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Zn-Catalyzed Enantio- and Diastereoselective Formal [4 + 2] Cycloaddition Involving Two Electron-Deficient Partners: Asymmetric Synthesis of Piperidines from 1-Azadienes and Nitro-Alkenes

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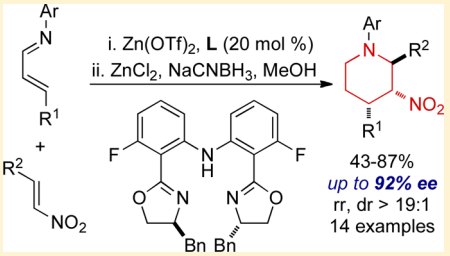
Supporting Information

ABSTRACT: We report a catalytic asymmetric synthesis of piperidines through [4 + 2] cycloaddition of 1-azadienes and nitro-alkenes. The reaction uses earth abundant Zn as catalyst and is highly diastereo- and regioselective. A novel BOPA ligand (F-BOPA) confers high reactivity and enantioselectivity in the process. The presence of *ortho* substitution on the arenes adjacent to the bis(oxazolines) was found to be particularly impactful, due to limiting the undesired coordination of 1-azadiene to the Lewis acid and thus allowing the reaction to be carried out at lower temperature. A series of secondary kinetic isotope effect studies using a range of ligands implicates a stepwise mechanism for the transformation, involving an initial Michael-type addition of the imine to the nitro-alkene followed by a cyclization event. The stepwise mechanism obviates the electronic requirement inherent to a concerted mechanism, explaining the successful cycloaddition between two electron-deficient partners.



INTRODUCTION

[4 + 2] Cycloadditions have shown extensive applications for the construction of cyclohexenes in the syntheses of simple biologically active molecules[1] or complex natural products.[2] They offer the advantages of a high level of stereochemical control and atom-economy and lead to a rapid escalation of molecular complexity. Unsurprisingly, tremendous attention has been paid to explore catalytic and enantioselective [4 + 2] cycloadditions of dienes and alkenes.[3] Despite the prevalence of piperidine derivatives in drug molecules (Figure 1), the aza-analogue of the all-carbon [4 + 2] cycloaddition is less well developed.[4]

Simple imines, 1-azadienes, and 2-azadienes[5] are three different classes of substrates. The use of 2-azadienes in catalytic, enantioselective [4 + 2] cycloaddition is mainly for the synthesis for polycyclic nitrogen heterocycles, as exemplified by the Povarov reaction.[6] Simple imines and 1-azadienes are more challenging substrates, although they can be readily prepared by the condensation of amines on aldehydes.[7,8] This may be attributed to the lack of a thermodynamic driving force since the breaking C−N π bonds are stronger and the forming C−N σ bonds are weaker compared to the corresponding C−C bonds (Figure 1).[9]

Catalytic, enantioselective [4 + 2] cycloadditions with simple imines for the syntheses of monocyclic piperidines are mainly restricted to the use of Danishefsky's diene.[10] There are limited examples of catalytic asymmetric [4 + 2] cycloadditions with 1-azadienes.[11] In 2007, Arrayas and Carretero reported a Ni-catalyzed enantioselective inverse-electron-demand Diels−Alder reaction with *N*-sulfonyl-1-azadienes and enol ethers (Scheme 1, eq 1).[12] More recently, Masson disclosed an asymmetric cycloaddition of *N*-aryl-1-azadienes and enecarbamates catalyzed by chiral phosphoric acid (Scheme 1, eq 2).[13] Various groups have also reported the cycloaddition of *N*-sulfonyl-1-azadienes with highly electron-rich alkenes generated from the activation of aldehydes with organocatalysts, such as NHCs,[14] secondary amines,[15,16] thioureas,[17] and isothioureas.[18] It is noteworthy that all these examples involve electron-rich

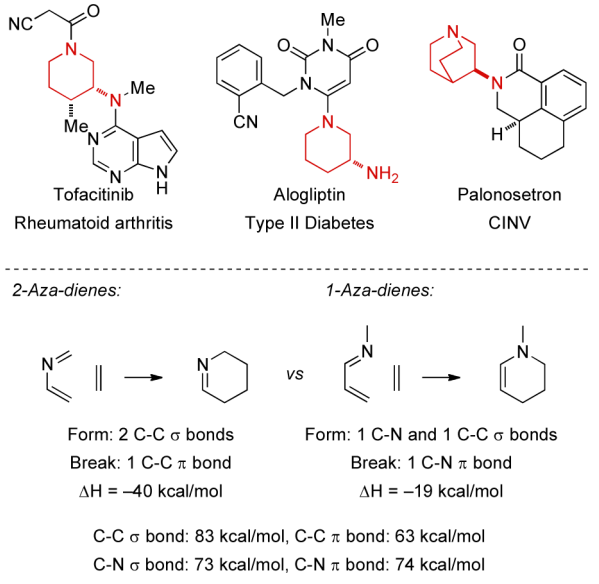


Figure 1. Examples of pharmaceuticals containing 3-aminopiperidines and a consideration of bond enthalpies.

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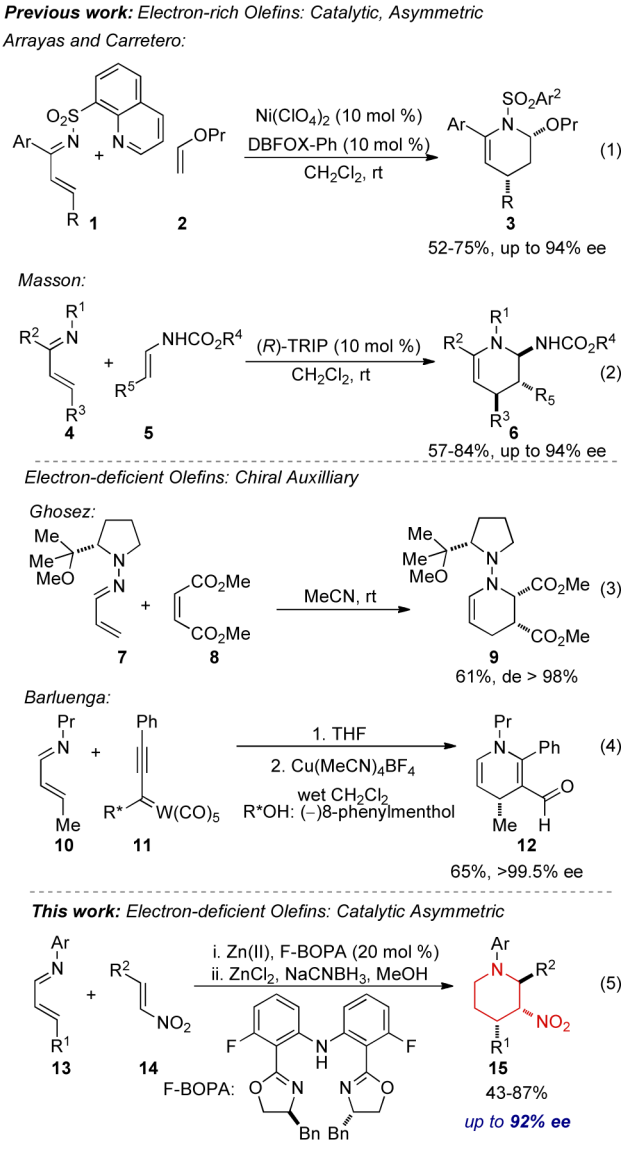
Scheme 1. 1-Azadiene [4 + 2] Cycloadditions



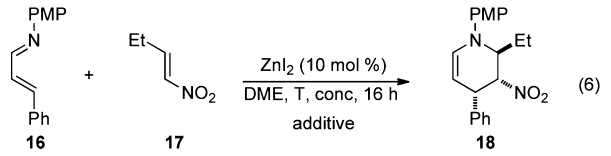
alkenes. Considering the relative electron deficiency of 1-azadienes, it can be expected that use of electron-poor alkenes as the coupling partner would be challenging if the reaction proceeds by a concerted mechanism.[19]

Current protocols for asymmetric [4 + 2] cycloadditions with 1-azadienes and electron-deficient olefins require chiral auxiliaries. Ghosez demonstrated that the cycloaddition of chiral hydrazones derived from enals with electron-deficient alkenes proceeds with excellent diasteroselectivity (Scheme 1, eq 3).[20] Barluenga reported that *N*-aryl-1-azadiene undergoes a highly diastereoselective [4 + 2] cycloaddition with a chiral tungsten alkynyl(alkoxy)carbene complex (Scheme 1, eq 4).[21] To the best of our knowledge, catalytic, asymmetric [4 + 2] cycloadditions of 1-azadienes and electron-poor alkenes have not been reported. Herein, we disclose the development of a Zn-catalyzed regio-, diastereo-, and enantioselective [4 + 2] cycloaddition of readily available 1-azadienes and nitro-alkenes (Scheme 1, eq 5).[22]

RESULTS AND DISCUSSION

Reaction Discovery. As a result of a high-throughput screen of first-row metal and Lewis acid catalysts, we identified that Zn(II) salts enable a [4 + 2] cycloaddition of 1-azadiene **16** and nitro-alkene **17** to form tetrahydropyridine **18** (Table 1, eq 6).[23] ZnI_2 is the most effective catalyst identified. Remarkably, only a single diastereomer and regioisomer of the product is obtained. The reaction does not proceed without ZnI_2. At high reaction concentration (0.3 M), no product is observed (entries 1–3). As the enamine functionality is prone to hydrolysis, we investigated the use of drying agent. The use of molecular sieves gives an improved yield of the cycloadduct relative to $MgSO_4$ (entries 4, 5). Surprisingly, the cycloaddition is highly sensitive to the number of equiv of **17**. A lower amount of **17** (1.5 equiv) leads to an improved yield relative to 2 equiv (entries 5, 6). With 2 equiv of **17**, we observe the formation of a 2:1 adduct (**17**:**18**).[24] The formation of this undesired product explains the decreased yield at higher concentration. With an even lower equiv of **17**, the reaction does not go to completion and leads to decreased yield (entry 7). At higher temperature, the yield drops significantly presumably due to further reaction of **18** with **17** (entry 8). Dioxane is found to be a better solvent than DME and provides the cycloadduct in good yield (entry 6).

Table 1. ZnI_2-Catalyzed [4 + 2] Cycloaddition of 1-Azadienes and Nitro-Alkenes To Form Tetrahydropyridines



entry	equiv **17**	T (°C)	conc (M)	additive	yield (%)[a]
1	2	50	0.05	–	12
2	2	50	0.1	–	15
3	2	50	0.3	–	0
4	2	50	0.1	$MgSO_4$	18
5	2	50	0.1	4 Å MS	28
6	1.5	50	0.1	4 Å MS	62 (78)[b]
7	1	50	0.1	4 Å MS	30
8	1.5	80	0.1	4 Å MS	27

[a]Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [b]Reaction conducted in dioxane.

Initial Screen of BOPA Ligands. An initial screen of commonly available ligands for Zn(II) resulted in low enantioselectivity.[25] Inspired by the work on Zn-catalyzed enantioselective Michael addition to nitro-styrenes by Du and co-workers, we explored the use of bis(oxazolinylphenyl)amide (BOPA ligand)[26] for rendering the cycloaddition asymmetric. We were delighted to find that BOPA **A** gives promising enantioselectivity under the reaction conditions reported by Du, although the yield is low (Scheme 2).[27,28] Ligand **B**, with a *cis*-relationship of the phenyl groups, or ligand **C**, with phenyl groups close to the oxazoline nitrogen, only provides a minor improvement in yield but not enantioselectivity. BOPAs **D** and **E**, which have significantly different steric environments, give similar yields and ee's. Gratifyingly, a much higher yield can be obtained with **F**, and its improved reactivity allows the reaction to be conducted at ambient temperature. Decreasing the temperature increases enantioselectivity with no loss in yield.

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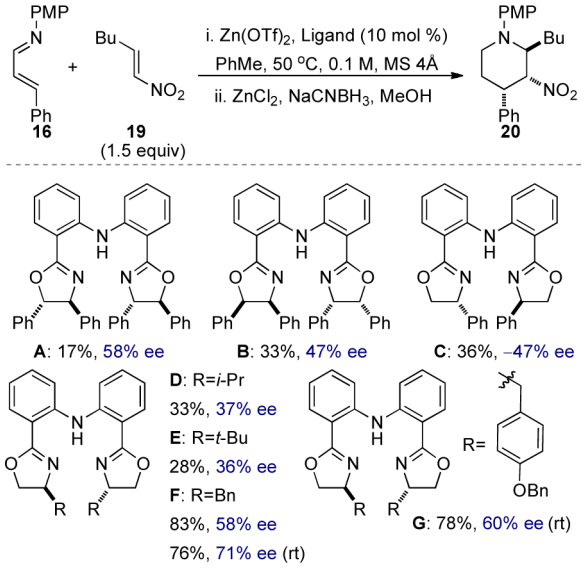
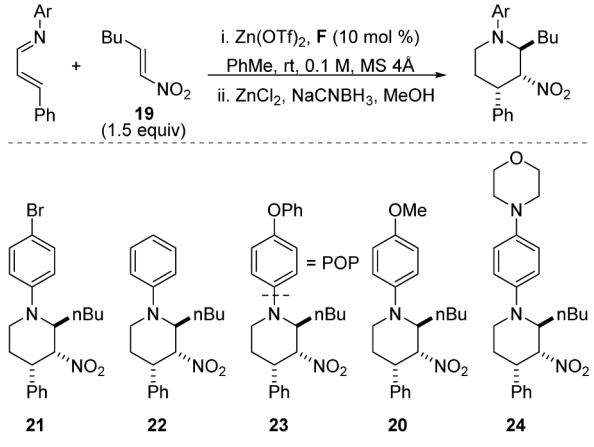
Scheme 2. Investigation of BOPA Ligands



Efforts to further enhance the enantioselectivity by lowering the temperature are unsuccessful since only a trace amount of product can be obtained at 0 °C. Modification of **F** by installation of a benzyloxy group (ligand **G**) does not improve yield and gives a slightly lower ee.

Electronic Effects of 1-Azadienes. With the hope that substrate design would improve enantioselectivity, we altered N-substituent electronics of the 1-azadienes (Scheme 3). No

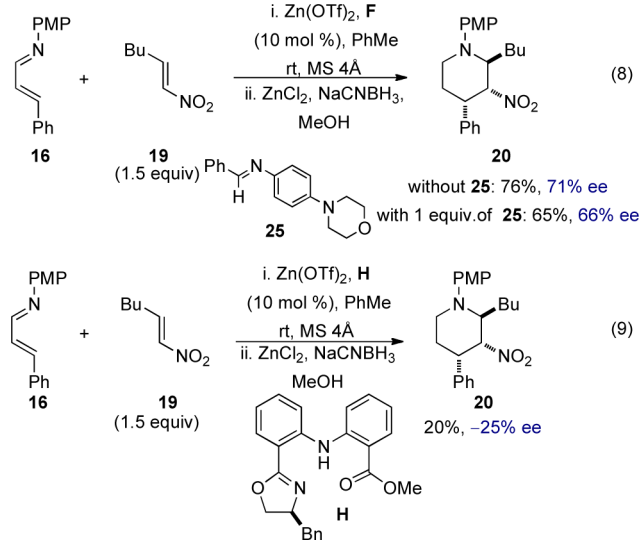
Scheme 3. Modification of 1-Azadiene Electronics



correlation between the electronics of the 1-azadienes and yield is seen. However, we do observe that ee increases as N-substituent electron density increases (**21**, **22**, **23**, and **20**). Unfortunately, addition of an electron-donating morpholine to the N-aryl substituent (**24**) provides no further increase in enantioselectivity.

Speculating that the presence of a more basic, more strongly coordinating nitrogen found in the morpholinyl azadiene was responsible for disappointing enantioselectivity found in **24**, we used spectator imine **25** to probe the effect that a competitive coordinating group had on ee. We find a small erosion of ee with the addition of imine **25** as a competitive coordinating group (Scheme 4, eq 8). Furthermore, removal of the C2

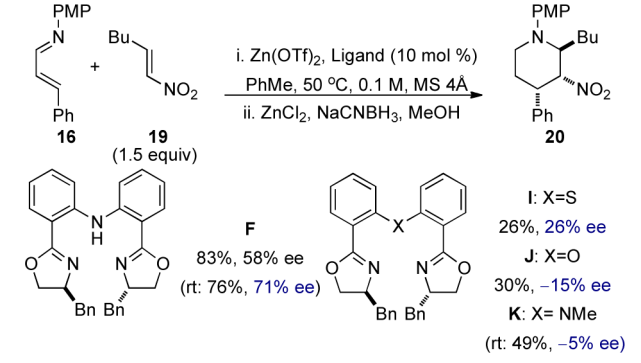
Scheme 4. Use of Spectator Imine and Mono-Oxazoline



symmetry of the BOPA ligand (mono-oxazoline **H**) gives a significant erosion of ee (Scheme 4, eq 9). Both oxazolines are necessary to achieve high levels of enantio-induction, and the selectivity is sensitive to the addition of strongly ligating imines.

Significance of BOPA N−H Bond. Eager to improve the enantioselectivity beyond what was possible with modification of 1-azadiene, we sought to understand how the structure of BOPA affects enantioinduction. Modification of the nitrogen bridging the aryls of BOPA had a surprising effect on both yield and enantioselectivity (Scheme 5). Compared to the parent

Scheme 5. Significance of N−H Bonds in BOPA Ligands



BOPA **F**, the sulfur analogue **I** gives a significant loss of enantioselectivity. Oxygen analogue **J**, despite having a similar C−X bond and C−X−C bond angle, favors the formation of the opposite enantiomer with low selectivity. Clearly, the N−H is crucial for high levels of selectivity. To assess whether the source of the enantioselectivity was the N or the H of the N−H bond, N−Me analogue **K** was synthesized and revealed to provide 5% ee, slightly favoring the opposite enantiomer. The importance of the N−H bond in achieving high ee is consistent with previously reported Zn·BOPA-catalyzed asymmetric Michael additions with nitro-alkenes.[29]

Electronic Effects of Ligands. Given the impact of the BOPA N−H bond on selectivity, we decided to study the effect of acidity of the N−H bond on enantioselectivity. Astonishingly, there seems to be no clear correlation of N−H acidity with ee (Scheme 6). Both ligands **L** and **M**, which bear less

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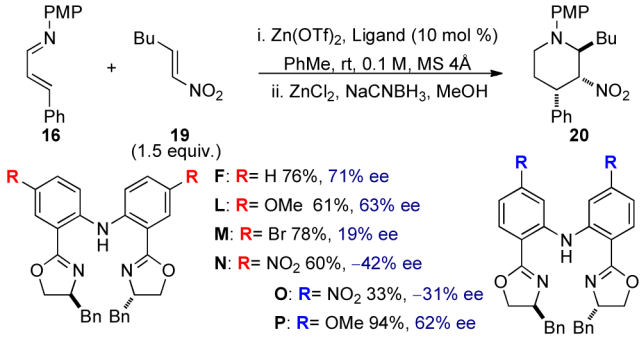
Scheme 6. Electronic Effects of Ligands on ee



acidic and more acidic N–H bonds respectively, lead to decreased ee. Therefore, we reason that the electronic effect of the ligands is due to the change in electron density of the oxazolines, instead of the N–H bonds. Indeed, the use of ligands **N** and **O**, despite having a significant difference in the acidity of the N–H bonds, gives a similar level of stereochemical control with a reversal of enantioselectivity.

A Hammett plot[31] substantiates our proposal that the electronics of the bisoxazolines, not the N–H bonds, govern the stereoselectivity since it reveals a linear relation between log (k_1/k_2) and the σ value of the substituents on the bisoxazolines (Figure 2), where k_1/k_2 is relative rate for the formation of one

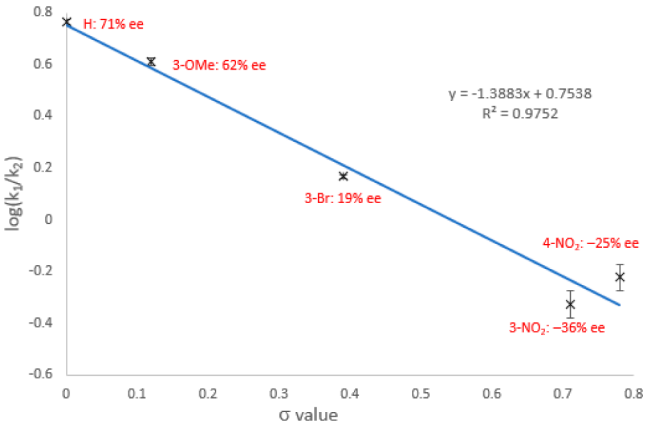
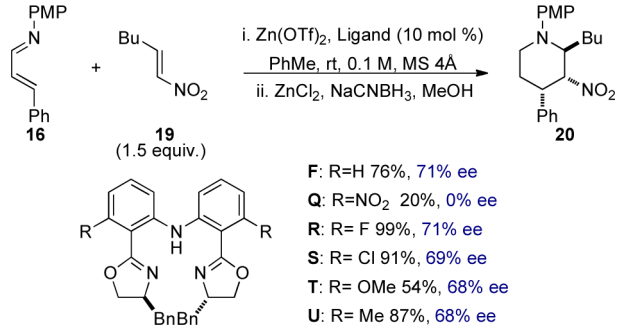


Figure 2. Hammett plot indicating linear relation between electronics of bisoxazolines and enantioselectivity.[30]

enantiomer to the other and is thus the enantiomeric ratio. The implication of the linear relation is that a higher enantioselectivity could be achieved with **P**, which bears seemingly electron-donating OMe groups in the *p*-positions. Disappointingly, **P** gives lower selectivity than H-BOPA **F** and contradicts the trend observed (Scheme 6). This irregularity can be explained by the perpendicularity of the oxazolines to the aromatic backbone for all ligands studied,[32] rendering the *p*-OMe group electron-withdrawing and thus similar to the *m*-OMe substituent.

Impact of *ortho*-Substitution on BOPA. Since our efforts to improve the enantioselectivity by rendering the bisoxazoline more electron rich were unsuccessful, we attempted to make the bisoxazoline highly electron deficient by installing strongly electron-withdrawing groups at the *o*-position of the oxazolines to favor the formation of the opposite enantiomer (Scheme 7). The use of BOPA **Q**, bearing nitro groups, leads to a much lower yield and no enantioselectivity. Presumably the bisoxazolines of **Q** are too electron deficient to coordinate zinc effectively. The reaction with fluorinated ligand **R** gives the same level of enantioselectivity as ligand **F** but with significantly higher yield; surprisingly, the enantiomer obtained is not the one predicted by the Hammett plot. Electronically different ligands **S**, **T**, and **U** give various yields but the same ee's, suggesting that the bisoxazoline electronic effect on enantioselectivity disappears with *ortho* substitution.[33]

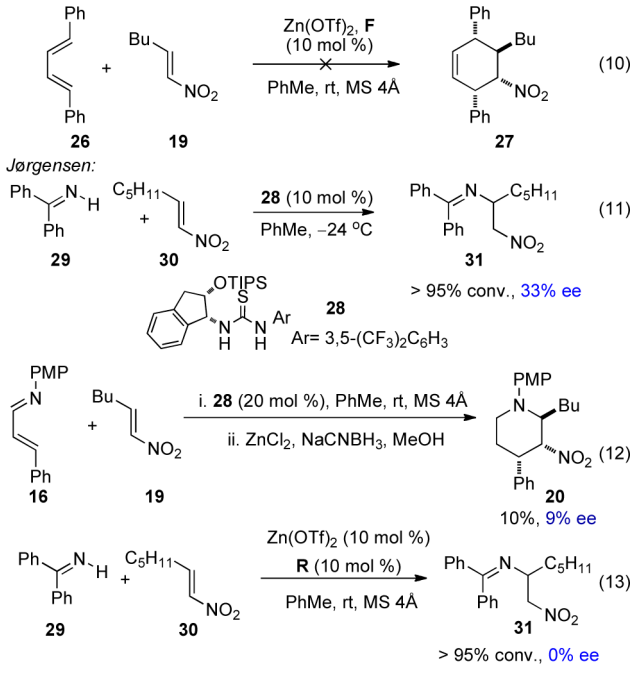
Scheme 7. Disappearing Electronic Effect with *ortho*-Substitution



Mechanistic Discussion. The cycloaddition can proceed by a concerted (Diels–Alder reaction, most likely asynchronous) or stepwise (Michael addition followed by cyclization) mechanism. We believe that the reaction occurs by a stepwise mechanism, although we cannot discount a concerted reaction mechanism.

First, to probe if a concerted mechanism is possible, we subjected 1,4-diphenylbutadiene, possessing a higher HOMO than the 1-azadiene, to the reaction conditions and observed no cycloadduct (Scheme 8, eq 10). Next, thiourea **28** is known to activate nitro-olefins for the aza-Michael addition of imines (Scheme 8, eq 11).[34] Indeed, thiourea **28** also induces the [4 + 2] cycloaddition, although the yield and ee are low (Scheme 8, eq 12), implicating that a stepwise mechanism is feasible. In

Scheme 8. Mechanistic Studies



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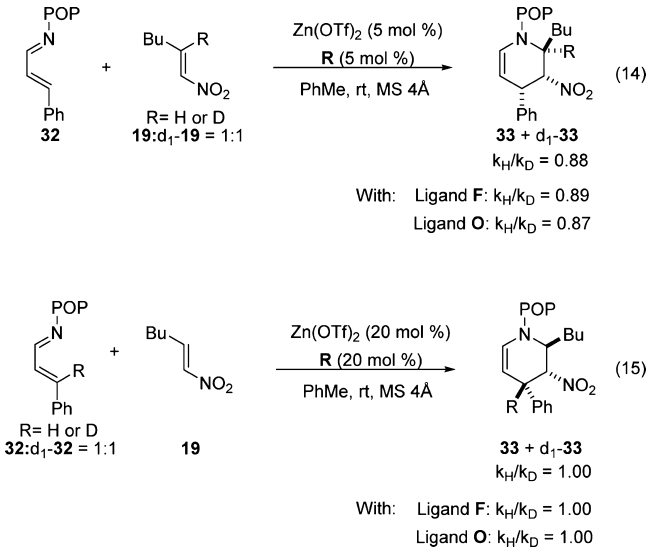
addition, we treated imine **29** with nitro-alkene **19** in the presence of the Zn·F-BOPA catalyst and found that the aza-Michael adduct is formed in excellent yield (Scheme 8, eq 13).

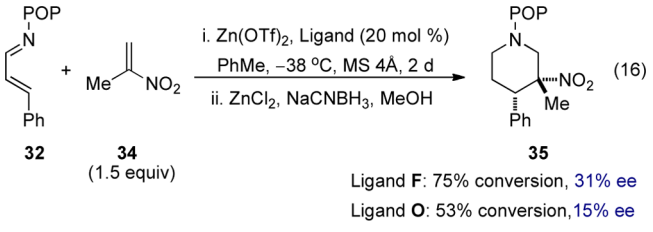
As a final test, we carried out kinetic studies with deuterated nitro-alkene **19** and 1-azadiene **32**.[35] We found that an inverse secondary kinetic isotope effect[36] was observed with **19** (Scheme 9, eq 14) but not with **32** (Scheme 9, eq 15). These results are consistent with a stepwise mechanism.

Scheme 9. Secondary Kinetic Isotope Effect



Origin of the Electronic Effect on Enantioselectivity. The change in the acidity of N−H bond is unlikely the origin of the electronic effect on enantioselectivity since ligands **N** and **O** give a similar level of stereochemical control.[37] As the ligand becomes more electron deficient, the Michael addition becomes faster and the cyclization becomes slower due to stronger Lewis acidity of Zn and more stabilized Zn nitronate, respectively. Therefore, we also considered a possible switch in enantio-determining step upon changing ligands. However, the presence of inverse secondary kinetic isotope effect with **19** but not **32** for all ligands suggests that the first step of Michael-addition is enantio-determining in all cases (Scheme 9, eqs 14 and 15). Further evidence that the establishment of the absolute stereochemistry occurs at the Michael addition is provided by the reaction with methyl nitro-ethylene **34** (Scheme 10, eq 16).[38] Since no stereogenic center is generated in Michael addition, we would expect a different major enantiomer with ligand **F** and **O** if the second cyclization step controlled the enantioinduction. In the event, low enantioselectivity is seen, and the formation of the same major enantiomer with ligands **F** and **O** from **34** suggests that

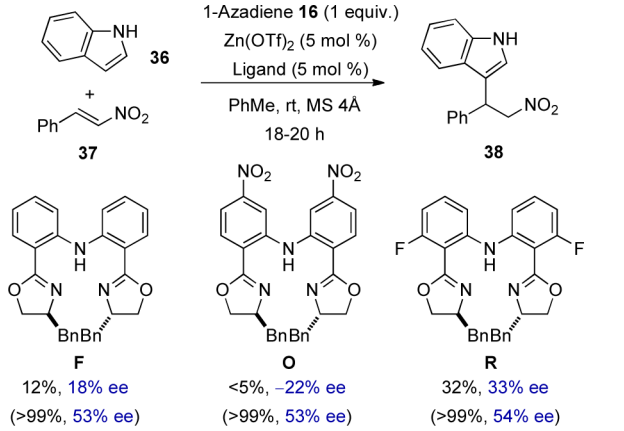
Scheme 10. Same Enantiomer from 34 with F and O



the Michael addition is responsible for controlling the degree of enantioselectivity observed with **19**.

Since the electronic effect on enantioselectivity is not present with previously reported asymmetric Michael addition of indole to nitro-alkenes,[39] a change in coordination geometry of Zn with different ligands is unlikely. On the other hand, the substrate 1-azadiene **16** could potentially coordinate to Zn, as suggested by the decreased ee in the presence of spectator imine **25** (Scheme 4, eq 8). Therefore, we hypothesize that as the bisoxazoline becomes less electron rich, 1-azadiene **16** becomes more competent to alter Zn coordination environment, leading to the observed electronic effect on enantioselectivity. In the presence of **16**, a more significant loss in yield and ee for **O** compared to **F** is consistent with this hypothesis (Scheme 11). Compared to **O**, the yield with **R** is partially

Scheme 11. Effect of Imine 16 as an Additive on Asymmetric Michael Addition[a]



[a]Yields and ee's obtained in absence of **16** in parentheses.

rescued presumably because the *ortho* substitution disfavors the coordination of imine **16** to Zn. The variation in yield and ee is caused by imine **16** since ligands **F**, **O**, and **R** induce the same level of efficiency and selectivity without imine **16**.[40]

Optimization Studies with F-BOPA (Ligand R). Consistent with our proposal that the *ortho* substitution in **R** disfavors undesired coordination of 1-azadiene to Zn, the cycloaddition with ligand **R** is more efficient than **O**, allowing the [4 + 2] cycloaddition to be conducted at lower temperatures (Table 2, eq 17). Since 1-azadiene **32** is more soluble in PhMe than **16**, it was used in the optimization. While the temperature has no effect on the yield (>90% NMR yields with 1,3,5-trimethoxybenzene as internal standard in all cases), it does affect reaction rate and enantioselectivity in that rate decreases and ee increases with decreasing temperature (Table 2, entries 1−4). We were excited to find that the cycloaddition affords piperidine **23** in excellent yield and enantioselectivity[41] at −38 °C, albeit with a long reaction time (entry 4). Increasing catalyst loading (entry 5), reaction concentration (entry 6), and the equivalents of nitro-alkene (entry 7) can be used to decrease reaction time. With 20 mol % of catalyst loading, 3 equiv of nitro-alkene[42] and a concentration of 0.18 M, reaction time can be effectively shortened to 24 h without diminishing yield or ee.

1-Azadiene Scope. With the optimized conditions in hand, we investigated the substrate scope of the reaction (Scheme 12). Regardless of the electronics of the aromatic ring on

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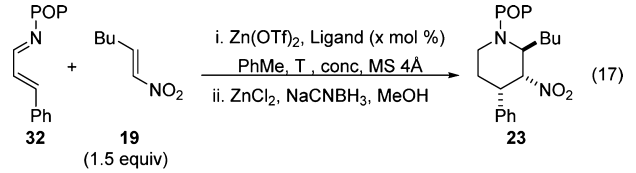
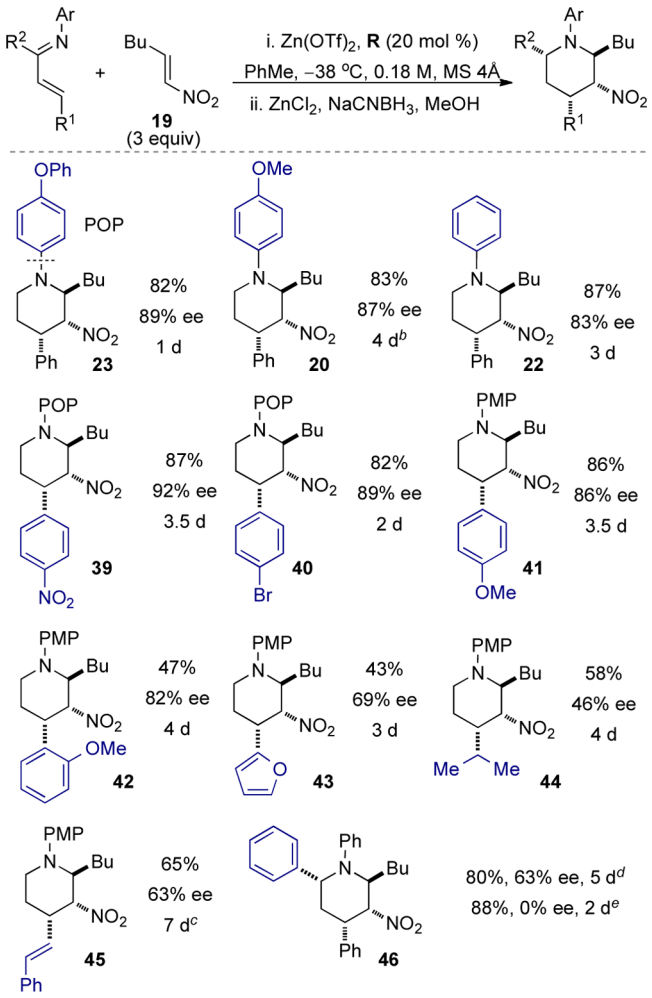
Table 2. Optimization Studies with Ligand R



entry	x	T (°C)	conc (M)	t (h)	ee (%)
1	10	rt	0.09	<24	61
2	10	3	0.09	<24	73
3	10	−18	0.09	48	78
4	10	−38	0.09	120	89
5	20	−38	0.09	72	89
6	20	−38	0.18	36	89
7	20	−38	0.18	24	89[a]

[a]3 equiv of **19**, 82% isolated yield.

Scheme 12. Scope of 1-Azadienes[a]



[a]All reported yields are isolated unless otherwise stated. [b]Reaction conducted at 0.09 M. [c]30 mol % catalyst, 5 equiv of 19. [d]30 mol % catalyst, 6 equiv of 19. [e]rt, 10 mol % catalyst, 1.5 equiv of 19, NMR yield with 1,3,5-trimethoxybenzene as internal standard.

nitrogen of the 1-azadienes, excellent isolated yields of the cycloadducts are obtained. The reaction time does not reflect the intrinsic reactivity of the 1-azadienes since they have different solubility at low temperature, affecting reaction rate. Compared to **23** bearing 4-phenoxyphenyl, both more electron-rich **20** and less electron-rich **22** are obtained with slightly lower ee's. This is consistent with our proposal that highly electron-rich 1-azadienes competitively coordinate to zinc and lead to an erosion of stereochemical control. It is noteworthy that **16** is not electron rich enough to cause a dramatic decrease in enantioselectivity at rt. This is not unreasonable because coordination of azadienes to Zn entails a higher entropic penalty at higher temperature. Different protecting groups on nitrogen are used in subsequent studies, and the one giving a higher solubility of the 1-azadiene is chosen in each case.

The electronic properties of the aryl ring at the 4-position of the 1-azadienes (**39**−**41**) also have no apparent effect on yields and ee's remain high in all cases. The enantioselectivity is higher with more electron-poor aryl groups, following the trend predicted by the potential coordination of 1-azadienes to zinc. *Ortho* substitution (**42**) is tolerated, although the reaction affords the cycloadducts in slightly lower yield and enantioselectivity. On the other hand, the reaction yielding furan-bearing **43** is sluggish and gives moderate enantioselectivity. Aliphatic enal-derived azadiene is not a competent substrate and gives the cycloadduct (**44**) in modest yield and ee. The reaction of more conjugated azatriene does not go to completion even in the presence of a large excess of the nitroalkene and more catalyst and gives the cycloadduct (**45**) in moderate yield and enantioselectivity.

The [4 + 2] cycloaddition of chalcone-derived azadiene requires a higher catalyst loading and the use of a large excess of nitro-alkenes and gives cycloadduct **46** in excellent yield but moderate enantioselectivity. When the reaction is carried out at ambient temperature, no enantioselectivity is observed.[43]

Nitro-Alkene Scope. Compared to **19**, the [4 + 2] cycloadditions of sterically more-demanding nitro-alkenes require either a longer reaction time or the use of more nitro-alkene and afford the cycloadducts (**47** and **48**) in synthetically useful yield and slightly decreased enantioselectivity (Scheme 13). An increased catalyst loading is needed for the sterically demanding isopropyl nitro-alkene, and a more drastic decrease in selectivity is observed (**49**). The silyl-protected alcohol (**50**) is tolerated and provides a handle in the cycloadduct for further functionalization. Nitro-ethylene shows reactivity under the reaction conditions, but the cycloadduct (**51**) is difficult to isolate due to its instability. α-Methyl nitro-ethylene also reacts, albeit with moderate yield and enantioselectivity (**52**). More conjugated nitro-alkenes are inert under the reaction conditions and afford no cycloadduct (**53** and **54**), although a higher electrophilicity is expected from the extended conjugation.

Utility of the Cycloadducts. The PMP or 4-phenoxyphenyl (POP) group of the cycloadducts can be easily removed by CAN to afford free secondary amine **55** (Scheme 14, eq 18). The medicinally significant structural motif 3-aminopiperidine can be obtained by the reduction of the nitro group with nickel boride[44] (Scheme 14, eq 19).

Stereochemical Model. On the basis of our mechanistic investigations noted above, we propose that the reaction proceeds in a stepwise fashion (Figure 3). The aza-diene adds to the Zn-coordinated nitro-alkene in Michael fashion, likely via its *s-trans* conformer. The relative stereochemistry is confirmed by X-ray analysis. A bond rotation then is required for the nitronate to cyclize onto the α,β-unsaturated iminium. This may proceed in clockwise fashion placing the phenyl group and the nitro on the same side of the piperidine ring (blue path) or

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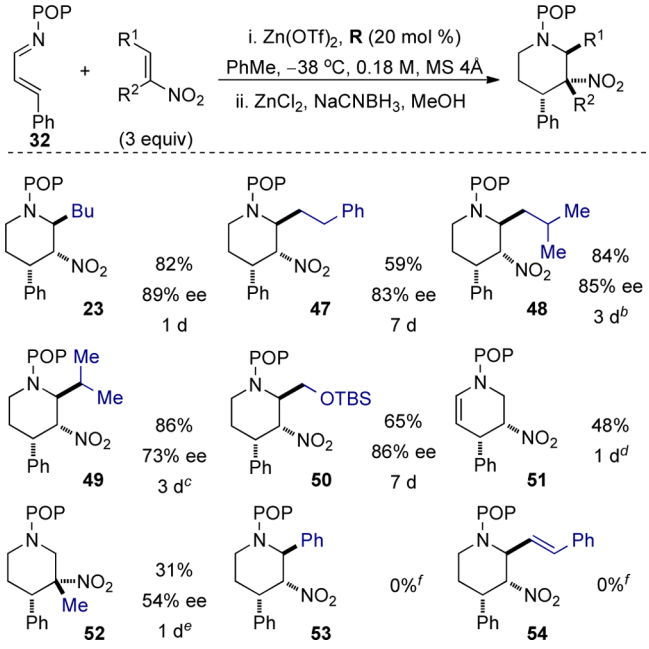
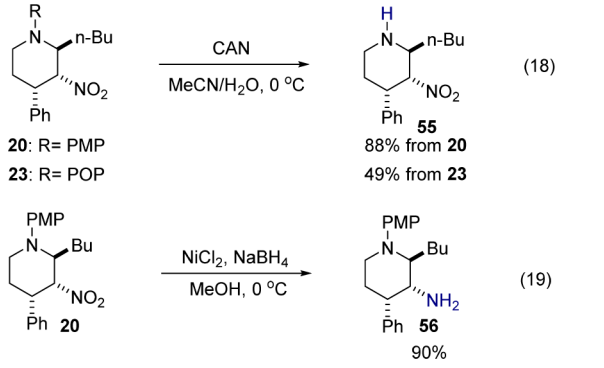
Scheme 13. Nitroalkene Scope[a]



[a]See footnote a, Scheme 12. [b]5 equiv nitro-alkene. [c]3- mol % catalyst, 6 equiv nitro-alkene. [d]NMR yield, no reductive workup, ee not determined. [e]rt, 10 mol % catalyst, 61% ee at −38 °C. [f]rt.

Scheme 14. Utility of cycloadducts



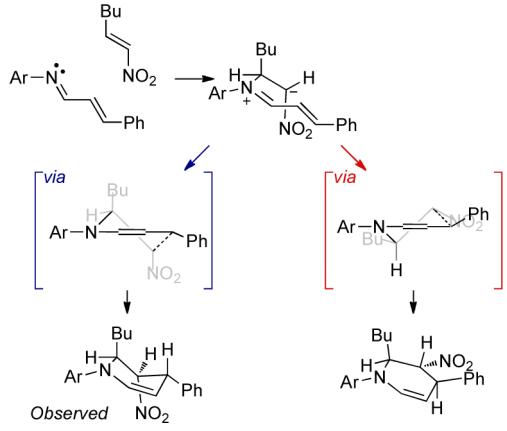


Figure 3. Proposed stepwise mechanism and diastereoselectivity model (Lewis acid not shown for clarity).

by counterclockwise rotation placing the substituents opposite. The blue path proceeds by minimalist reorganization of the intermediate and leaves the butyl group in a pseudoaxial orientation on the piperidinyl half-chair. The red path results in a conformational switch placing the butyl substituent in a pseudoequatorial position and is disfavored by reason for $A_{1,3}$-strain.

The electrostatic interaction between the nitronate and the positively charged iminium may also play a significant role since we observe the same levels of diastereoselectivity when nitroethylene is used as a substrate (Scheme 13, **51**). In addition, the *cis* relationship cannot be explained by the sterics of the nitro group, as, in the case of the cycloaddition with α methyl nitroethylene, the phenyl group is also *cis* to the nitro group (**52**). Finally, the ligand environment does not induce a *cis* relationship because this orientation also occurs with ZnI_2 in the absence of a ligand. It is noteworthy that no matter which direction this bond rotates, an *anti* relationship between the butyl group and the nitro group is expected.

CONCLUSION

We developed a catalytic enantioselective [4 + 2] cycloaddition of readily prepared 1-azadienes and nitro-alkenes. The cycloaddition requires inexpensive earth-abundant Zn as catalyst and is highly regio- and diastereoselective. Mechanistic evidence suggests that the reaction proceeds with a stepwise mechanism. An electronic effect of the bisoxazoline ligand on the enantioselectivity is observed and can be explained by the deleterious coordination of 1-azadiene to Zn. The key to achieving high enantioselecitivity of the reaction is the use of a novel fluorinated BOPA ligand, whose *ortho* substitution disfavors the undesired coordination of 1-azadienes to Zn. The utility of the cycloadducts is demonstrated by the easy reduction of the nitro group to give medicinally interesting 3-aminopiperidines.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization of all new compounds and ligands (**G**, **H**, **J**–**U**). This material is free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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