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Development of Bifunctional Aza-Bis(oxazoline) Copper Catalysts for Enantioselective Henry Reaction

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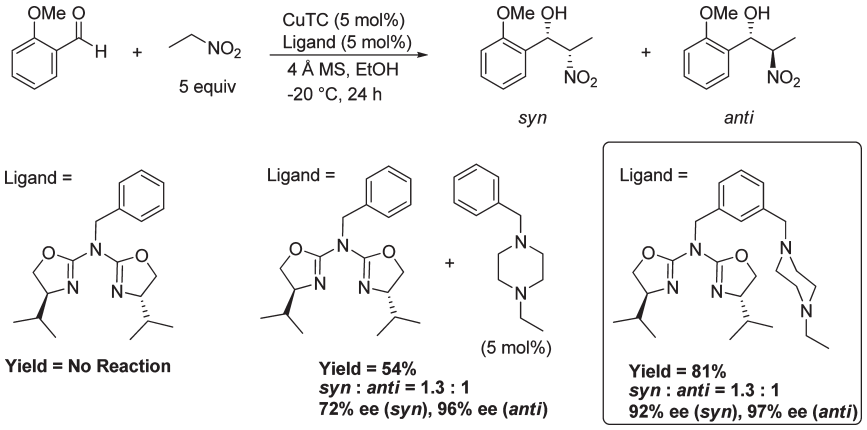

Base-functionalized aza-bis(oxazoline) ligands were prepared to explore the concept of dual activation through the Lewis acid and a tethered tertiary amine base. The catalytic activity of the Cu complex was evaluated for the asymmetric Henry reaction. Compared with a corresponding unfunctionalized copper complex with external 1-benzyl-4-ethylpiperazine base, the ethylpiperazine-functionalized aza-bis(oxazoline) copper catalyst resulted in rate acceleration (2.5 times) as well as improved enantioselectivity (72% ee vs 92% ee).

Introduction

The concept of dual activation is very attractive for developing highly efficient catalysts in asymmetric reactions.[1] Bifunctional catalysts equipped with two orthogonal functionalities can provide simultaneous activation of both reaction partners such as a nucleophile and an electrophile, resulting in high efficiency under mild conditions. In addition, higher selectivity can be achieved by placing two reactants in close proximity and fixed orientation. This dual activation is a general reaction strategy in nature, which has been evolved to achieve high efficiency and selectivity in biochemical transformations. For example, type II aldolase effectively catalyzes asymmetric aldol reactions through two active sites.[2]

Recently, there have been growing efforts to develop abiotic dual activation catalysts enabling cooperative activation of both reaction partners. Several highly stereoselective bimetallic catalysts were developed for reactions where the mechanism requires dual activation from two metal centers (Figure 1A).[3−8] Dual activation has also been achieved through bifunctional organocatalysts (Figure 1B)[9,10] or metal/base catalysts (Figure 1C).[11,12] Bifunctional organocatalysts usually consist of a proton donor such as a (thio) urea for electrophile activation and a tertiary amine for nucleophile activation. A chiral backbone bringing two substrates in well-defined alignment is usually the key for high reactivity and stereoselectivity. A similar type of cooperative activation can be achieved with Lewis acid metal centers and amines.

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For example, Lectka's bifunctional systems using In(III) in combination with cinchona alkaloid catalyzed the formation of β-lactams where the tertiary amine attacked a ketene to form an enolate nucleophile, and In(III) activated the imino ester electrophile (Figure 1C).[11a] Currently, only several successful examples of covalently bonded metal/amine catalysts have been developed and systematically studied in asymmetric catalysis,[11] because metal/base bifunctional catalysts are challenging to achieve: one difficulty is that the acid and base tend to sequester each other and lose activity.[1b]

As a part of our research program directed toward development of dinuclear/bifunctional catalysts,[7a] we envisioned a series of novel dual activation catalysts (either bimetallic or bifunctional catalysts) could be developed taking advantage of facile functionalization of the central nitrogen of the azabis(oxazoline) (aza-Box) units (Figure 2). As privileged chiral ligands,[13] bis(oxazoline) and its related structures such as pyBox and bora-Box have been well studied for a broad variety of enantioselective reactions.[14] Among these ligands, aza-Box was successfully developed by Reiser and exhibited high activity for a number of asymmetric transformations including cyclopropanation reactions, kinetic resolutions of 1,2-diols, conjugate reduction of α,β-unsaturated carbonyl compounds, and Michael additions of indole.[15] Importantly, Reiser and co-workers nicely developed recyclable catalysts by immobilizing aza-Box ligands on polymeric support or nanoparticles through alkylation of the central nitrogen.[16a−d] Recently, García and co-workers developed a new self-supported Cu coordination polymer catalyst based on a ditopic chiral ligand bearing two aza-Box units for

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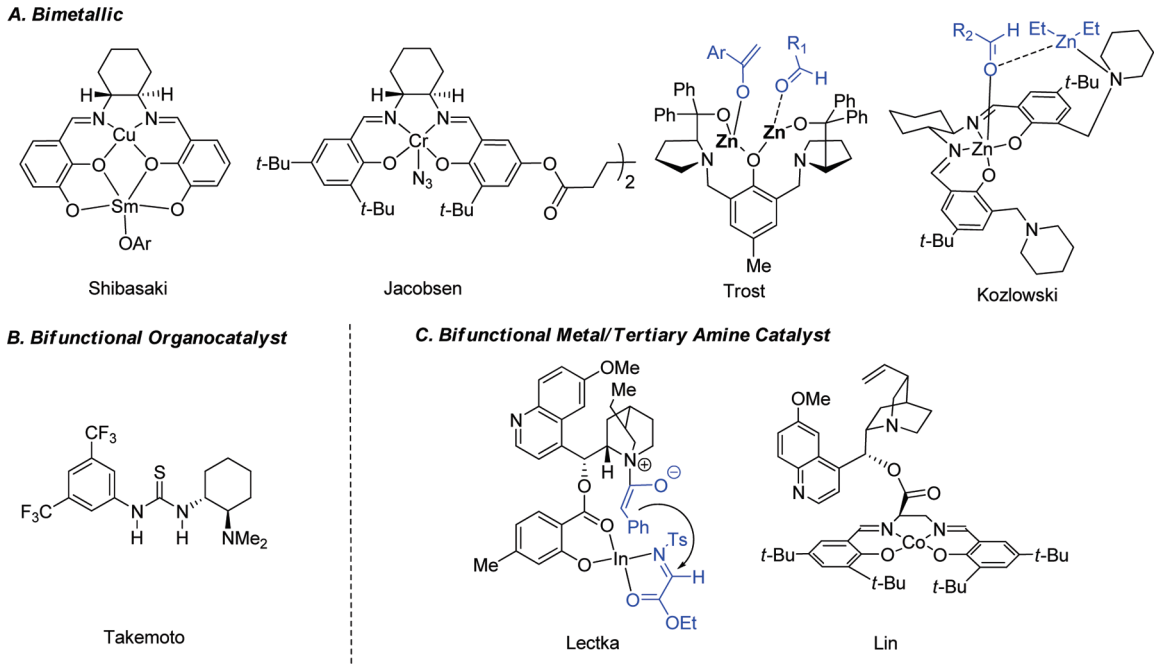

FIGURE 1. Abiotic catalysts for dual activation.

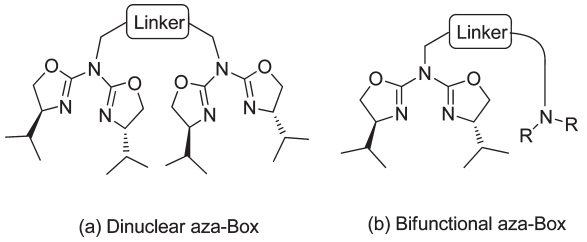

FIGURE 2. Design of dual-activation ligands with aza-bis-(oxazoline) units: (a) dinuclear aza-Box and (b) base-functionalized aza-Box.

efficient catalyst recovery and reuse.[16e] However, to the best of our knowledge, there is no example of dual activation catalysts featuring aza-Box ligands.

The asymmetric nitro-aldol (Henry) reaction[17−19] was chosen as the test reaction to evaluate new dual activation aza-Box catalysts because historically the asymmetric Henry reaction has provided a good platform for testing the dual activation of bimetallic catalysts or bifunctional organocatalysts.[3c,5c,7a,17b,18b,c,j] In addition, Box-Cu(II) catalysts have been independently reported by Evans[18a] and Jørgensen[20a−c] for highly enantioselective Henry and aza-Henry reactions, respectively. It is important to note that in both cases, the nature of the base plays a crucial role to achieve high efficiency as well as high stereoselectivity. Therefore, we anticipated that the novel functionalized aza-Box-Cu catalysts would provide improved catalytic efficiency through synergistic dual activation, compared to the known monomeric, nonfunctionalized Box-Cu catalysts.

Herein, we report the design and synthesis of base-functionalized aza-Box CuTC catalysts that exhibit good catalytic activity for the Henry reaction. Rationale behind the development of the bifunctional aza-Box ligands including kinetic/mechanistic studies and their improved catalytic behavior compared to the unfunctionalized aza-Box catalysts will be presented in detail.

Results and Discussion

1. Synthesis of Bimetallic Aza-Box and Bifunctional Aza-Box Ligands. New dinucleating aza-Box ligand **2** and tertiary amine-functionalized aza-Box ligands **4a**/**4b**/**4c** were synthesized through alkylation of the known lithium amide of **1**[15a] with α,α′-dibromo-*m*-xylene and amine-functionalized benzyl bromides **3a**/**3b**/**3c**, respectively (Scheme 1). Addition of a catalytic amount of KI (2 mol %) during the alkylation proved to be important in achieving good yields.

2. Reaction Optimization with Unfunctionalized Aza-Box. According to Evans' report,[18a] either the *i*-Pr-Box or the

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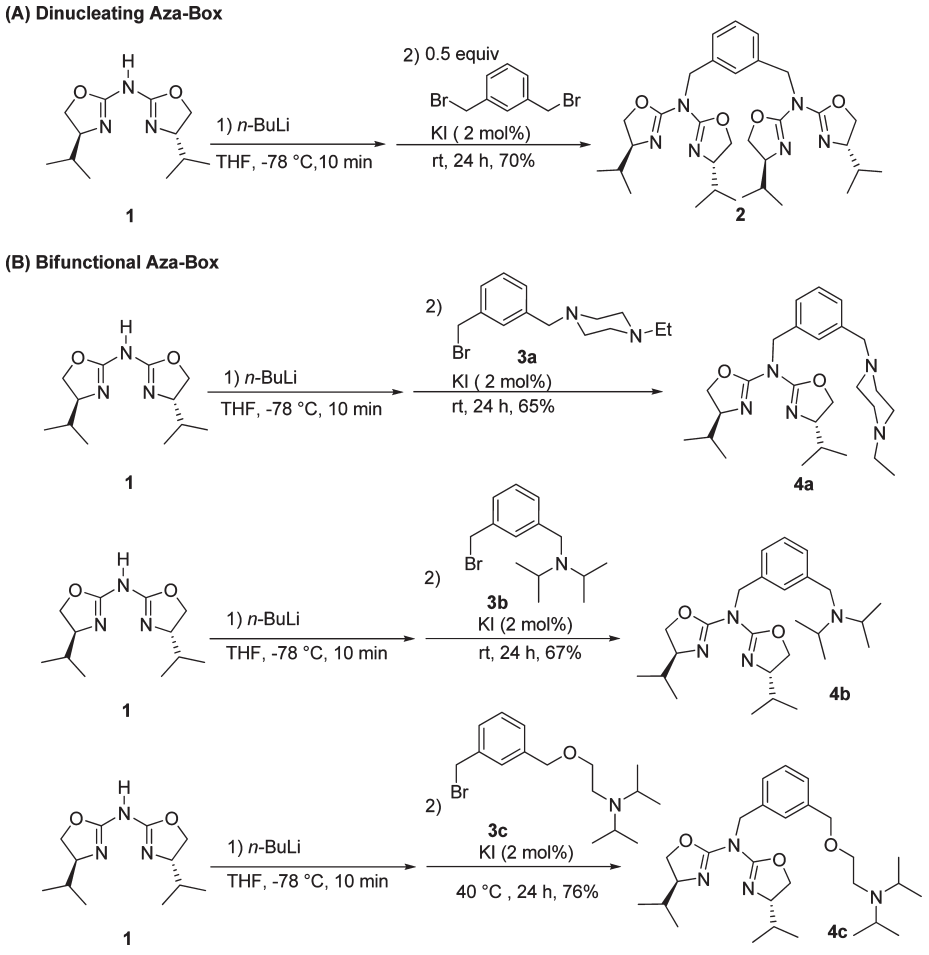
SCHEME 1. Synthesis of Dinucleating and Bifunctional Aza-Box Ligands



Inda-Box ligand with $Cu(OAc)_2 \cdot H_2O$ gave the nitro aldol product of 4-nitrobenzaldehyde in 67% ee and 74% ee, respectively (Figure 3). Changing the solvent from methanol to ethanol further improved enantioselectivity to 81% ee.

When we initiated this project, application of aza-Box ligand in asymmetric Henry reaction had not been reported.[21] Therefore, the reaction conditions needed to be optimized with respect to monomeric aza-Box ligands. We were pleased to find that *i*-Pr-aza-Box ligand **9** was effective under conditions similar to those adopted by Evans and co-workers (Table 1). Without the metal, racemic product was obtained presumably because the free ligand could act as a base (entry 1). It is interesting to note that Cu(I) precatalysts seemed to show better reactivity than Cu(II) precatalysts (entries 2−6 vs entries 7−11). The outcome of the reaction was also highly dependent on the counterion. Although $Cu(OAc)_2 \cdot H_2O$ was effective, the use of $Cu(OTf)_2$ gave no product (entry 2 vs entry 3). CuTC (TC = thiophene-2-carboxylate) with aza-Box proved to be the most promising combination, exhibiting good enantioselectivity (69% ee) and high yield (95%) after only 4 h at room temperature (entry 11). The reaction selectivity was further improved to 87% ee when the temperature was lowered to −20 °C (entry 12). At first, all the Cu(I) promoted reactions were conducted under argon atmosphere. However, it turned out that the aza-Box CuTC system gave the same reactivity and enantioselectivity if the reaction was run under aerobic conditions (entry 10 vs entry 11). Therefore, all Henry reactions were carried out under air atmosphere unless noted otherwise. Whether Cu(I) or Cu(II) is the actual reactive species in the aza-Box CuTC catalyzed system is still not clear.

However, under the conditions optimized with *p*-nitrobenzaldehyde (Table 1, entry 12), the reaction failed to proceed for the less reactive benzaldehyde. It has been reported that a tertiary amine base can facilitate the deprotonation of nitromethane and boost the catalytic activity for Lewis acid catalyzed (aza) Henry reactions, and equimolar amounts of base and Lewis acid are often used to minimize the possible background reaction from the base.[18e,20] We were also able to further improve the catalytic activity by incorporating *i*-Pr_2NEt and 4 Å molecular sieves. Thus, under the optimized conditions, the aza-Box 9 CuTC complex catalyzed the reaction between benzaldehyde **5b** and nitromethane to afford nitroaldol product **6b** in 95% yield and 92% ee at −30 °C (Table 2, entry 2). Four additional aza-Box ligands as well as the original Evans *i*-Pr-Box ligand **7**

(20) (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222–2223. (b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875–4881. (c) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362–1364. (d) Ma, K.; You, J. *Chem.—Eur. J.* **2007**, *13*, 1863–1871.

(21) Recently, Reiser and co-workers reported that the *N*-Me-*i*-Pr-aza-Box ligand with $Cu(OAc)_2$ promoted the asymmetric Henry reaction between benzaldehyde and nitromethane at room temperature in THF in 76% yield and 92% ee. See: Rasappan, R.; Olbrich, T.; Reiser, O. *Adv. Synth. Catal.* **2009**, *351*, 1961–1967.

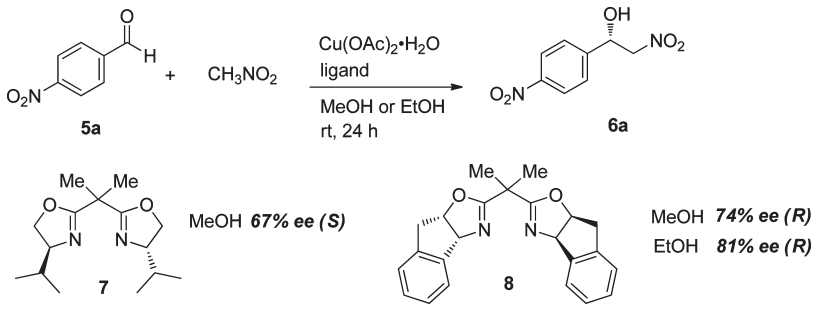
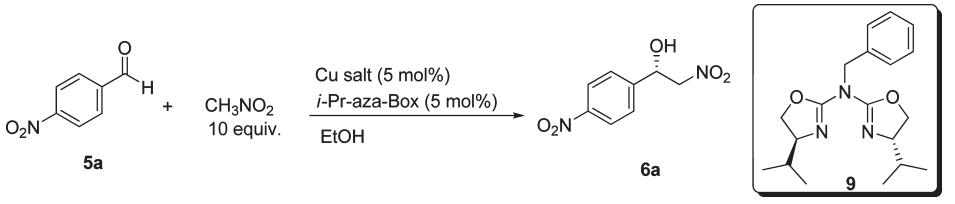


FIGURE 3. Optimized Box ligand structures from Evans' work.[18a]

TABLE 1. Cu Precursor and Reaction Temperature Optimization[a]



entry	Cu precursor	temp (°C)	time (h)	yield (%)[b]	ee (%)[c,d]
1[e]	No Cu	rt	5	90	racemic
2	$Cu(OTf)_2$	rt	48	0	
3	$Cu(OAc)_2 \cdot H_2O$	rt	16	95	75
4	$Cu(OAc)_2 \cdot H_2O$	−20	36	trace	
5	CuF_2	rt	48	69	5
6	$CuCl_2$	rt	48	0	
7[f]	CuCl	rt	5	87	59
8[f]	CuCl	0	12	87	67
9[f]	$CuBr \cdot (Me_2S)$	rt	4	99	42
10[f]	CuTC	rt	4	92	69
11	CuTC	rt	4	95	69
12	CuTC	−20	24	83	87

[a]All reactions were conducted on a 0.5 mmol scale with ligand **9** (5 mol %), copper salt (5 mol %), and nitromethane (10 equiv) in EtOH (0.75 mL). [b]Isolated yield. [c]Determined by HPLC with a Chiralpak IB column. [d]The *S* chirality of product was determined by comparison of the retention time of the literature data.[18a] [e]Ligand **9** (5 mol %) was added to the reaction mixture without adding metal salt. [f]Reaction under argon atmosphere. TC = thiophene 2-carboxylate.

were surveyed to determine the optimum aza-Box unit to be incorporated (Table 2). Under these conditions, both *i*-Pr substituted Box 7 and corresponding aza-Box 9 gave high enantioselectivity (entries 1 and 2). Increasing steric bulk from *i*-Pr substituted aza-Box 9 mainly resulted in lower yields and/or ee (entries 2 vs 3−6). C_1-symmetric substituted aza-Box ligand **13** also afforded high selectivity (93% ee); however, the reaction was significantly slower than that with C_2-symmetric *i*-Pr-aza-Box 9.

As shown in Table 3, substrate scope was briefly explored with use of optimized conditions. The reaction works for both aromatic aldehydes bearing electron-withdrawing groups and electron-donating groups. High yield (88−99%) and excellent enantioselectivity (70−97% ee) were obtained (entries 1−7). Reaction of hydrocinnamaldehyde **5h** with nitromethane also proceeded, and after 60 h, 85% yield and 90% ee were obtained (entry 8). The results with unfunctionalized aza-Box ligands served as reference points when evaluating novel bimetallic and bifunctional aza-Box systems.

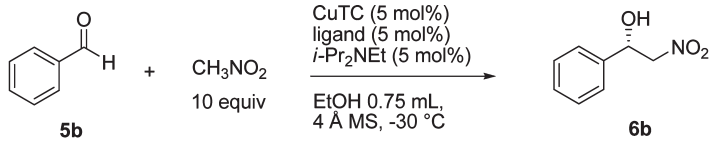
3. Designing Dual Activation Catalysts. We envisioned that simple kinetic studies could help us to rationally design bimetallic or bifunctional aza-Box ligands without random screening. Thus, kinetic studies were conducted in order to identify the nuclearity of the catalytically active species in this reaction and explore the benefits of further design of the azabox unit for dual activation catalysts.

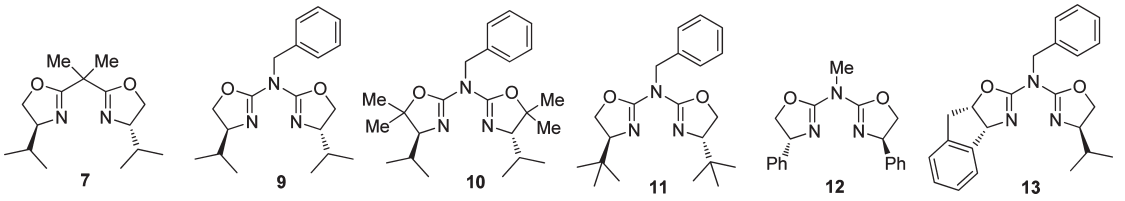
a. Reaction Order in Aza-Box-CuTC Concentration. A kinetic study of the reaction **5c** → **6c** was undertaken using HPLC by varying the catalyst concentration. Different k_{obs} values were obtained from the linear plots of $-\ln[SM]_t/[SM]_0$ versus time (h) by changing the catalyst concentration over a ~10-fold range (see the Supporting Information). A plot of k_{obs} versus precatalyst concentration indicates that the reaction is first order in aza-bis(oxazoline)-CuTC concentration (Figure 4), which implies that a monomeric aza-Box-CuTC species is involved in the transition state. Therefore, it could be predicted that the bimetallic aza-Box might not bring significant advantage over the monometallic aza-Box based on the first-order kinetic behavior.

b. Reaction Order in Tertiary Amine Base 14. Similar kinetic experiments were conducted by varying the tertiary amine base concentration. 1-Benzyl-4-ethylpiperazine **14**

(22) In the absence of Lewis acid, base **14** failed to promote the Henry reaction at −30 °C. The reaction for base kinetic study with up to 30 mol % of base gave 90−95% ee after the full conversion, which minimized the factors from racemic background reactions (rate = k_{chiral}[Cu][amine] + $k_{racemic}$[amine], where $k_{racemic}$[amine] is negligible). Also see ref 20b for further discussion on base effect.

TABLE 2. Ligand Survey[a]

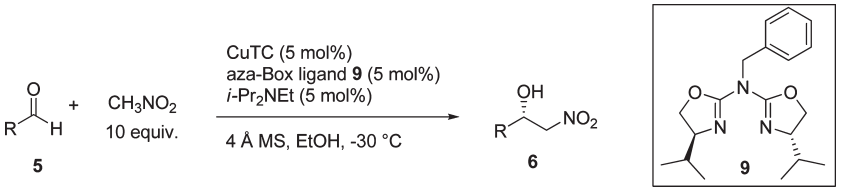


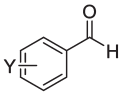
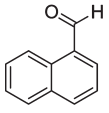
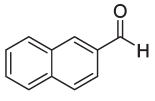
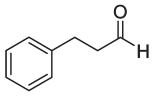


entry	ligand	time (h)	yield (%)[b]	% ee[c] (abs config)
1	**7**	36	77	93 (*S*)
2	**9**	36	95	92 (*S*)
3	**10**	36	57	74 (*S*)
4	**11**	48	12	73 (*S*)
5	**12**	48	56	89 (*R*)
6	**13**	48	41	93 (*R*)

[a]All reactions were performed on a 0.5 mmol scale with CuTC (5 mol %), *i*-Pr_2NEt (5 mol %), ligand (5 mol %), nitromethane (10 equiv), and 100 mg of 4 Å molecular sieves in EtOH (0.75 mL). [b]Isolated yield. [c]Determined by HPLC with a Chiralpak IB column.

TABLE 3. Reaction Scope[a]



entry	substrate		time (h)	yield (%)[b]	ee (%)[c]
1		**5a** Y = 4- NO_2	16	99	70
2		**5b** Y = H	36	95	92
3		**5c** Y = 4-F	24	99	94
4		**5d** Y = 4-MeO	36	88	96
5		**5e** Y = 2-MeO	20	95	97
6		**5f**	24	95	93
7		**5g**	24	91	90
8		**5h**	60	85	90

[a]All reactions were conducted on a 0.5 mmol scale with the monomeric ligand **9** (5 mol %), CuTC (5 mol %), nitromethane (10 equiv), *i*-Pr_2NEt (5 mol %), and 100 mg of 4 Å molecular sieves. [b]Isolated yield. [c]Determined by HPLC with a Chiralpak IA or IB column.

was chosen for the kinetic study because 1-ethylpiperazine can be easily incorporated into the design of catalyst **4a** (Figure 5).[22] With use of the same protocol as when studying the aza-Box-CuTC system, k_{obs} values were obtained. To see if the base-promoted racemic reaction contributed to k_{obs}, the reactions were worked up after 24 h. No dramatic ee drop

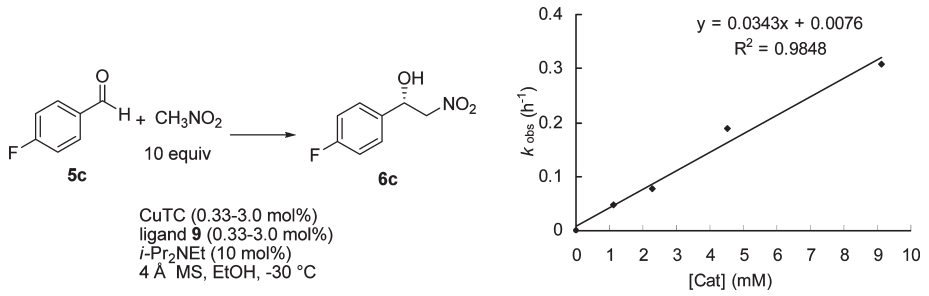


FIGURE 4. Determination of reaction order in aza-Box Cu concentration for the Henry reaction.

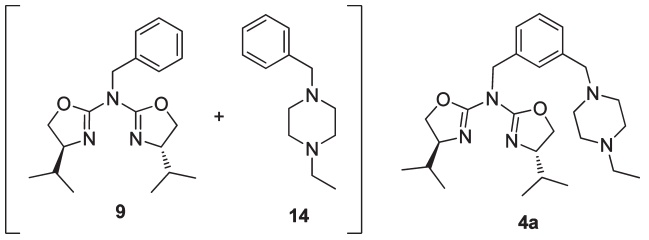


FIGURE 5. Design of bifunctional aza-Box ligand **4a** by tethering 1-benzyl-4-ethylpiperazine **14** to the aza-Box core.

was observed for up to 30 mol % loading of base, which is very different from Jørgensen and You's systems where an excess amount of base impacts the enantioselectivity.[20b,d] The plot of k_{obs} versus concentration of **14** indicates that the reaction is first order in tertiary amine concentration (Figure 6). This result implies that tertiary amine **14** is involved in the rate-determining step, and that it might be possible to further increase the reaction rate if the amine is properly tethered to the aza-Box ligand.

c. Dual Activation Catalyst. The reaction exhibits first-order dependence on both tertiary amine and aza-Box-Cu, which indicates that the rate determining transition state contains one metal center (Lewis acid) and tertiary amine. This suggests that covalently linked metal/tertiary amine catalysts such as **4a** might exhibit better performance due to a proximity effect. It also predicts that a dinuclear aza-Box such as **2** might not be more advantageous than the mononuclear aza-Box. To test this hypothesis, both dinucleating ligand **2** and bifunctional ligand **4a** were evaluated in the asymmetric Henry reaction, to make a comparison to corresponding unfunctionalized, monomeric aza-Box 9.

Dinucleating ligand **2** shows virtually no difference in the asymmetric Henry reaction when compared to monomeric ligand **9** (Tables 4 and 5). Under these conditions, both ligands showed very similar reaction rates and stereoselectivities, which is consistent with the rate law (rate = k[catalyst]^1). Note that both mono- and bimetallic systems catalyzed the sluggish nitroethane Henry reactions with high efficiency at −20 °C (Table 5). In addition, the stoichiometry of nitroethane could be reduced from 10 to 5 equiv while maintaining the same yield and selectivities (Table 5, entries 1, 3, 5, 7 vs entries 2, 4, 6, 8).

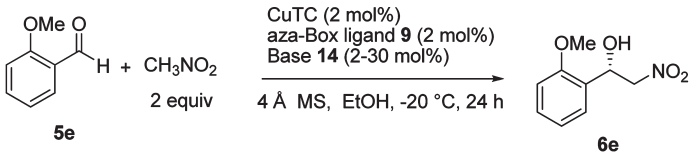
In contrast, "bifunctional", amine-tethered aza-Box ligand **4a** exhibited rate acceleration (Figure 7). k_{obs} for bifunctional ligand **4a** is 2.5 times greater than that of the unfunctionalized ligand **9** with external base additive **14**. Although its magnitude is rather moderate, the rate acceleration can be attributed to the fact that **4a** might allow a higher local concentration of amine around the copper center.

New bifunctional aza-Box-CuTC (**4a-CuTC**) is an efficient catalyst for enantioselective Henry reactions (Table 6). Good yield (80−99%) and excellent enantioselectivity (90−95% ee) were obtained for various aldehydes. Control experiments revealed that the combination of unfunctionalized ligand **9** with base **14** gave lower yield under the identical reaction conditions, which is in accord with aforementioned kinetic study results (Table 6, entries 2, 4, 6 vs entries 1, 3, 5). However, it is worthwhile mentioning that base **14** may not be the optimal base additive for this reaction, as the catalytic system consisting of **9-CuTC** with i-Pr$_2$NEt shown in Table 3 is more efficient than the combination of **9-CuTC** with **14** under the same conditions (Table 3, entries 3, 5, 6 vs Table 6, entries 2, 4, 6).

Aforementioned results suggest that more efficient bifunctional catalyst systems can be constructed if the optimal base (i-Pr$_2$NEt) is properly incorporated into the aza-Box scaffold. In this regard, two bifunctional catalysts (**4b** and **4c**) were prepared (Scheme 1), varying the length of the tether linking diisopropylamine functionality to the aza-Box core. When tested in enantioselective Henry reactions (Table 7), DIPEA-bifunctional catalyst **4c** gave high yield (85−99%) and excellent enantioselectivity (mostly 90−97% ee). It is interesting to note that bifunctional catalyst **4c** featuring diisopropylamine moiety is more efficient than **4a** including ethylpiperazine moiety, in parallel to the trends with base additive studies (Table 7 vs Table 6). However, compared to the combination of **9-CuTC** and external base i-Pr$_2$NEt, bifunctional catalyst **4c** does not show clear advantage as both catalytic systems give very similar results (Table 7, entries 1, 3, 5, 7, 9, 11, 13, 15 vs entries 2, 4, 6, 8, 10, 12, 14, 16). The relatively rigid, confined geometry resulting from the piperazine ring structure in **4a** (vs the flexible linker portion in **4c**) might be one of the key elements essential for bifunctional rate acceleration. Introduction of the more rigid tether linking diisopropylamine unit to the aza-Box core would be interesting to probe this hypothesis.

The results in diastereoselective nitro-aldol reactions with nitroethane nicely demonstrate the unique feature of the new bifunctional aza-Box catalyst (Table 8). The aza-Box Cu catalyst without the tertiary amine base additive did not catalyze the diastereoselective nitro-aldol reaction at −20 °C (Table 8, entry 1). Adding tertiary amine additive **14** into the reaction mixture turned out to be pivotal to generate the

(23) Two equivalents of nitromethane were used to get more precise kinetic data: First, the slower reaction rate with reduced amount of nitromethane provided more data points in reaction monitoring by HPLC. Second, use of 2 equiv of nitromethane also facilitates the peak separation in HPLC. With 10 equiv of nitromethane, the large nitromethane peak tends to overlap with the 2-methoxy benzaldehyde peak.



entry	base (mol %)	yield (%)	ee (%)
1	2	56	95
2	5	76	93
3	10	86	90
4	15	87	93
5	30	85	90

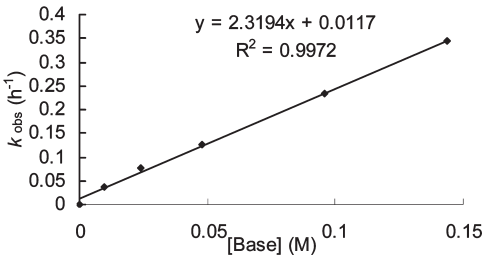
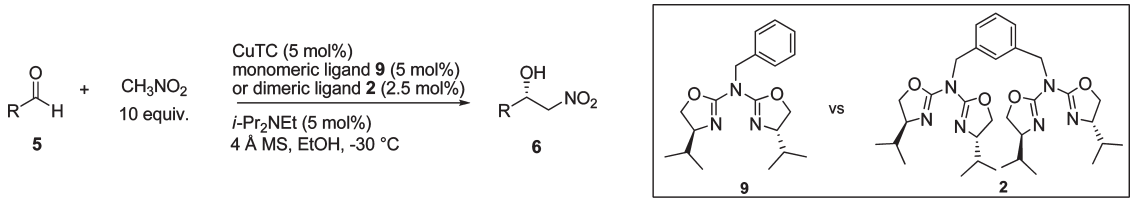
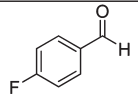
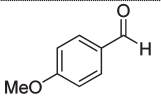
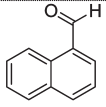
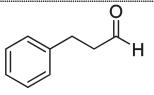


FIGURE 6. Determination of reaction order in tertiary amine concentration.[23]

TABLE 4. Enantioselective Henry Reaction (Mononuclear vs Dinuclear Catalyst)[a]

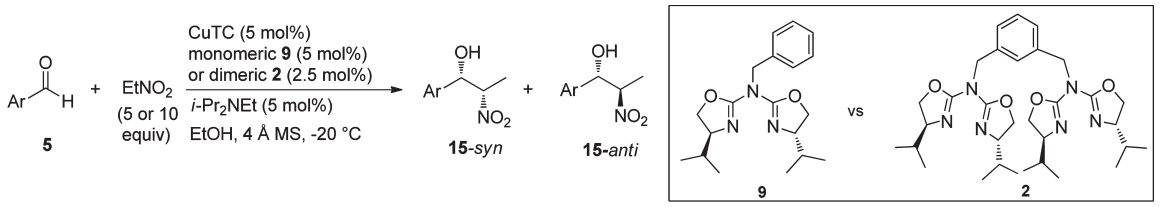


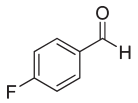
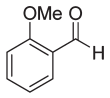
entry	substrate		ligand	time (h)	yield (%)[b]	ee (%)[c]
1		**5c**	**9**	24	99	94
2			**2**	24	99	94
3		**5d**	**9**	36	88	96
4			**2**	36	90	95
5		**5f**	**9**	24	95	93
6			**2**	24	95	94
7		**5h**	**9**	60	85	90
8			**2**	60	83	91

[a]All reactions were conducted on a 0.5 mmol scale with monomeric ligand **9** (5 mol %) or dimeric ligand **2** (2.5 mol %), CuTC (5 mol %), nitromethane (10 equiv), *i*-Pr_2NEt (5 mol %), and 100 mg of 4 Å molecular sieves. [b]Isolated yield. [c]Determined by HPLC with a Chiralpak IA or IB column.

nitroaldol products in 54% yield, although moderate 72% ee was observed for the major *syn* adduct (entry 2). Interestingly, the use of bifunctional aza-Box ligand **4a** resulted in higher yield (81%) and ee (92% ee for *syn*, 97% ee for *anti*: entry 3). Note that identity of tertiary amine base, the tether length, and tether rigidity play important roles. Thus, when the diisopropylamine is tethered to the aza-Box by a shorter linker such as **4b**, much slower reaction rate (27% yield after 144 h) as well as lower enantioselectivity (80% ee for *syn*) were obtained (entry 4). Because the diisopropylamine moiety in **4b** cannot reach the Cu metal center due to the geometrical constraint, this observation suggests that the tertiary amine site should be in close proximity to the Lewis acidic copper metal center to improve reaction rate and enantioselectivity. In contrast, when the diisopropylamine unit is linked to the aza-Box through a longer and more flexible linker as in **4c**, higher yield (99%) and ee (92% ee for *syn*, 96% ee for *anti*: entry 5) were obtained. This implies that the tertiary amine might be important not only for generating the nitronate anion through deprotonation, but also for the possible stabilization of the resulting nitronate anion that can coordinate to the Cu metal center (Figure 8). The plausible transition state model depicted in Figure 8 based on a working model proposed by Evans and Jørgensen is also consistent with the aforementioned observations: (1) k_{obs} is first order with respect to both Cu and amine concentration, (2) bifunctional aza-Box-Cu (**4a-CuTC**) catalyzed the Henry reaction 2.5 times faster than that catalyzed by unfunctionalized aza-Box-Cu (**9-CuTC**) and external base **14**, and (3) bifunctional aza-Box 4b4 featuring a shorter tether exhibited

TABLE 5. Diastereoselective Henry Reaction (Mononuclear vs Dinuclear Catalyst)[a]



entry	substrate	$EtNO_2$ (equiv.)	ligand	time (h)	yield (%)[b]	*syn*:*anti*[c]	ee (*syn*) (%)[d,e]	ee (*anti*) (%)[d]
1		**5**	**9**	48	94	1.9:1	83	67
2		**10**	**9**	48	99	1.9:1	83	66
3		**5**	**2**	48	95	3.1:1	91	68
4	**5c**	**10**	**2**	48	97	2.3:1	91	68
5		**5**	**9**	24	96	1.6:1	94	95
6		**10**	**9**	24	97	1.4:1	94	93
7		**5**	**2**	24	96	1.6:1	94	97
8	**5e**	**10**	**2**	24	99	1.4:1	94	97

[a]All reactions were conducted on a 0.5 mmol scale with monomeric ligand **9** (5 mol %) or dimeric ligand **2** (2.5 mol %), CuTC (5 mol %), nitroethane (5 or 10 equiv), *i*-Pr_2NEt (5 mol %), and 100 mg of 4 Å molecular sieves. [b]Isolated yield. [c]Determined by ^1H NMR analysis. [d]Determined by HPLC with a (*S*,*S*) Whelk-O1 column. [e]Absolute configuration of the major *syn* isomer was determined to be (1*S*,2*S*) by comparison of the retention time of literature data (see the Supporting Information).

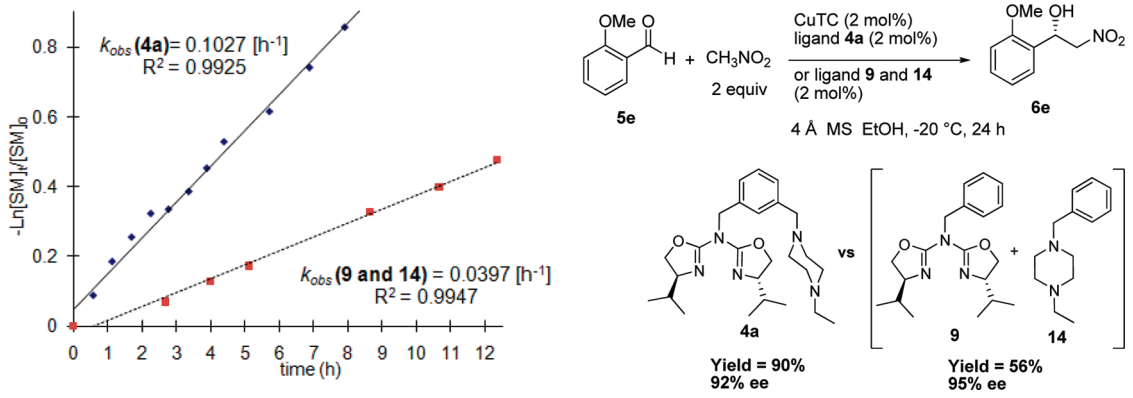


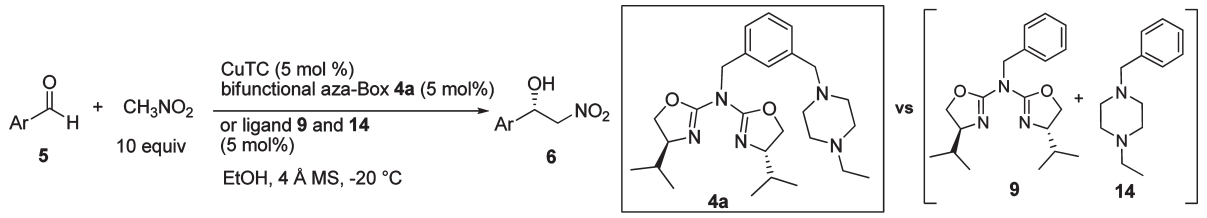
FIGURE 7. Kinetic plots of **4a** versus **9** and **14**.

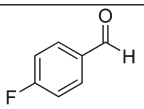
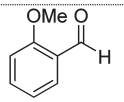
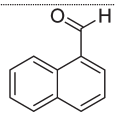
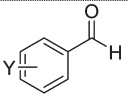
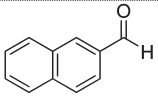
a much slower reaction rate compared to unfunctionalized aza-Box-Cu (**9-CuTC**) and external base **14**, whereas bifunctional aza-Box 4c4 featuring a longer tether exhibited a fast reaction rate and high enantioselectivity. However, **4c-CuTC** did not provide much advantage over the combination of **9-CuTC** with external base *i*-Pr_2NEt (Table 8, entry 5 vs entry 6). Presumably, the flexible linker in **4c** may not provide enough system rigidity to hold two reaction centers in close proximity. Development of new bifunctional catalysts featuring both the diisopropylamine unit and a relatively rigid tether would be highly desirable based on this study.

Conclusion

In conclusion, base-functionalized aza-bis(oxazoline) ligands were prepared to explore the concept of dual activation in the Cu-catalyzed asymmetric Henry reaction. Kinetic studies indicated that the reaction is first order in Cu concentration and tertiary amine additive concentration, which steered our research into the development of tertiary amine tethered aza-Box ligands. The ethylpiperazine-functionalized aza-Box copper catalyst (**4a-CuTC**) resulted in rate acceleration (2.5 times) as well as improved enantioselectivity (72% ee vs 92% ee) compared to the corresponding unfunctionalized aza-Box copper catalyst with external 1-benzyl-4-ethylpiperazine base (**9-CuTC** and **14**). The identity of tertiary amine base and the tether length were also found to be very important for good reaction rates and stereoselectivities. Thus, the diisopropylamine-functionalized aza-Box copper catalyst featuring a flexible linker (**4c-CuTC**) showed the best performance among three bifunctional catalysts tested in asymmetric nitroethane Henry reactions

TABLE 6. Enantioselective Henry Reaction (Bifunctional 4a-CuTC vs 9-CuTC and 14)[a]



entry	ligand & base	substrate	time (h)	yield (%)[b]	ee (%)[c]
1	**4a**	 **5c**	36	81	93
2	**9 & 14**		36	61	90
3	**4a**	 **5e**	16	99	92
4	**9 & 14**		24	78	95
5	**4a**	 **5f**	24	83	90
6	**9 & 14**		24	48	91
7	**4a**	 **5i** Y = 2-F	24	86	93
8	**4a**	**5d** Y = 4-MeO	36	80	95
9	**4a**	**5j** Y = 2-Cl	24	88	95
10	**4a**	 **5g**	36	86	93

[a]All reactions were conducted on a 0.5 mmol scale with base-attached ligand **4a** (5 mol %), or ligand **9** with **14** (5 mol % each), CuTC (5 mol %), nitromethane (10 equiv), and 100 mg of 4 Å molecular sieves. [b]Isolated yield. [c]Determined by HPLC with a Chiralpak IB or (*S*,*S*) Whelk-O1 column.

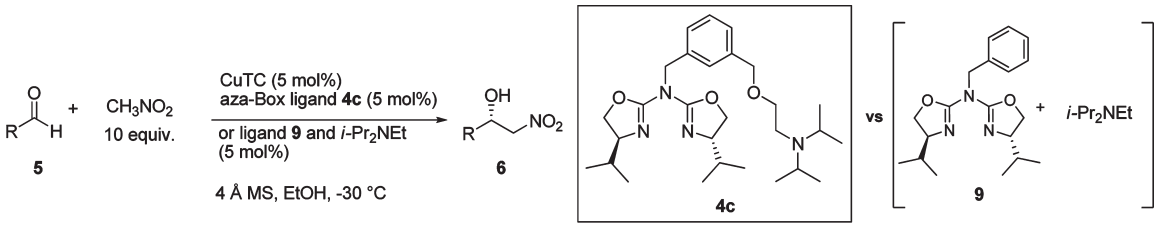
(99% yield, *syn*:*anti* = 1.5:1, 92% ee for *syn*, 96% ee for *anti*). However, bifunctional ligand **4c** does not provide much advantage over the combination of unfunctionalized ligand **9** with *i*-Pr_2NEt additive, implying that development of bifunctional aza-Box ligand featuring both diisopropylamine unit and a more confined tether would be highly desirable. Research efforts toward the design and synthesis of such base-tethered bifunctional aza-Box ligands are underway in our laboratory.

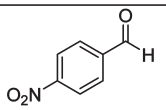
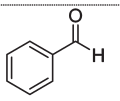
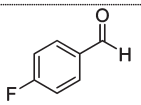
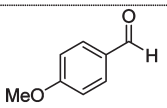
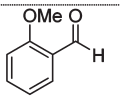
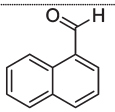
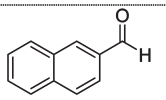
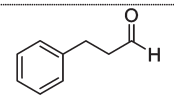
Experimental Section

General Procedure for the Enantioselective Henry Reaction. To a 3.0 mL vial were added CuTC (5.0 mg, 0.025 mmol), 500 μL of ligand in CH_2Cl_2 (0.05 M for ligand **9**, 0.025 M for dimeric ligand **2**), and EtOH (750 μL). The mixture was stirred at −30 °C under air atmosphere for 1.5 h until the solution became deep blue. Then, 100 mg of 4 Å molecular sieves and CH_3NO_2 (270 μL, 5.0 mmol) were added to this mixture. DIPEA or base **14** (25 μL, 1 M in EtOH, 0.025 mmol) was added. Then the mixture was stirred at −30 °C for another 30 min. After that, aldehyde **5e** (0.5 mmol) was added and the mixture was stirred at −30 °C for 20−24 h. The reaction mixture was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc 15:1 then 3:1) to give the nitroaldol adduct **6e** as a colorless oil (94 mg, 95% yield, 97% ee). For those **4c-Cu**-catalyzed reactions, the procedure was the same except that no external base was necessary. For those **4a-Cu**-catalyzed reactions, the procedure was the same except that no external base was necessary and the reaction temperature was maintained at −20 °C. **6e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J = 7.6, 1.7 Hz, 1 H), 7.33 (td, J = 7.9, 1.7 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 6.91 (d, J = 8.2 Hz, 1 H), 5.55−5.69 (m, 1 H), 4.64 (dd, J = 13.0, 3.4 Hz, 1 H), 4.56 (dd, J = 13.0, 9.1 Hz, 1 H), 3.88 (s, 3 H), 3.20 ppm (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 130.0, 127.4, 126.1, 121.4, 110.7, 80.1, 68.0, 55.6 ppm; HRMS (GC−CI) calcd for $C_9H_{11}NO_4$ $[M]^+$ 197.0688, found 197.0688; enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-hexane/*i*-PrOH 90:10, 1 mL/min, 215 nm); minor t_r = 9.9 min; major t_r = 10.9 min; 97% ee. The absolute configuration of the major isomer of **6e** was determined to be (*S*) by comparison of the retention time with the literature data.[18a]

Procedure for Dimeric Ligand 2 Preparation. To a 10 mL flame-dried Schlenk flask were added *i*-Pr aza-bis(oxazoline) **1** (4.0 mL, 0.5 M in THF, 2.0 mmol) and KI (5 mg). Under argon atmosphere, anhydrous THF (12.0 mL) was added and the reaction mixture was cooled to −78 °C for 10 min. Then *n*-BuLi (880 μL, 2.5 M in *n*-hexane, 2.2 mmol) was slowly added into the reaction flask and the reaction mixture was kept at −78 °C for another 10 min. 1,3-Bis(bromomethyl)benzene (253 mg, 0.96 mmol) in THF (4.0 mL) was slowly added into the reaction flask at −78 °C. The cold bath was removed and the flask was warmed slowly to room temperature. Reaction proceeded for another 14 h at this temperature. Loading all the reaction mixture into a short column (1.0 cm diameter, 5.0 cm height of basic alumina, 60−325 Mesh) and flushing by *n*-hexane/EtOAc 3:1 gave **2** as a yellow oil (406 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$)

TABLE 7. Enantioselective Henry Reaction (Bifunctional 4c-CuTC vs 9-CuTC and *i*-Pr_2NEt)[a]



entry	ligand & base	substrate		time (h)	yield (%)[b]	ee (%)[c]
1	**4c**		**5a**	16	99	70
2	**9** & *i*-Pr_2NEt			16	99	70
3	**4c**		**5b**	24	95	93
4	**9** & *i*-Pr_2NEt			36	95	92
5	**4c**		**5c**	24	99	91
6	**9** & *i*-Pr_2NEt			24	99	94
7	**4c**		**5d**	36	85	93
8	**9** & *i*-Pr_2NEt			36	88	96
9	**4c**		**5e**	16	99	97
10	**9** & *i*-Pr_2NEt			20	95	97
11	**4c**		**5f**	24	93	93
12	**9** & *i*-Pr_2NEt			24	95	93
13	**4c**		**5g**	24	94	92
14	**9** & *i*-Pr_2NEt			24	91	90
15	**4c**		**5h**	60	87	90
16	**9** & *i*-Pr_2NEt			60	85	90

[a]All reactions were conducted on a 0.5 mmol scale with the monomeric ligand **4c** (5 mol %), or ligand **9** (5 mol %) with *i*-Pr_2NEt (5 mol %), CuTC (5 mol %), nitromethane (10 equiv), and 100 mg of 4 Å molecular sieves. [b]Isolated yield. [c]Determined by HPLC with a Chiralpak IA or IB column.

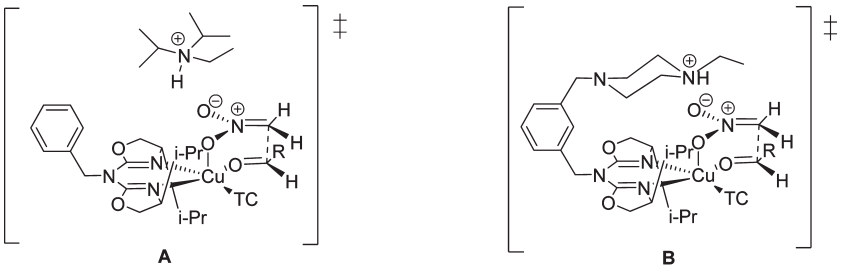
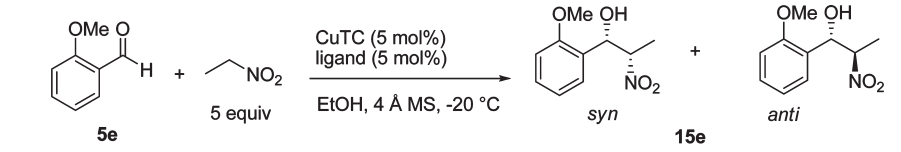
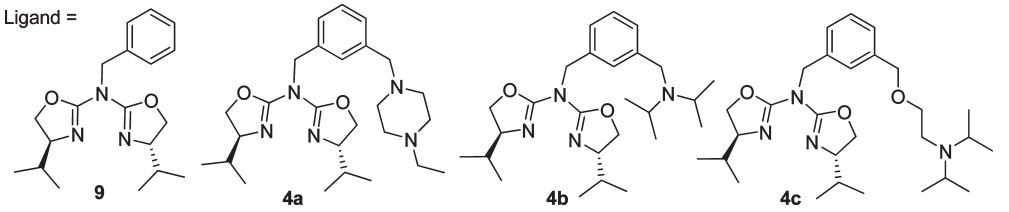


FIGURE 8. Plausible transition state model.

TABLE 8. Diastereoselective Henry Reactions Catalyzed by Bifunctional Catalyst[a]





entry	ligand	additive	time (h)	yield (%)[b]	*syn*:*anti*[c]	ee (*syn*) (%)[d,e]	ee (*anti*) (%)[d]
1	**9**		24	0			
2	**9**	**14** (5 mol %)	24	54	1.3:1	72	96
3	**4a**		24	81	1.3:1	92	97
4	**4b**		144	27	1.4:1	80	92
5	**4c**		24	99	1.5:1	92	96
6	**9**	*i*-Pr_2NEt (5 mol %)	24	96	1.6:1	94	95

[a]All reactions were conducted on a 0.5 mmol scale with ligand **9**, **4a**, **4b**, or **4c** (5 mol %), CuTC (5 mol %), nitroethane (5 equiv), and 100 mg of 4 Å molecular sieves. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC with a (*S*,*S*) Whelk-O1 column. [e]Absolute configuration of major *syn* isomer was determined to be (1*S*,2*S*) by comparison of the retention time of literature data (see the Supporting Information).

δ 6.96−7.44 (m, 4 H), 4.87−5.07 (m, 4 H), 4.32 (t, J = 8.8 Hz, 4 H), 4.01−4.10 (m, 4 H), 3.82 (dt, J = 9.1, 6.6 Hz, 4 H), 1.57−1.73 (m, 4 H), 0.83 (d, J = 6.5 Hz, 12 H), 0.75 ppm (d, J = 6.8 Hz, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 137.6, 128.2, 127.5, 126.6, 71.5, 70.1, 53.0, 33.0, 18.8, 17.9 ppm; HRMS (ESI) m/z calcd for $C_{32}H_{48}N_6O_4Na$ $[M + Na]^+$ 603.3629, found 603.3621; $[\alpha]^{26}_D$ −25.4 (c 1.0, $CHCl_3$).

General Procedure for Synthesis of Base-Tethered Ligands. To a 5.0 mL flame-dried Schlenk flask were added *i*-Pr aza-bis-(oxazoline) **1** (0.65 mmol in 1.3 mL THF) and KI (3 mg). Under argon atmosphere, THF (6.0 mL) was added and the reaction mixture was cooled to −78 °C for 10 min. Then 2.5 M *n*-BuLi (290 μL, in *n*-hexane, 0.73 mmol) was slowly added into the reaction flask and the reaction mixture was kept at −78 °C for another 10 min. 1-(3-(Bromomethyl)benzyl)-4-ethylpiperazine (**3a**) (265 mg, 0.89 mmol) in THF (2.0 mL) was slowly added into the reaction flask at −78 °C. The cold bath was removed and the flask was slowly warmed to the room temperature or 40 °C as indicated in Scheme 1. The reaction proceeded for another 24 h at this temperature. The reaction mixture was purified by flash column chromatography on basic alumina (*n*-hexane/EtOAc 9:1) to give compound **4a** (192 mg, 65%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06−7.39 (m, 4 H), 4.86−5.15 (m, 2 H), 4.28−4.42 (m, 2 H), 4.09 (t, J = 7.6 Hz, 2 H), 3.85 (dt, J = 9.1, 6.5 Hz, 2 H), 3.46 (s, 2 H), 2.30−2.60 (m, 10 H), 1.57−1.76 (m, 2 H), 1.06 (t, J = 7.2 Hz, 3 H), 0.85 (d, J = 6.7 Hz, 6 H), 0.77 ppm (d, J = 6.7 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 138.2, 137.7, 128.9, 128.3, 128.2, 126.6, 71.5, 70.1, 63.2, 53.3, 53.1, 53.1, 52.5, 33.0, 18.8, 17.9, 12.2 ppm; HRMS (ESI) calcd for $C_{26}H_{42}N_5O_2$ $[M + H]^+$ 456.3333, found 456.3331; $[\alpha]^{26}_D$ −17.7 (c 4.0, $CHCl_3$).

Acknowledgment. We thank the University of Florida for support of this research and Mr. Michael Rodig for helpful discussion.

Supporting Information Available: Experimental details, HRMS, NMR spectra for new compounds, kinetic data, and HPLC analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.