolipram, Scheme 15)[69] is competitive with competing methodologies.[70] Conformational influences around the amide bond necessitate using a protected amide. In the example of rolipram (**67**), the *N*-cumyl group was found to be an effective protective group in establishing the amide

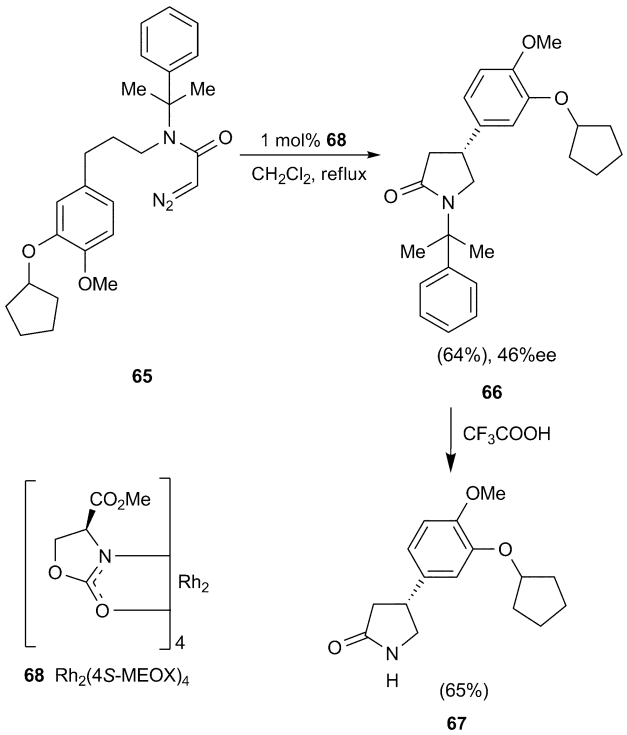


Scheme 14

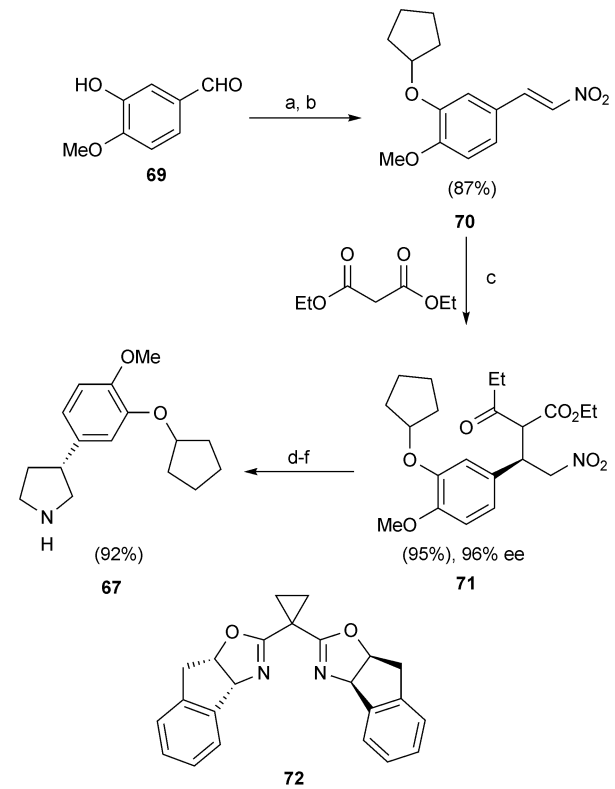


(1)

conformation that is most suitable for C–H insertion, and the *N*-cumyl group could be easily removed from the product lactam (with trifluoroacetic acid). However, alternate methodologies to asymmetric catalytic C–H insertion are favored for the synthesis of β-lactams.[68]



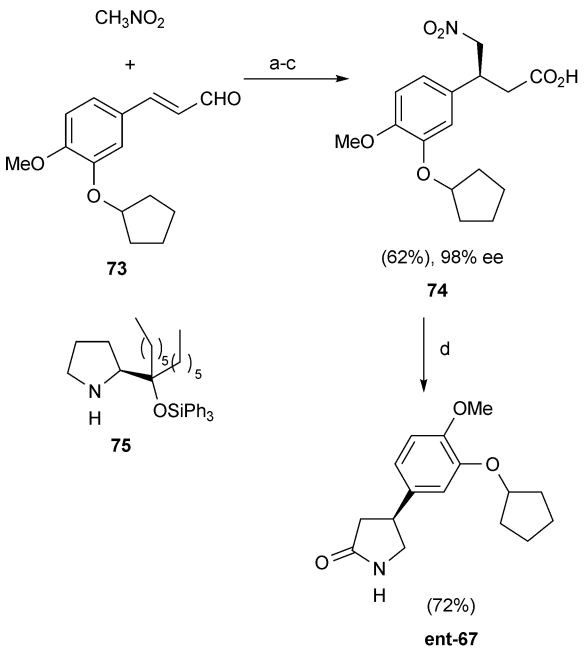
Scheme 15



(a) cyclopentyl bromide, K_2CO_3; (b) $MeNO_2$, NH_4OAc; (c) 5 mol% $Mg(OTf)_2$, 5.5 mol% **71**, 6 mol% N-methylmorphine; (d) Ra-Ni/H_2; H_3PO_4; (e) NaOH; (f) TsOH.

Scheme 16

A competing methodology that provides the highest overall yield (76%) for a 6-step synthesis is shown in Scheme 16. In this synthesis chiral magnesium complex catalyzed addition of ethyl malonate to **70** (96% ee) occurs in the key step followed by a reduction of nitro group on RANEY®-Ni, intramolecular lactamization, and decarboxylation.[70d] A similar synthetic scheme is realized with chiral urea derivatives as organocatalysts.[70a] The other synthetic strategy uses catalyzed reactions of nitromethane with Michael acceptors. One of the most efficient routes, presented in Scheme 17 (4 steps, 45% yield), provides excellent enantiocontrol in the key step.[70c] Disadvantages of a moderate yield in one of the steps in the reaction sequence is balanced with a record-short number of steps of the developed route. Similar syntheses that take advantage of chiral urea derivatives[70b] or Lewis acid[70e] catalyzed nitromethane addition to Michael acceptors are possible alternatives.



(a) 5 mol% **74**, $PhCO_2H$, H_2O; (b) MeOH, CH_3CN, H_2O, KH_2PO_4, $NaClO_2$, 35% H_2O_2; NH_4OAc; (c) $N_2CHSiMe_3$, $MeOH/C_6H_6$; (d) H_2, Pd/C.

Scheme 17

Conclusions

Asymmetric intramolecular carbon–hydrogen insertion reactions of diazoacetates are a highly effective methodology for the synthesis of γ-lactones, and similar reactions with protected diazoacetamides yield γ-lactams with high stereoselectivity. Enantiomeric excesses higher than 90% are routinely obtained. The preferred catalyst is the chiral dirhodium(II) carboxamidate, $Rh_2(MPPIM)_4$, which is effective even at catalyst loadings of one mole percent. Insertion reactions onto cyclic hydrocarbons occur with high diastereocontrol. This methodology provides efficient access to a number of natural products and those of pharmaceutical interest, often occurring in fewer steps and with higher stereocontrol than alternative processes.

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