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Chemistry of Heterocyclic Compounds **2016**, *52*(9), 616–626

REVIEWS

Asymmetric reactions employing 1,3-dipoles

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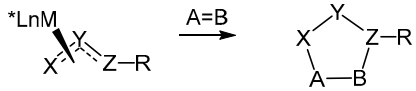

The preparation of heterocyclic compounds using 1,3-dipolar cycloaddition chemistry is now well recognized in the fields of organic synthesis, drug discovery efforts, polymer chemistry, and materials science. As highlighted in this review, a growing area of interest in organic synthesis involves the enantioselectivity aspects of dipolar cycloaddition chemistry for the preparation of many different classes of natural products. Asymmetric synthesis of natural products using chiral substrates has been elegantly accomplished over the past decade using an assortment of dipole intermediates and represents the focus of this review article.

Keywords: azomethine imines, azomethine ylides, carbonyl ylides, diazoalkanes, 1,3-dipoles, nitrones, asymmetric synthesis, cycloaddition.

1,3-Dipolar cycloaddition reactions are among the most powerful methods in organic synthesis.[1] A particularly attractive feature is their ability to rapidly increase molecular complexity and lead to a high degree of functionality. These unique reactions were extensively studied by the Huisgen group starting in the early 1960's and their rate and regioselectivity can be understood through FMO analysis.[2–4] (3+2) Cycloadditions are also extremely useful for the synthesis of natural products, pharmaceutical agents, and other biologically important structures employing rather simple starting materials. Dipolar cycloadditions using chiral substrates for asymmetric synthesis have been extensively explored since the 1990's.[5] Several reviews and articles have been published dealing with enantioselectivity aspects of dipolar cycloaddition chemistry,[6–8] therefore this minireview is intended to provide a selective rather than an exhaustive survey of the enantiospecific chemistry of some of the more common 1,3-dipoles, reported over the past several years.

Diazoalkanes

In recent years, the development of catalytic asymmetric methods has proved to be quite fruitful and the use of diazoalkane cycloadditions has garnered a lot of interest. For example, the Maruoka lab demonstrated that titanium BINOLate complexes promote an enantioselective cycloaddition of diazoacetates to acrolein derivatives with modest yield but good to excellent enantioselectivity. Thus, the addition of *t*-butyl diazoacetate (**1a**) with 2-methylpropenal (**2a**) was promoted by 10 mol % of a 2:1 (*S*)-BINOL:Ti(O*i*-Pr)$_4$ complex to give the 4,5-dihydro-1*H*-pyrazole derivative **3a** in 52% yield and with 91% enantiomeric excess (Scheme 1).[9] Under similar catalytic conditions, the reaction of diazoacetate **1a** with 2-substituted propenal **2b** afforded dihydropyrazole derivative **3b** in 63% yield and with 82% *ee*, and the reaction of diazoacetate **1a** with 2-substituted propenal **2c** furnished the dihydropyrazole **3c** in 82% yield and with 92% *ee*. This methodology was applied to the enantioselective synthesis of manzacidin A (**7**). In this example, catalytic amounts of bis{((*S*)-binaphthoxy)(isopropoxy)titanium} oxide mediated the cycloaddition of ethyl diazoacetate (**1b**) with 2-methylpropenal (**2a**) to give dihydropyrazole **3d** in 52% yield and with 95% enantiomeric excess. The reduction of the aldehyde functionality in intermediate **3d** by the action of $NaBH_4$ and reaction of the resulting alcohol with methyl orthoformate under acidic conditions gave the bicyclic compound **4** in 65% yield over two steps. Exposure of compound **4** to H_2 on Raney nickel provided an 85:5 mixture of the recyclized compound **5** and an epimer at the indicated carbon. This diastereoselectivity is attributed to the epimerization of the ester followed by selective lactonization and hydrolysis rather than a selective reduction. Finally, reaction of the alkoxide anion derived from compound **5** with trichloromethyl ketone **6** furnished the chiral product **7** in 50% yield from the bicyclic intermediate **4**.

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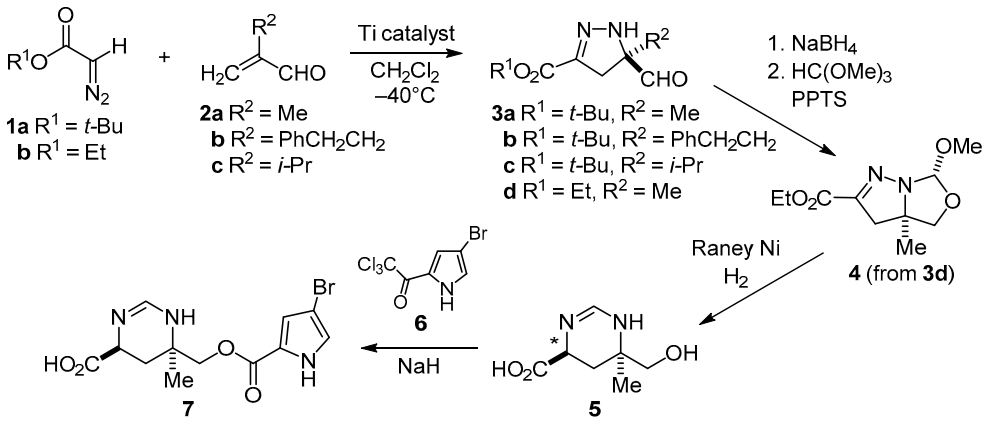
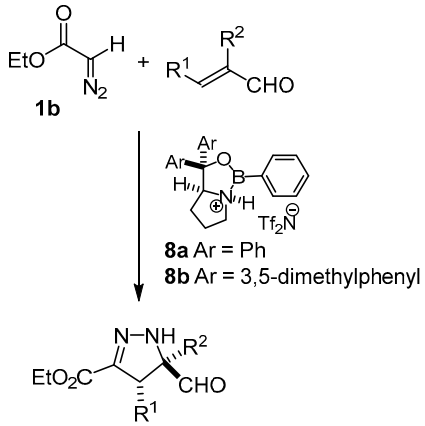
Scheme 1



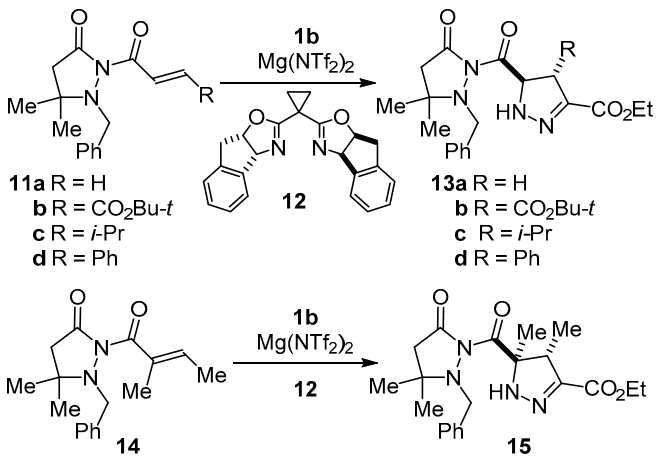
Building upon Maruoka's work, Ryu's group explored the use of chiral oxazaborolidinium ion **8** to catalyze the cycloaddition of diazoacetates with acrolein derivatives.[10] In this case, catalyst **8a** (20 mol %) mediated the cycloaddition of diazoacetate **1b** with acrolein derivative **2a** to give the dihydropyrazole **3d** in 87% yield and 91% *ee* (Scheme 2). Likewise, the reaction with acrolein derivative **2c** produced the dihydropyrazole **10a** in 97% yield and with 92% *ee*. In both of these cases, the enantioselectivities were similar to those in experiments involving Maruoka's BINOLate catalyst, but the yields were significantly improved. In the case where R^1 = Bn (compound **9a**), the use of catalyst **8a** led to the isolation of dihydropyrazole **10b** in 72% yield, but with only 76% *ee*. Alternatively, the use of catalyst **8b** improved the enantioselectivity, producing the dihydropyrazole **10b** in 72% yield and 91% *ee*. Disubstituted acrolein derivatives also performed well. Dimethylacrolein (**9b**), for example, reacted with ethyl diazoacetate (**1b**) in the presence of compound **8a** to give compound **10c** in 93% and with 92% *ee*. The cyclopentenyl carbaldehyde **9c** reacted to give dihydropyrazole **10d** in 73% yield and with 97% *ee*, while the cyclohexenyl carbaldehyde **9d** afforded dihydropyrazole **10e** in 75% yield and in 92% enantiomeric excess.

Sibi and coworkers used chiral magnesium complexes to promote the enantioselective addition of ethyl diazoacetate (**1b**) to electron-deficient alkenes.[11] The reaction of ethyl diazoacetate with alkene **11a** in the presence of $Mg(NTf_2)_2$ and ligand **12** at –20°C produced the dihydropyrazole **13a** in 72% yield with 99% *ee* (Scheme 3). A variety of α,β-unsaturated amides gave good yields and excellent enantiomeric excess. The reaction with fumaric acid derivative **11b**, which contains a second carbonyl conjugated to the double bond of dipolarophile, gave dihydropyrazole **13b** in 91% yield and 99% *ee* under similar conditions, while the more sterically demanding alkene **11c** reacted with the magnesium complex of ligand **12** at room temperature to provide the dihydropyrazole **13c** in 79% yield and 98% *ee*. An aryl-substituted compound also gave good chemical yield, though the enantioselectivity was somewhat lower. The magnesium complex-mediated reaction of cinnamic acid derivative **11d** with ethyl diazoacetate (**1b**) at 40°C furnished the product **13d** in 76% yield with good 88% *ee*. More highly substituted alkenes were also reactive, although the yields were significantly reduced. Ethyl diazoacetate (**1b**), for example, reacted with alkene **14** to afford product **15** in 61% yield but with 99% *ee*.

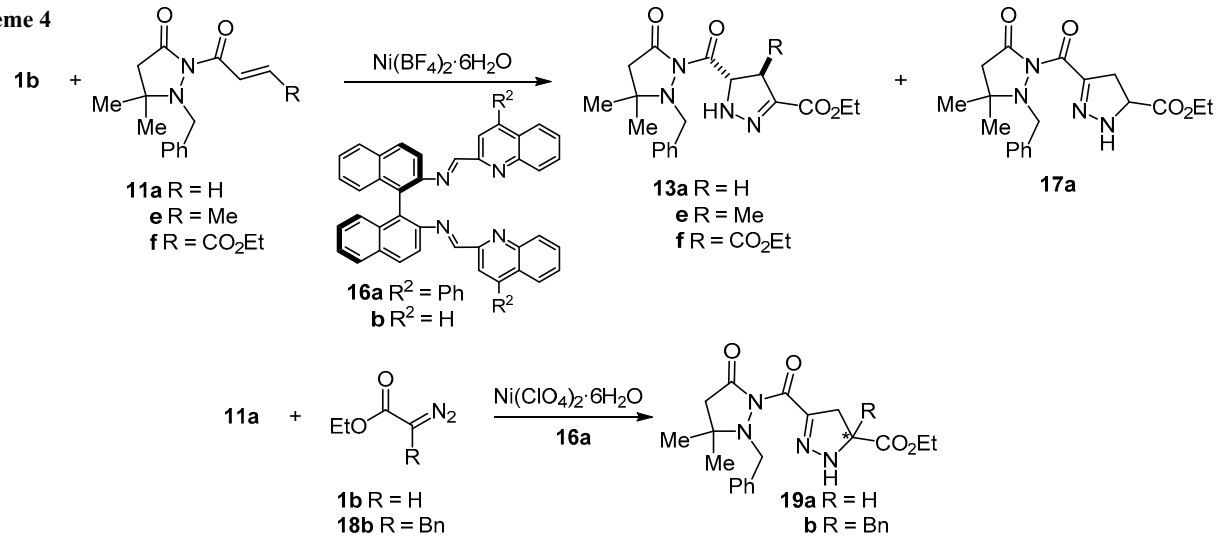
Scheme 2



Scheme 3



Scheme 4



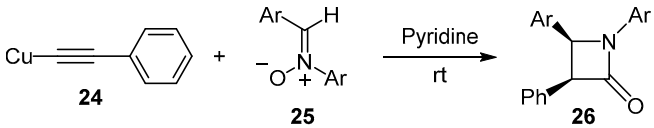
After considerable experimentation, the Suga group found conditions that employ chiral Ni(II) catalysts to facilitate enantioselective cycloadditions.[12] The substrates that worked best were the same general pyrazolidinone derivatives used in Sibi's work.[11] Ethyl diazoacetate (**1b**) added to acrylamide **11a** in the presence of a complex formed between $Ni(BF_4)_2 \cdot 6H_2O$ and ligand **16a** at –45°C to give a mixture (85:15) of product **13a** and isomer **17a** in 87% yield (Scheme 4). The stereoselectivity of the reaction was excellent, with the product **13a** being produced with 97% enantioselectivity. Alternatively, reaction of acrylamide **11e** with ethyl diazoacetate (**1b**) mediated by the nickel complex with ligand **16b** at room temperature produced only the isomer **13e** in 94% yield with 93% *ee*. The use of the catalyst derived from ligand **16a** also promoted the reaction, although in slightly diminished yield (87%). The counterion of the Ni(II) complex also affected the enantioselectivity, with BF_4^- generally giving better results. In the case of fumaric acid derivative **11f**, however, the reaction with ethyl diazoacetate (**1b**) was best promoted using $Ni(ClO_4)_2$ to form the catalytic complex with ligand **16b**, furnishing dihydropyrazole **13f** in 92% yield and 85% *ee*. Importantly, substituted α-diazoacetates also produced cycloadducts. The reaction of ethyl diazoacetate (**1b**) with acrylamide **11a** in the presence of ligand **16a** and $Ni(ClO_4)_2$ gave compound **19a** in only 15% yield and 70% *ee*, the remainder of the products were related to a cyclopropane and an alkene derived from the cycloadduct. Other catalyst complexes increased the yield (up to 40%) at the expense of enantioselectivity. In contrast, the substituted diazoacetate **18b** gave product **19b** in 73% yield and 75% *ee* under similar conditions.

Nitrones

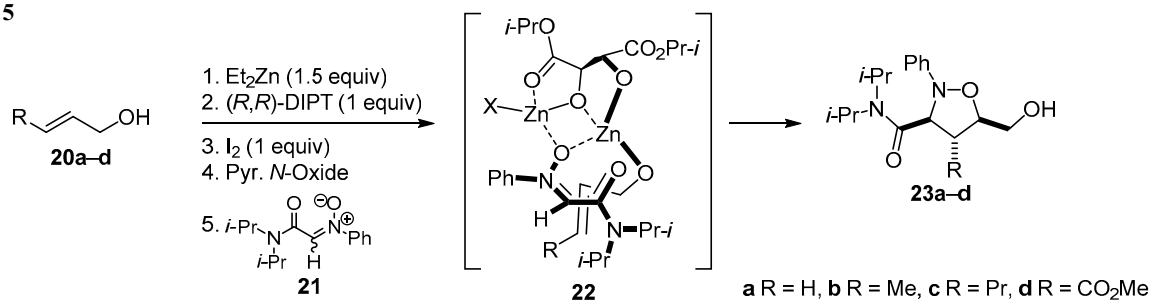
Cycloaddition between the zinc salts of allylic alcohols and various electron-poor nitrones produced isoxazolidines in good yield with excellent enantioselectivity in the presence of diisopropyl tartrate (DIPT).[13] For example, the cycloaddition reaction of allyl alcohol (**20a**) with nitrone **21** under the conditions specified in Scheme 5 gave isoxazolidine **23a** in 69% yield and with 98% *ee*. Under similar conditions, 2-buten-1-ol (**20b**) reacted to give 64% yield of isoxazolidine **23b** with >99% *ee*, although in this case it required more equivalents of reagents to induce reaction with nitrone **21**. Alcohols **20c**,**d** afforded isoxazolidines **23c**,**d** with >99% *ee* (48% yield) and 97% *ee* (63% yield), respectively.

Another interesting cascade involving nitrones is the copper-catalyzed reaction with alkynes producing β-lactams that was originally reported by Kinugasa.[14] Stoichiometric amounts of copper(I) phenylacetylide (**24**) reacted with

Scheme 6



Scheme 5

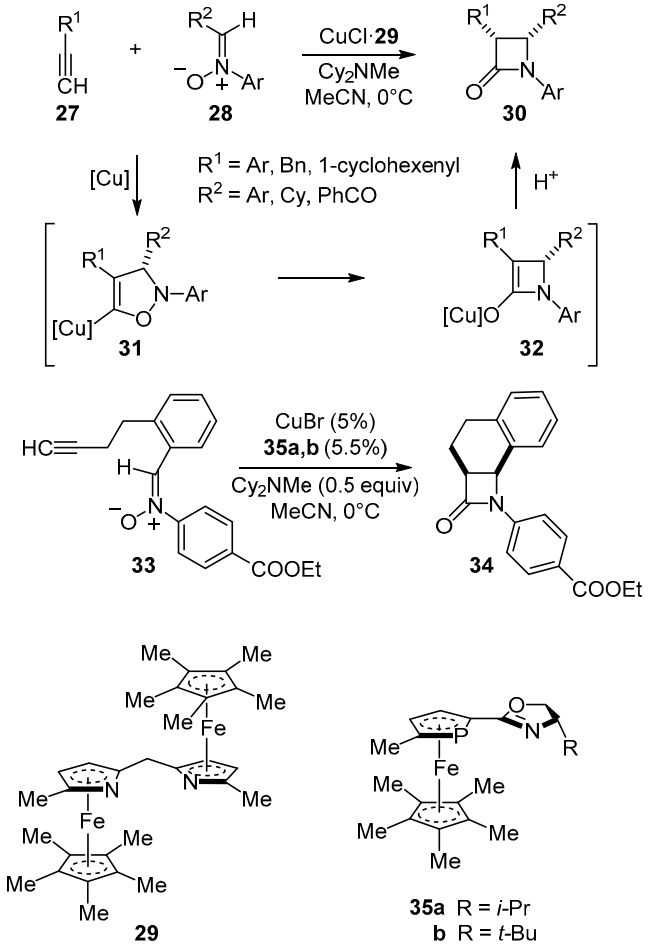


various aryl nitrones **25** in pyridine and gave β-lactams **26** in 50–60% yield (Scheme 6). In each case, only the *cis*-lactams were isolated.

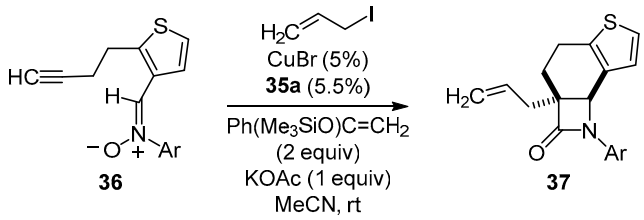
Miura and coworkers showed that the reaction could also be carried out using catalytic amounts of CuI in the presence of pyridine.[15] Asymmetric reactions were reported to occur with chiral bisoxazoline ligands producing β-lactams with moderate (40–68%) enantiomeric excess. The use of an oxazolidinone with a chiral auxiliary attached to the alkyne did provide enantiomerically pure products.[16] In all of these latter reports, mixtures of *cis*- and *trans*-lactam isomers were obtained in which the *trans*-product predominated. It was also shown that the *cis*-isomer could easily be converted to the *trans*-product when exposed to base.

The Fu group recently reported the use of *C*2-symmetric planar-chiral bis(azaferrocene) ligands for the catalytic enantioselective Kinugasa reaction.[17] A variety of terminal alkynes **27** (R^1 = Ar, Bn, 1-cyclohexenyl) were allowed to react with nitrones **28** (R^2 = Ar, Cy, PhCO; R^3 = Ar) in the presence of catalytic amounts of the CuCl·**29** complex to give diastereomeric mixtures (>90:10) predominating in *cis*-substituted β-lactams **30** in moderate to good yields (45–90%) and with good enantiomeric excess (67–92%; Scheme 7). With regard to the R^3 group on nitrone **28**, electron-rich aromatic groups increased the enantioselectivity, although the yields were somewhat lower. An intramolecular variant of this catalytic enantioselective process was also reported. Nitrone **33** was converted to azetidinone **34** in the presence of the CuBr·**35a** complex in 74% yield and with 88% *ee*.[18] Ligand **35b** was also quite effective, providing compound **34** with 90% *ee*, though the yield was only 47%. The mechanism for the Kinugasa reaction[14] is thought to involve a (3+2) cycloaddition of the nitrone with the respective copper acetylide to give isoxazolidine copper salt **31**. Rearrangement of compound **31** then provided the copper enolate of the corresponding β-lactam (i.e., compound **32**), which was subsequently protonated to provide the observed product. The proton source for this last step was most likely the conjugate acid of the base used to generate the copper acetylide. Through considerable experimentation, the Fu group developed conditions that allowed for the reaction of the enolate with added electrophiles. Thus, exposing starting material **36** to CuBr·**35a** in the presence of KOAc, allyl iodide, and the silyl enol ether of acetophenone gave rise to β-lactam **37** in 70% yield and with 90% *ee* (Scheme 8).[18]

Scheme 7



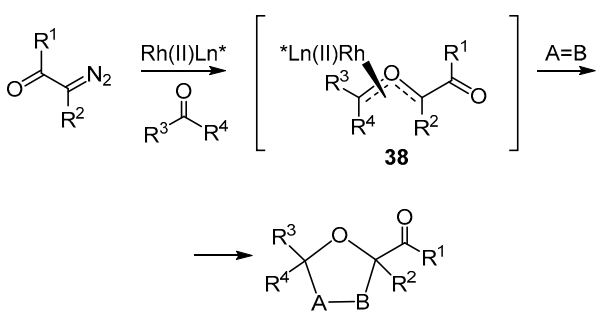
Scheme 8



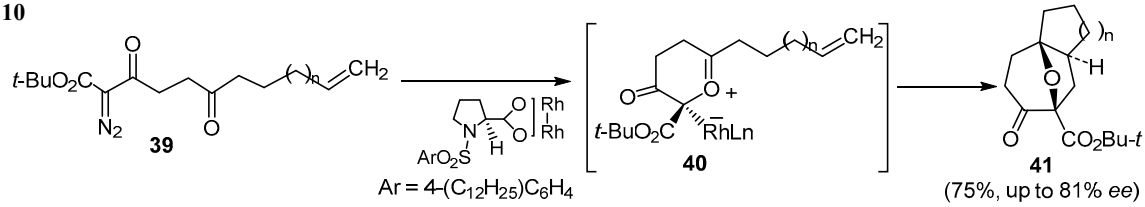
Carbonyl ylides

The creation of carbonyl ylide dipoles from the reaction of α-diazo compounds with ketones through the intermediates **38** in the presence of Rh(II) catalysts (Scheme 9) has significantly broadened their applicability for natural product synthesis.[19–28] The ease of generating the 1,3-dipole, the rapid accumulation of polyfunctionality in a relatively small molecular framework, the high stereochemical control of the subsequent (3+2) cycloaddition, and the fair predictability of its regiochemistry have contributed to the popularity of the reaction.[29,30] When the reacting components are themselves cyclic or have ring substituents, complex multicyclic arrays, such as those contained in drugs and natural products, can be constructed in a single step.

Scheme 9



Scheme 10



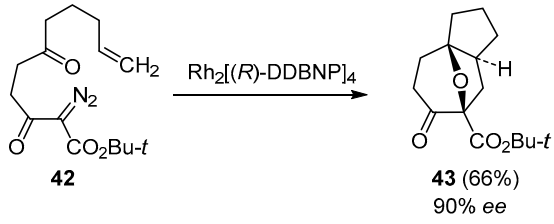
Recent developments over the past several years have shown that a number of catalytic asymmetric carbonyl ylide cycloadditions is possible.[31] Hodgson and coworkers reported the first examples of enantioselective carbonyl ylide cycloaddition (up to 81% *ee*) using unsaturated α-diazo β-keto esters (Scheme 10).[32] Because the catalyst-free carbonyl ylide would be achiral, the observation of enantioselectivity provides unambiguous evidence for an enantioselective ylide transformation taking place *via* a catalyst-complexed intermediate (i.e., the complex **40**).

In a later report by this same group, the scope and generality of the catalytic enantioselective intramolecular tandem carbonyl ylide cycloaddition was further evaluated using a series of related unsaturated 2-diazo-3,6-diketo esters.[33] The cycloadditions were found to proceed in moderate to good yields, with a difference in *ee* exhibited by the electronically different α-diazo keto esters used (Scheme 11). Values for *ee* up to 90% for alkene dipolarophiles and up to 86% for alkyne dipolarophiles were obtained.

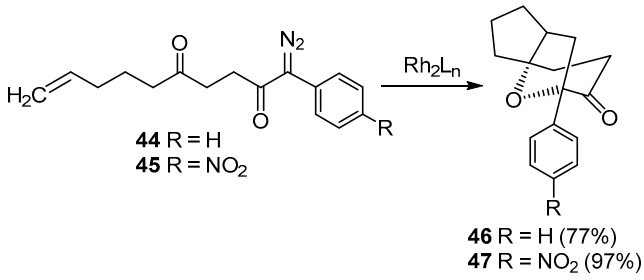
An evaluation of α-aryl-α-diazodiones in tandem intramolecular carbonyl ylide formation, enantioselective (3+2) cycloaddition, was also carried out by the Hodgson group.[34] The substrates were designed to allow investigation of the electronic characteristics of the dipole upon asymmetric induction. Once again, electronic factors were found to play a key role in determining the outcome of the cycloaddition reactions with enantioselectivities of up to 97% *ee* (Scheme 12).[35]

An efficient 15-step synthesis of the antimitotic alkaloid (−)-colchicine (**50**) involved a Rh-catalyzed transformation of α-diazo ketone **48** to produce an oxatetracyclic key intermediate **49** through an intramolecular (3+2) cycloaddition of an *in situ* generated carbonyl ylide dipole (Scheme 13).[36] In this manner both the seven-membered rings B and C were formed in one step with concomitant installation of the oxygen functions in positions C-9 and C-10. Moreover, the intramolecular mode of the cycloaddition step permitted the use of an unactivated dipolarophile and thus allowed for the installation of the C-7 stereocenter prior to cyclization. The key cycloadduct **49** was obtained in 64% yield with high enantioselectivity (99% *ee*) and was easily converted to the alkaloid **50** in several additional steps.

Scheme 11



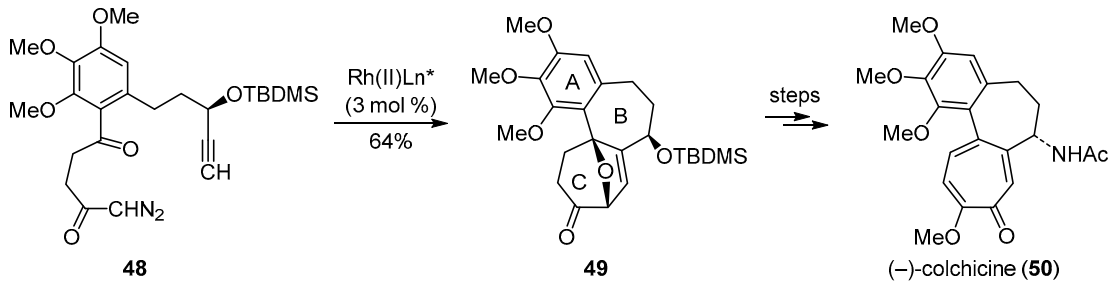
Scheme 12



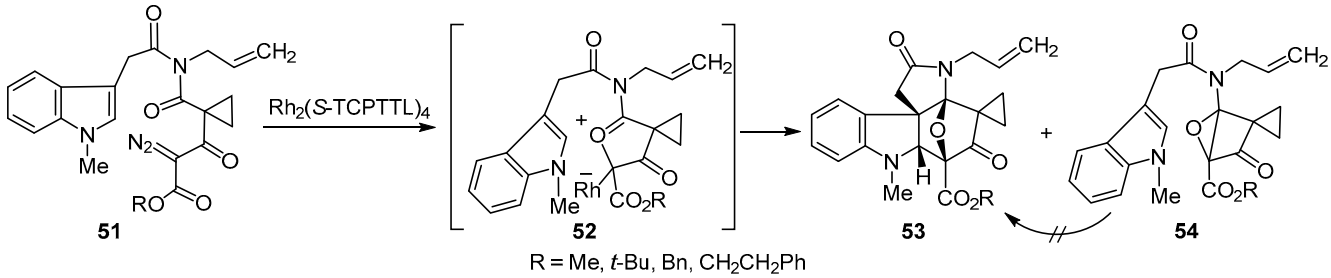
The Hashimoto group described a modified enantioselective protocol that uses chiral dirhodium(II) carboxylates to control the facial selectivity of the cyclization for assembling the pentacyclic ABCDE framework of the aspidosperma alkaloid family.[37] Cycloaddition of the carbonyl ylide derived from indolyl-substituted diazoimides **51** under the influence of Rh_2(*S*-TCPTTL)$_4$ provided cycloadduct **53** in 43% yield and 66% *ee* with complete *endo* diastereoselectivity (Scheme 14). The undesired bicyclic epoxide **54** was also obtained in 42% yield as the other major by-product.

Attempts to convert compound **54** into the cycloadduct **53** under the same conditions failed, leading the authors to hypothesize that the epoxide did not serve as an intermediate in the reaction. This system represents the first example of asymmetric induction in an intramolecular cycloaddition of a carbonyl ylide dipole across an indolyl π-bond.

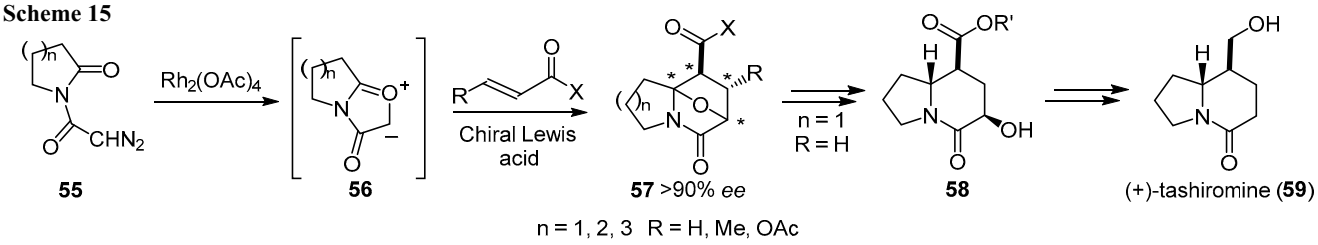
Scheme 13



Scheme 14



Scheme 15

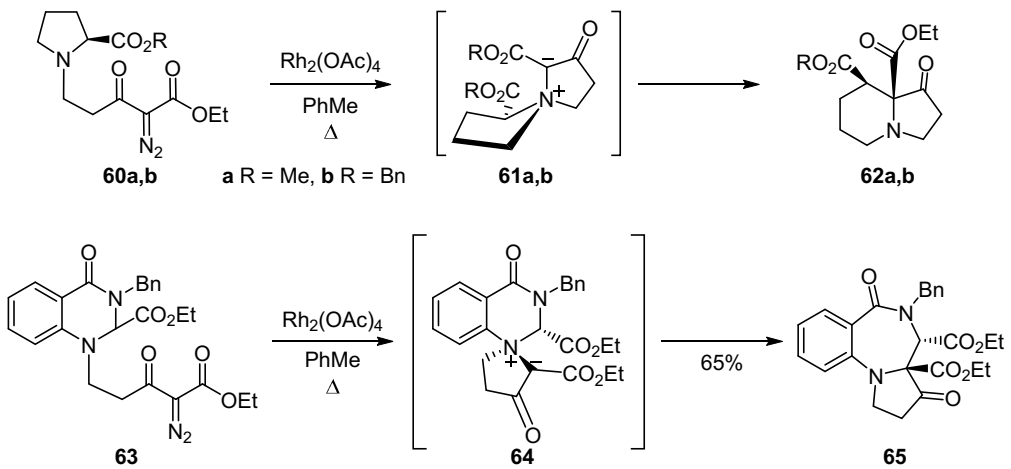


Suga and coworkers have reported on a highly enantioselective 1,3-dipolar cycloaddition reaction between several 3-(2-alkenoyl)-2-oxazolidinones and carbonyl ylides that were generated from the Rh(II)-catalyzed reaction of *N*-diazoacetyl lactams of type **55**. *N*-Diazoacetyl lactams that possess 5-, 6-, and 7-membered rings were transformed to the corresponding epoxy-bridged indolizidines, quinolizidines, and 1-azabicyclo[5.4.0]undecanes with good to high enantioselectivities according to this method. A regio- and stereoselective ring opening of the epoxy-bridged indolizidine cycloadduct **57** gave the corresponding alcohol **58** as a single diastereomer. The sequence of an asymmetric cycloaddition reaction followed by ring opening was applied to the syntheses of several chiral indolizidine derivatives, including (+)-tashiromine (**59**) (Scheme 15).[38]

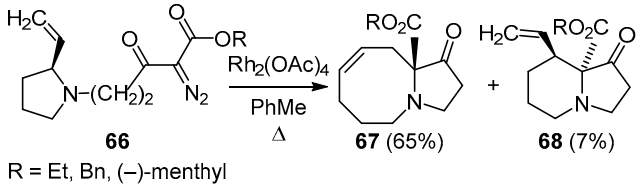
Saba and coworkers used proline-derived α-diazo compounds for the enantioselective synthesis of the indolizidine skeleton, notably creating a quaternary center adjacent to nitrogen.[39] In this report, the α-diazo keto ester **60a** was refluxed in toluene in the presence of $Rh_2(OAc)_4$ to give a mixture (60:40) of indolizidine **62a** and the *trans*-stereoisomer in 84% combined yield, and the indolizidine **62a** was produced with high enantioselectivity (80% *ee*) (Scheme 16). Subjecting benzyl ester **60b** to the same reaction conditions produced a mixture in which the indolizidine **62b** was the major diastereomer, while the diastereoselectivity increased to 72:28 and the product **62b** was isolated with 84% *ee*. In both cases, the use of $Cu(acac)_2$ led to slightly higher yields (90% in each case) but with a significant erosion in diastereoselectivity. Of particular interest was that the ammonium ylides **61a**,**b** were isolable, and each was heated to produce product **62a**,**b** with complete selectivity and with 95% *ee*. This provided further evidence of the stereoselective nature of the [1,2]-shift. A related reaction was also observed using α-diazo keto ester **63** producing the cyclized product **65** in 65% yield *via* ammonium ylide **64**.[40]

The Saba group also demonstrated that the [2,3]-rearrangement strategy could be used for the synthesis of azabicyclo-[6.3.0]undecane systems containing quaternary carbon atoms adjacent to the nitrogen atom.[41] Proline derivative **66** reacted with catalytic amounts of $Rh_2(OAc)_4$ in refluxing toluene to give a 9:1 mixture of [2,3]:[1,2]-rearrangement products **67** and **68** in 72% yield (Scheme 17). Analysis of

Scheme 16



Scheme 17



a Mosher's ester derivative suggested that the product **67** was formed with 98% enantiomeric excess.

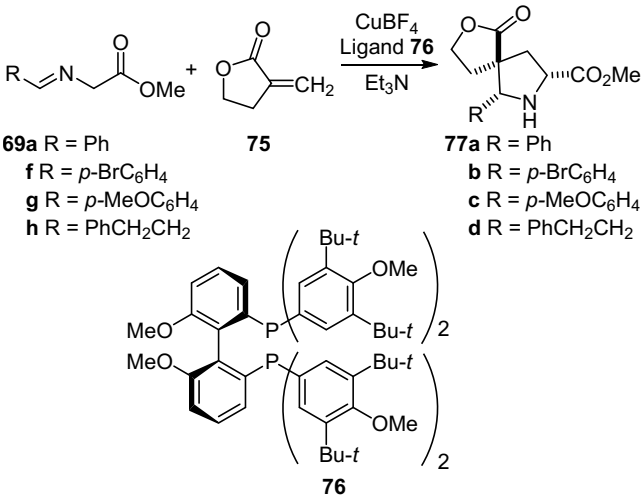
Azomethine ylides

The Oh research group examined the ability of copper complexes derived from brucine diol derivative **71** to effect a concerted (3+2) cycloaddition between azomethine ylide dipoles obtained from imines **69** and nitroalkenes **70** (Scheme 18).[42] Schiff base **69a**, obtained by the condensation of benzaldehyde and methyl glycine, reacted with β-nitrostyrene (**70a**) in the presence of 20 mol % each of $Cu(OTf)_2$, ligand **71**, and DBN to give *endo* adduct **72a** as a single diastereomer in 97% yield and with 84% enantiomeric excess. Similarly, the adduct **72b** was isolated in 92% yield and with 92% *ee* and adduct **72c** was isolated in 92% yield and with 90% *ee*. The nitroalkene could be substituted with little impact on the diastereoselectivity or enantioselectivity as shown in Scheme 18. The presence of a methyl group in alanine derivative **69d** reduced the yield slightly (76%) but the enantioselectivity was still excellent (94% *ee*). A stepwise reaction mechanism, wherein a conjugate addition of the reactive azomethine ylide to the nitroalkene occurs first, followed by a Mannich-like cyclization, was ruled out by studies that showed the second step of such a mechanism as too slow to account for the rate of the reactions catalyzed by the copper–**71** complex.

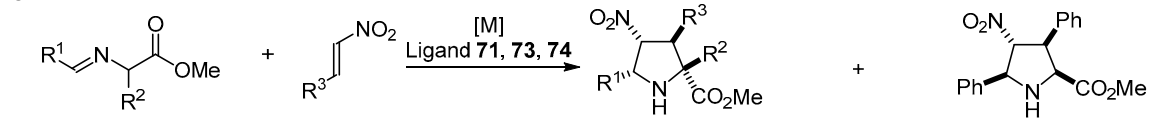
Fukuzawa and coworkers showed that AgOAc and ligand **73** promoted the reaction of imines **69** and β-nitrostyrenes **70** to give predominantly *endo* adducts **72** in good yields and excellent stereoselectivities (Scheme 18).[43] For example, the adduct **72a** was produced (94:6 *dr*) in 70% yield and with 96% *ee*. Pyrrolidines **72b**,**c**,**f** were formed in 71–80% yields and with enantiomeric excesses ranging from 91% (compound **72f**) to 97%. In these cases, the catalyst loading was only 5 mol %. Sansano and coworkers, however, demonstrated that ligand **74** together with either $Cu(OTf)_2$ or Ag(I) salts in the presence of Et_3N effected the cycloaddition, also at 5 mol % catalyst load, but with the opposite diastereoselectivity.[44] For example, the imino ester **69a** reacted with β-nitrostyrene **70a** in the presence of AgOBn, ligand **74**, and Et_3N to give a 91:9 mixture of *exo* and *endo* diastereomers, this time favoring the product *exo*-**72a**. The *exo* adduct was isolated in 88% yield and with >98% enantiomeric excess. Similar diastereoselectivities, yields, and enantioselectivities were observed for a variety of subsituted imino esters and nitroalkanes.

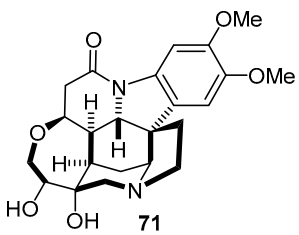
The cycloaddition reaction of methylene lactone **75** with imino esters **69** in the presence of $CuBF_4$ and chiral bisphosphine **76** (3 mol % each) gave spirocycles **77a**–**d** in good yields and with excellent enantioselectivity (i.e., 99% *ee*) (Scheme 19).[45] Varying the electronics of the aryl substituent did not significantly affect the reaction. Alkyl-substituted imino esters participated in the cycloaddition, but the yields were poorer.

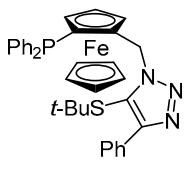
Scheme 19

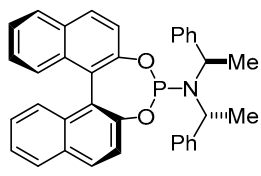


Scheme 18

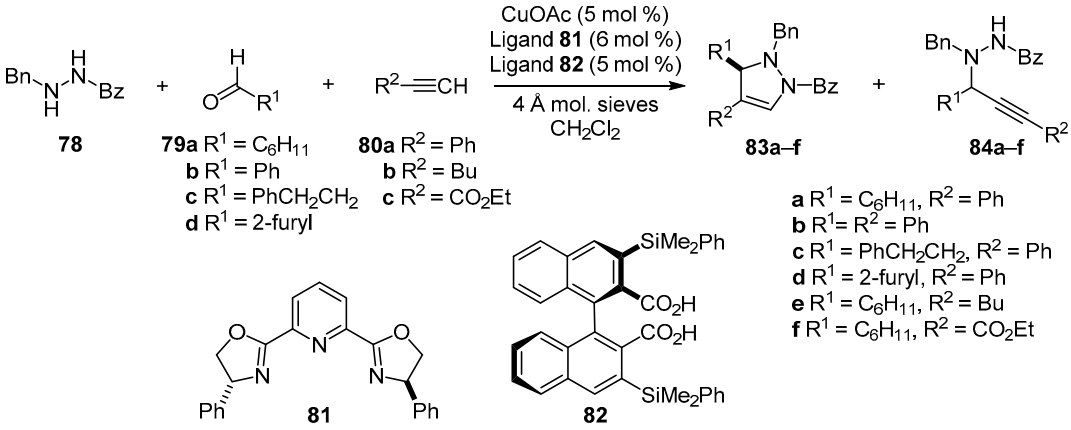




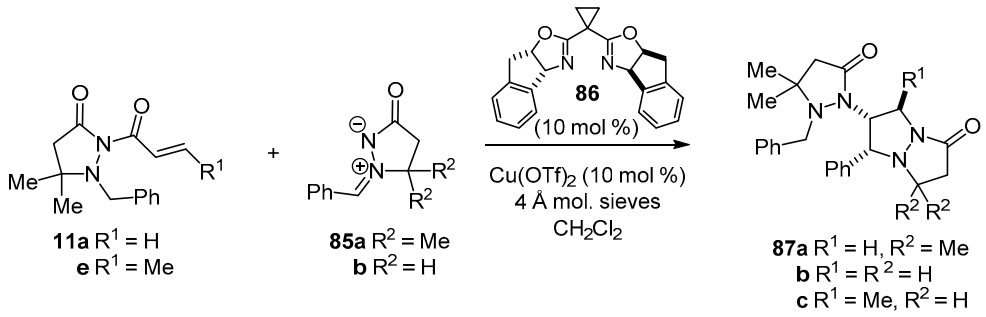




Scheme 20



Scheme 21



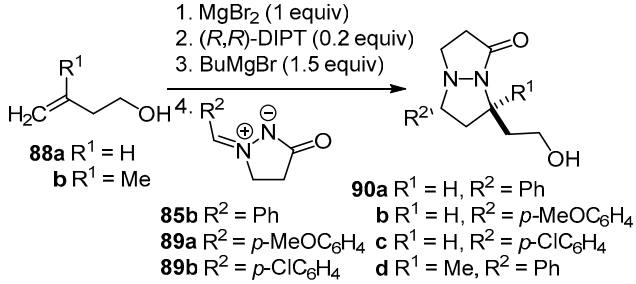
Azomethine imines

Asymmetric cycloadditions of azomethine imines have also received considerable attention. Various metal complexes have promoted the formation of cycloadducts with good to excellent enantioselectivities, diastereoselectivities, and chemical yields. For example, Maruoka's group developed a three-component reaction wherein a mixture of hydrazide **78**, aldehyde **79b**, and alkyne **80a** were reacted in the presence of CuOAc, Ph-pybox **81**, diacid **82**, and 4 Å molecular sieves to give >95:5 mixture of compound **83b** and the corresponding alkyne addition product **84b** in 95% yield and with 99% *ee* (Scheme 20).[46] Under these conditions, various aldehydes successfully participated in the reaction, with aldehydes **79b**–**d** giving mixtures (>95:5) favoring products **83b**–**d** in 96, 87, and 92% yield, respectively, with 96, >99, and 88% enantiomeric excesses, respectively. Several substituted alkynes also provided similar mixtures (>95:5) in excellent yields and enantioselectivities (product **83e**, 87% yield and 99% *ee*; product **83f**, 94% yield, 96% *ee*). It is not yet entirely clear if these reactions are concerted or, as Kobayashi and coworkers demonstrated,[47] they are stepwise addition/cyclization reactions.

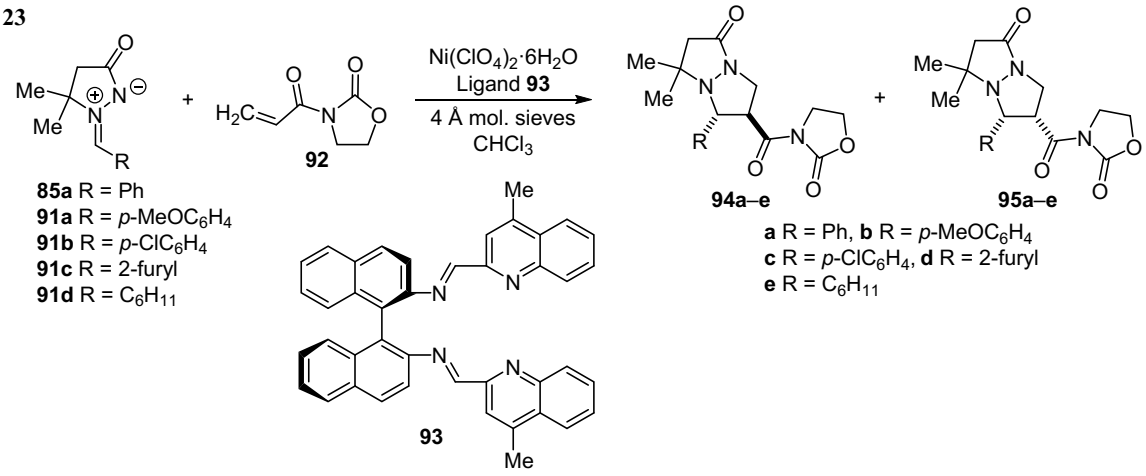
Sibi and coworkers reported an *exo*-selective cycloaddition of acrylamide **11a** with compound **85a** mediated by a copper complex containing ligand **86** that gave product **87a** in 90% yield with an 88:12 diastereomeric ratio and with 94% *ee* (Scheme 21).[11] Compound **85b** reacted under similar conditions to give the product **87b** in 79% yield and with 95% *ee*. The crotonamide **11e** reacted with compound **85b** to give product **87c** as a single isomer in 77% yield but with only 67% *ee*. Crotonamide **11e** failed to react with compound **85a**, even with 100 mol % of the copper complex.

Inomata, Ukaji, and coworkers developed asymmetric methods for adding azomethine imines such as **85b** to allylic alcohols with good enantioselectivities[48,49] and they expanded the methodology to the more challenging homoallylic alcohols. Magnesium alkoxide derived from 3-buten-1-ol (**88a**) reacted with compound **85b** in the presence of (*R*,*R*)-DIPT to provide product **90a** in 76% yield and with 93% enantiomeric excess (Scheme 22).[50] Likewise, compounds **89a**,**b** reacted to give products **90b**,**c** in 72 and 87% yields, respectively, with 93% *ee* in each case. Azomethine imines derived from aliphatic aldehydes provided highly variable chemical yield and moderate to good enantioselectivity (63–83% *ee*). Under the standard conditions, the more highly substituted homoallylic alcohol **88b** reacted with compound **85b** to give product **90d** in 78% yield and with 95% *ee*.

Scheme 22



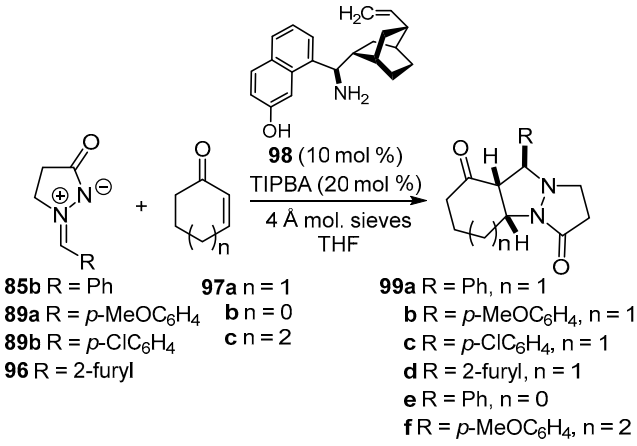
Scheme 23



Suga's lab examined the use of a Ni(II) complex to effect asymmetric azomethine imine cycloadditions. In one example, chloroform solutions of dipole **85a** added to acrylimide **92** in the presence of Ni(II) and ligand **93**, furnishing a 93:7 mixture of product **94a** and its *cis*-isomer **95a** in 93% yield and with 97% *ee* (Scheme 23).[51] The electronic nature of the aryl group of the azomethine imine had little impact on the reaction. Compound **91a** afforded an 80:20 mixture of products **94b** and **95b**, with the product **94b** being produced with 90% *ee*. Alternatively, dipole **91b** furnished products **94c** and **95c** (91:9 *dr*) in quantitative yield, with product **94c** having 95% *ee*. Heterocyclic substituents were successfully deployed with dipole **91c** returning mixtures predominating in product **94d** (64:36 *dr*) in 83% yield and 95% *ee*. Reactions with alicyclic derivatives proceeded with diminished yield and enantioselectivity, with dipole **91d** giving products **94e** and **95e** (82:18 *dr*) in 74% yield, but with product **94e** being produced with only 74% *ee*. The sterically less demanding dipole **85b** reacted under similar conditions to give good yields and diastereoselectivities, but with low enantiomeric excess.

Organocatalysts are also effective promoters of azomethine imine cycloadditions. 1,3-Dipolar cycloadditions of cyclic enones remain challenging substrates for LUMO-lowering iminium-based catalysis. The Chen's group, however, used the cinchona alkaloid derivative **98** to promote the addition of dipole **85b** with cyclic enone **97a** in the presence of 2,4,6-triisopropylbenenesulfonic acid (TIPBA) to furnish product **99a** in 89% yield and with 90% *ee* (Scheme 24).[52] Variously substituted aryl groups, such as in dipoles **89a** and **89b**, also participated in the reaction with enone **97a**, giving products **99b** and **99c** in 73 and 99% yields, respectively, and with 92% *ee* in both cases. The furyl-substituted dipole **96** reacted with enone **97a** to give product **99d** in 99% yield and 95% *ee*. The use of cyclopentenone **97b** required 20 mol % of the catalysts, but it reacted with dipole **85a** (see Scheme 21) to afford product **99e** with 90% enantiomeric excess, although in a somewhat diminished yield (78%). Similarly, the seven-membered ring dipolarophile **97c** underwent cycloaddition

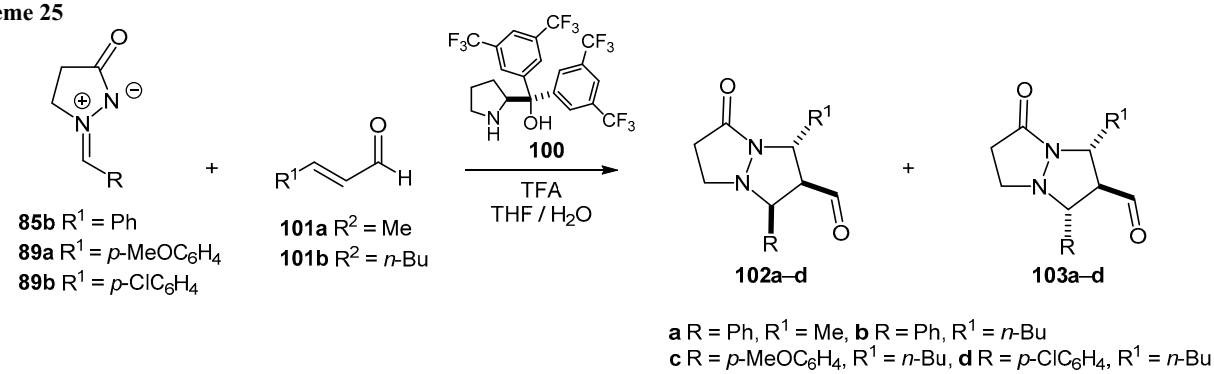
Scheme 24



with dipole **89a** in the presence of 10 mol % of catalyst **98** to give 76% yield of product **99f** with 93% *ee*.

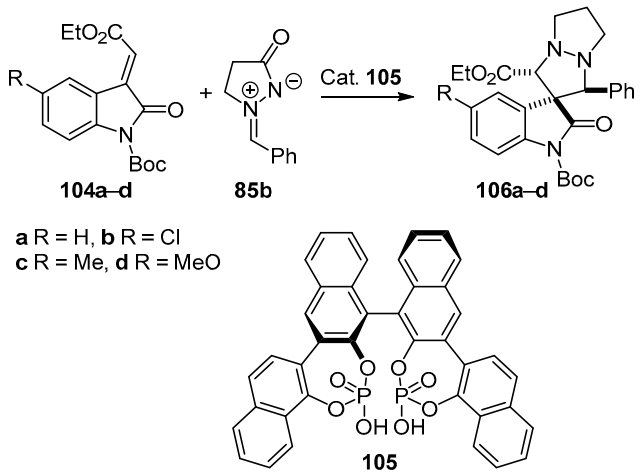
Chen's group also examined the use of catalyst **100** to promote the *exo*-selective cycloaddition of dipole **85b** with iminium ions derived from α,β-unsaturated aldehydes, that provided modest to good yields and good to excellent enantioselectivity (Scheme 25).[53] Dipole **85b**, for example, reacted with a mixture of aldehyde **101a** (10 mol %) and TFA in aqueous THF to give an 81:19 mixture of diastereomers **102a** (96% *ee*) and **103a** in 85% yield. The use of longer-chain aldehydes led to somewhat diminished yields but excellent enantioselectivities, as demonstrated by the reaction of dipole **85b** with 2-heptenal (**101b**) that yielded 85% of products **102b** (94% *ee*) and **103b** as an 85:15 mixture. As with other examples using this dipolarophile, varying the electronic nature of the aromatic substituent did not significantly affect the stereoselectivity of the reactions. Azomethine imine **89a** reacted with the iminum ion derived from 2-heptenal (**101b**) and catalyst **99**, to produce an 88:12 mixture of products **102c** (92% *ee*) and **103c** in 66% yield, and the dipole **89b** reacted under similar conditions to afford an 83:17 mixture of products **102d** (95% *ee*) and **103d** in 77% yield.

Scheme 25



Wang and coworkers used chiral *bis*-phosphoric acid **105** to construct spirocyclic oxindoles **106a**–**d** (Scheme 26).[54] Reaction of dipolarophile **104a** and dipole **85b** in the presence of 10 mol % of catalyst **105** afforded the product **106a** in 93% isolated yield with 98% *ee*. As with other reports, varying the electronic nature of the aryl substituent on the dipole (e.g., in compounds **89a**,**b** or **96**) did not significantly change the yields or enantioselectivities of the reactions. Neither did changing the substitution pattern on the oxindole dipolarophile. Compounds **104b**,**c** underwent cycloaddition mediated by catalyst **105** to provide spirocyclic products **106b**,**c** in 84 and 93% yields, respectively, with 96% *ee* in both cases. Similarly, the dipolarophile **104d** reacted to give spiro compound **106d** in 87% yield and with 99% enantiomeric excess.

Scheme 26



The impact of 1,3-dipolar cycloaddition chemistry is now well recognized in the fields of organic synthesis, drug discovery efforts, polymer chemistry, and materials science. By using chiral starting materials for the cycloaddition reactions, it is possible to completely control the enantioselectivity as well as regio- and diastereoselectivity. In recent years, steady progress has also been made in metal-catalyzed asymmetric dipolar cycloaddition chemistry. Forthcoming developments will also depend on gaining a greater understanding of the mechanistic details of this fascinating and synthetically important process.

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