

Stereodivergency in Catalytic Asymmetric Conjugate Addition Reactions of Glycine (Ket)imines

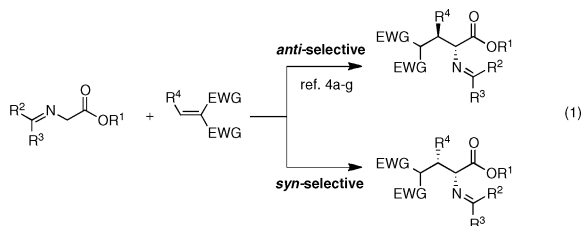
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Supporting Information

ABSTRACT: Stereodivergent catalytic asymmetric conjugate reactions of glycine (ket)imines with nitroalkenes have been achieved using various chiral catalyst systems derived from a multidentate amino alcohol (**1**). The stepwise nature of the [3 + 2] cycloaddition reactions of N-metalated azomethine ylides has also been demonstrated by highly enantio- and diastereoselective syntheses of *exo*-**5** and *endo*-**8** from the respective *syn*-**4** and *anti*-**7** conjugate addition products in a one-pot tandem fashion.

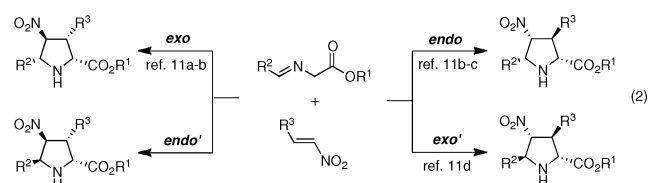
Conjugate addition, one of the most useful carbon–carbon bond-forming reactions in organic synthesis,¹ plays a pivotal role in domino (or cascade) reaction sequences, providing facile access to complex molecular architectures with impressive levels of stereocontrol.² Although significant progress in the development of catalytic asymmetric conjugate reactions has been made in the past decades,^{3a} there remains an important challenge in diversifying the stereochemical outcome of catalytic asymmetric conjugate reactions.^{3b} For example, several research groups have reported the development of catalytic asymmetric conjugate additions of glycine (ket)imines to β -alkyl- α,β -unsaturated esters,^{4a} β -aryl nitroalkenes,^{4b} β -aryl- α,β -unsaturated ketones,^{4c,d} arylidene malonates,^{4e,f} and alkylidene bisphosphonates,^{4g} all leading to *anti*-selective conjugate reaction products (eq 1). In contrast, there are no



examples of catalytic enantio- and *syn*-selective conjugate reactions of glycine imines. As a consequence, there is a clear void in the development of catalytic asymmetric *syn*-selective conjugate reactions and the possible use of such products in cascade reaction sequences.

In the pursuit of a solution to this stereodivergence issue, we became interested in the stereochemical pathways of the [3 + 2] cycloaddition reaction between glycine imines and electron-deficient alkenes. Since the seminal contribution of Grigg in 1991,⁵ significant progress on catalytic asymmetric [3 + 2] cycloaddition reactions of N-metalated azomethine

ylides with alkenes has been made.⁶ The elucidation of their reaction pathways, however, still remains challenging. Both the concerted supra–supra mechanism⁷ and the stepwise mechanism⁸ have been considered as possible pathways, each with strong computational evidence⁹ but without clear experimental evidence.¹⁰ The involvement of stepwise reaction mechanisms has been suggested in the catalytic asymmetric *exo*-,^{11a,b} *endo*-,^{11b,c} and *exo'*-selective^{11d} [3 + 2] cycloaddition reactions of N-metalated azomethine ylides and nitroalkenes (eq 2). This



notion of a stepwise reaction process in the [3 + 2] cycloaddition reactions of N-metalated azomethine ylides implies a new possibility of developing catalytic asymmetric systems for the conjugate reaction pathway.

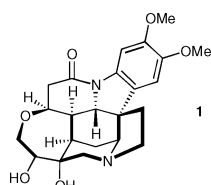
We previously reported that catalyst–substrate arrangements are controlled by multiple binding modes of multidentate amino alcohol **1** through either metal coordination or the hydrogen-bonding network.¹² When glycine imines were treated with various α,β -unsaturated esters under chiral copper(I) and silver(I) catalysis, the exclusive formation of *endo*-pyrrolidines was observed, possibly through a concerted [3 + 2] cycloaddition pathway.^{12a} Given the possibility of different preferential interactions between acyclic Michael acceptors and nucleophiles under various chiral catalyst conditions, we envisioned the use of nitroalkenes in our catalyst system to develop stereodivergent conjugate addition reactions. We describe herein the first example of such a switch in selectivity to provide respective *anti*- and *syn*-1,4-addition products using chiral catalyst systems derived from a single chiral source.¹³

Initially, we examined the copper-catalyzed asymmetric conjugate addition of glycine imine **2** in the presence of 10 mol % ligand **1** at $-15\text{ }^{\circ}\text{C}$ (Table 1). The use of the CuCl/Et₃N catalyst system predominantly led to the decomposition of **2** and failed to provide either conjugate addition or pyrrolidine products (entry 1). Efforts to minimize the decomposition of **2** using 4 Å molecular sieves (MS) were

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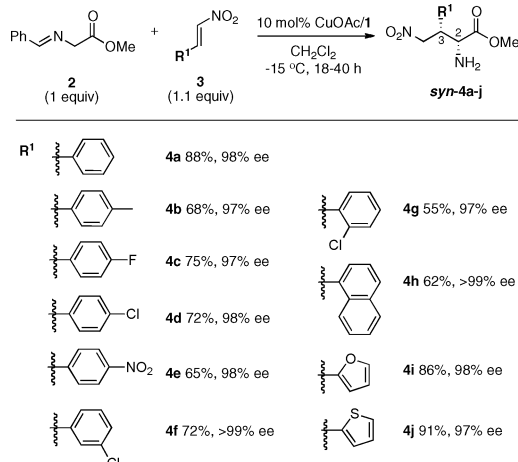

Table 1. Optimization of *Syn*-Selective Conjugate Reaction Conditions

entry	metal	solvent	yield (%) ^a	ee (%) ^b
1	CuCl/Et ₃ N	CHCl ₃	ID	—
2 ^c	CuCl/Et ₃ N	CHCl ₃	ID	—
3 ^d	CuCl/Et ₃ N	THF	NR	—
4	CuOAc	CHCl ₃	70	97
5 ^e	CuOAc	TCE	30	25
6	CuOAc	PhCH ₃	ID	—
7 ^d	CuOAc	THF	NR	—
8	CuOAc	CH ₂ Cl ₂	88	98
9 ^e	Cu(OAc) ₂	CH ₂ Cl ₂	18	98

^aIsolated yields after hydrolysis of imine **2**. ID = imine decomposition, NR = no reaction. ^bDetermined by HPLC using a chiral column. ^cUsing 4 Å MS (20 wt %). ^dReaction time of 48 h. ^eDecomposition of **2**.

not successful (entry 2). Although changing the solvent to tetrahydrofuran (THF) resulted in a drastic improvement in the stability of **2**, no reaction was observed after a prolonged reaction time (entry 3). We previously observed the beneficial effect of acetate in our copper(I)- and silver(I)-catalyzed asymmetric reactions,^{12a,b} where acetate played the role of mild base. To our delight, employing the chiral catalyst system derived from CuOAc exclusively provided *syn* conjugate addition products in 70% yield with 97% ee (entry 4). In a stark contrast, solvent screening revealed that the decomposition of **2** was the major pathway in 1,1,2-trichloroethane (TCE) and toluene, while no reaction was observed in THF (entries 5–7). Finally, dichloromethane was identified as an optimal solvent, leading to the exclusive formation of *syn*-**4** in 88% yield with 98% ee (entry 8). The importance of the copper(I) source in the current catalyst system was further investigated using Cu(OAc)₂, where high enantio- and diastereoselectivities were observed, but with a significant loss in the catalyst efficiency (entry 9).

With the optimized asymmetric conditions in place, the scope of the catalytic conjugate reaction of nitroalkenes was investigated (Chart 1). The reaction was applicable to a variety of aryl and heteroaryl nitroalkenes with electron-donating and electron-withdrawing groups. In general, *exclusive syn*-selectivity with excellent enantioselectivity (>25:1 dr, 97–99% ee) was observed at –15 °C. The limitation of the current asymmetric conjugate addition reaction lies with use of aliphatic nitroalkenes, where no reaction was observed despite a longer reaction time (48 h) and higher reaction temperature (23 °C). Nevertheless, our results presented herein describe the first *syn*-selective catalytic asymmetric conjugate addition reaction of glycine imines. Our current efforts are directed toward employing other metal salts to catalyze conjugate addition reactions with aliphatic nitroalkenes. The relative and absolute stereochemistry of *syn*-**4** was confirmed to be (2*R*,3*S*) by X-ray

Chart 1. Scope of the *Syn*-Selective Conjugate Reaction


crystallographic analysis of the (–)-camphanyl derivative of *syn*-**4a** [see the Supporting Information (SI) for details].

With the objective of understanding the stereochemical outcome of the intramolecular Mannich reaction of *syn*-**4** under our current catalyst conditions, we raised the reaction temperature to 23 °C after completion of the conjugate addition reaction of **2** (Table 2). The exclusive formation of

Table 2. Optimization of the Intramolecular Mannich Reaction of *syn*-4a****

entry	base	solvent	yield (%) ^a	dr (exo:endo) ^b
1	Et ₃ N	CH ₂ Cl ₂	>95	4:1
2	Et ₃ N	THF	15	15:1
3	Et ₃ N	CH ₃ CN	>95	>25:1
4	Et ₃ N	MeOH	>95	5:1
5	Et ₃ N	PhCH ₃	—	—
6	DBU	CH ₂ Cl ₂	85	>25:1
7	<i>t</i> -BuOK	CH ₂ Cl ₂	84	>25:1
8 ^c	DBU	CH ₂ Cl ₂	81	>25:1
9 ^d	Et ₃ N	CH ₂ Cl ₂	57	4:1

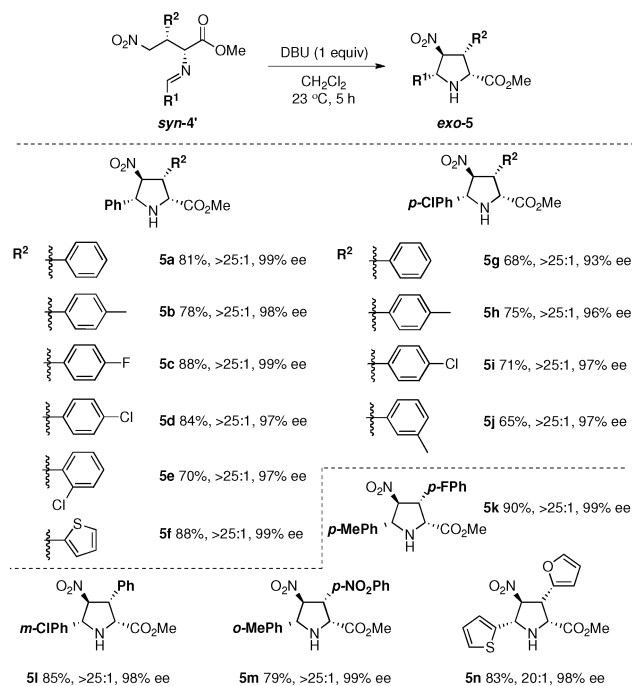
^aIsolated yields. ^bDetermined by crude ¹H NMR analysis. ^cReaction time of 5 h using 1 equiv of DBU. ^dCuOAc-free reaction, *syn*-**4a** was recovered in 42% yield with 97% ee.

highly enantiopure *exo*- and *endo*'-pyrrolidines **5** (4:1 dr) clearly demonstrated the stepwise nature of the [3 + 2] cycloaddition reaction of glycine imines and nitroalkenes (entry 1). A subsequent solvent screening revealed that highly *exo*-selective cyclization reactions are possible in THF and acetonitrile solution (entries 2–3), while modest selectivity was observed in MeOH (entry 4). Interestingly, no cyclization occurred in toluene even using 1 equiv of Et₃N (entry 5). For operational convenience, we also investigated a one-pot cyclization of *syn*-**4a** in CH₂Cl₂ using different base catalysts (entries 6–8). Pleasingly, the use of stronger bases provided the exclusive formation of *exo*-**5a** in >25:1 dr, with the use of 1 equiv of base shortening the reaction time to 5 h at 23 °C. The minimal effect of the chiral copper catalyst in the stereoselective

intramolecular Mannich reaction was obtained when a crude reaction mixture of *syn*-4a that was free of chiral copper catalyst was subjected to cyclization under catalysis by Et₃N to give identical diastereoselectivities (entries 9). The stereochemical integrity of the recovered *syn*-4a was not compromised.

Chart 2 summarizes the scope of the stepwise one-pot *exo*-selective [3 + 2] cycloaddition of glycine imines and

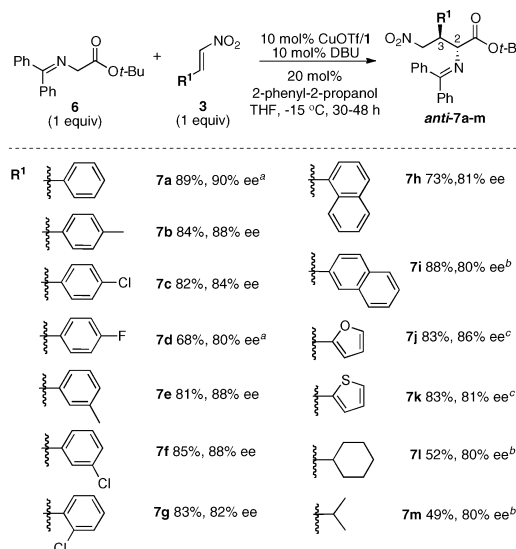
Chart 2. Scope of the Stepwise One-Pot [3 + 2] Cycloaddition Reaction



nitroalkenes via *syn*-selective conjugate addition products 4. After reactions at $-15\text{ }^{\circ}\text{C}$ for 18–40 h, a simple addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) followed by warming the reaction mixture to $23\text{ }^{\circ}\text{C}$ afforded the highly *exo*-selective cyclization of *syn*-4. A wide range of *syn*-4 diastereomers derived from electron-rich or electron-poor and sterically diverse aryl nitroalkenes (5a–f) as well as various glycine imines (5g–n) provided good to excellent yields with excellent enantio- and diastereoselectivities.

After establishing this facile access to chiral pyrrolidines *exo*-5 through a catalytic *syn*-selective conjugate addition reaction, we also investigated *anti*-selective conjugate addition reactions of glycine imines that potentially lead to diastereomeric pyrrolidines. After extensive attempts to isolate *anti*-selective conjugate addition products, we found that although the highly enantio- and diastereoselective [3 + 2] cycloaddition product *endo*-5a can be obtained,¹⁴ the transient nature of the *anti*-selective conjugate addition product could not be confirmed from the reaction of glycine imine 2 and nitroalkenes. Pleasingly, the use of glycine ketimine 6 turned out to be a key factor in identifying the *anti*-selective conjugate addition product.¹⁵ Thus, a series of reaction optimizations was conducted using CuOTf as a metal source with various bases, solvents, and protic additives to provide the optimal reaction conditions, in which the combination of DBU in THF in the presence of *t*-BuOH or 2-phenyl-2-propanol led to the formation of *anti*-7a in 89% yield with 90 and 85% ee, respectively (see the SI for details). Chart 3 summarizes the

Chart 3. Scope of the *Anti*-Selective Conjugate Reaction

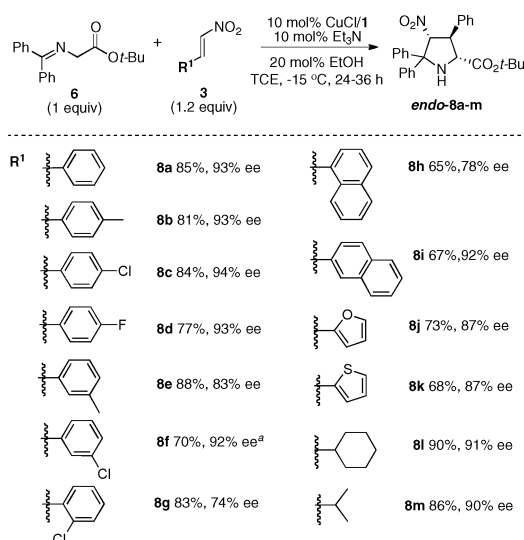


^aReaction used 60 mol % *t*-BuOH. ^bReaction used 20 mol % catalyst. ^cNo additive was used.

scope of the catalytic *anti*-selective conjugate addition of glycine ketimine 6. The *exclusive* formation of *anti*-7 with high enantioselectivity and yield was achieved for various nitroalkene derivatives with different electronic (7a–d) and steric (7e–i) effects. Synthetically useful levels of enantioselectivity in the 80–90% ee range were observed, although sterically demanding substrates proved to be less enantioselective (7g–i). The use of heteroaromatic nitroalkenes also provided satisfactory selectivities (7j, 7k) in the absence of protic additives, but lower reactivities were observed for aliphatic nitroalkenes (7l, 7m). The relative and absolute stereochemistry of *anti*-7 was confirmed to be (2*R*,3*R*) by comparison of its HPLC retention times with those of authentic samples (see the SI for details).

The stereochemical outcome of the intramolecular Mannich reaction of *anti*-7 under base catalysis was also investigated. As anticipated, the *exclusive* formation of *endo*-8a was observed regardless of the nature of base.¹⁶ Alternatively, the use of CuCl led to the generation of catalytically active chiral copper complexes that provided the [3 + 2] cycloaddition reaction product, *endo*-8a, through a stepwise reaction sequence.¹⁷ After some experimentation, we found that the combination of Et₃N in TCE in the presence of EtOH led to the formation of *endo*-8a in 85% yield with 93% ee (see the SI for details). The scope of the catalytic *endo*-selective [3 + 2] cycloaddition reaction of glycine ketimine 6 was evaluated under the optimized reaction conditions (Chart 4). The reaction was readily applicable to a wide range of aromatic, heteroaromatic, and aliphatic nitroalkenes. In general, *exclusive endo* selectivity and high enantioselectivity were achieved for nitroalkenes with *para*-substituted phenyl groups, where little electronic effect was observed (8a–d). Nitroalkenes with *ortho*- and *meta*-substituted aryl groups, however, exerted steric effects on the current catalyst system, leading to lower enantioselectivities of 78–82% (8g, 8h). The use of heteroaromatic nitroalkenes was also satisfactory (8j, 8k). Notably, aliphatic nitroalkenes were well-tolerated in our catalyst system, providing an excellent level of enantioselectivity (8l, 8m).

In summary, we have developed a stereodivergent catalytic asymmetric conjugate reaction of glycine (ket)imines with

Chart 4. Scope of the *Endo*-Selective [3 + 2] Cycloaddition Reaction

^aAfter a single recrystallization from a crude mixture of **8f** with 80% ee.

nitroalkenes, where respective *syn* and *anti* addition products were obtained with high diastereo- and enantioselectivities. In addition, the stereoselective formation of *exo*-5 and *endo*-8 has also been achieved from *syn*-4 and *anti*-7, respectively, under base catalysis, clearly demonstrating the stepwise nature of the [3 + 2] cycloaddition reactions of N-metalated azomethine ylides. The preparation of a diverse array of chiral compounds using various chiral catalyst species, particularly derived from a single chiral source, should enrich our molecular-level understanding of asymmetric catalysis. Mechanistic studies and the extension of the stereodivergent catalysis approach to other carbon–carbon bond-forming reactions are currently underway, and our results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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■ REFERENCES

- (1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, U.K., 1992.
- (2) For recent reviews, see: (a) Enders, D.; Grondal, C.; Hüttel, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.
- (3) (a) *Catalytic Asymmetric Conjugate Reactions*; Cordova, A., Ed.; Wiley-VCH, Weinheim, Germany, 2010. (b) For a recent example,

see: Anderson, J. C.; Stepney, G. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. J. *Org. Chem.* **2011**, *76*, 1961.

(4) (a) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321. (b) Li, Q.; Ding, C.-H.; Hou, X.-L.; Dai, L.-X. *Org. Lett.* **2010**, *12*, 1080. (c) Hua, M.-Q.; Wang, L.; Cui, H.-F.; Nie, J.; Zhang, X.-L.; Ma, J.-A. *Chem. Commun.* **2011**, *47*, 1631. (d) Ma, T.; Fu, X.; Kee, C. W.; Zong, L.; Pan, Y.; Huang, K.-W.; Tang, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 2828. (e) Wang, M.; Shi, Y.-H.; Luo, J.-F.; Du, W.; Shi, X.-X.; Fossey, J. S.; Deng, W.-P. *Catal. Sci. Technol.* **2011**, *1*, 100. (f) Hernández-Toribio, J.; Arrayás, R. G.; Carretero, J. C. *Chem.—Eur. J.* **2011**, *17*, 6334. (g) Xue, Z.-Y.; Li, Q.-H.; Tao, H.-Y.; Wang, C.-J. *J. Am. Chem. Soc.* **2011**, *133*, 11757.

(5) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817.

(6) For recent reviews, see: (a) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6272. (b) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (c) Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2047. (d) Bonin, M.; Chauveau, A.; Micouin, L. *Synlett* **2006**, 2349. (e) Panday, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (f) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (g) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (h) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784.

(7) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633. (b) Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291. For unique stepwise reaction mechanisms, see: (c) Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* **1986**, *108*, 6401. (d) Mloston, G.; Huisgen, R. *Tetrahedron Lett.* **1989**, *30*, 5373.

(8) Neumann, F.; Lambert, C.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1998**, *120*, 3357.

(9) For a recent review, see: de Cózar, A.; Cossío, F. P. *Phys. Chem. Chem. Phys.* **2011**, *13*, 10858.

(10) (a) Ayerbe, M.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 1795. (b) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078.

(11) (a) Cabrera, S.; Arrayás, G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (b) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. (c) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338. (d) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7895.

(12) (a) Kim, H. Y.; Shih, H.-J.; Knabe, W. E.; Oh, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7420. (b) Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682. (c) Kim, H. Y.; Kim, H.; Oh, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 4476. (d) Kim, H. Y.; Oh, K. *Org. Lett.* **2011**, *13*, 1306.

(13) For recent examples of Mannich-type reactions, see: (a) Jiang, J.; Xu, H.-D.; Xi, J.-B.; Ren, B.-Y.; Lv, F.-P.; Guo, X.; Jiang, L.-Q.; Zhang, Z.-Y.; Hu, W.-H. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (b) Lu, G.; Yoshino, T.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4382.

(14) Under unoptimized conditions using 10 mol % CuOTf/1/Et₃N in THF, the formation *endo*-5a was observed in 90% yield with 87% ee (*endo:exo* >25:1). Our full account for the *endo*-selective reactions will be reported elsewhere.

(15) No *syn* addition product was identified in thermal and catalyzed reactions of **6**. For the structural misassignment of *anti*-7 as *syn*-7 and *endo*-8 as *anti*-7, see: Li, W.; Liu, H.; Du, D.-M. *Synlett* **2009**, 925.

(16) For example, the use of 10 mol % Et₃N or DBU in MeOH led to the exclusive formation of *endo*-8 in 95% yield within 18 h at 23 °C.

(17) The stepwise nature of the reaction was confirmed by interrupting an unfinished reaction to identify *anti*-7 and by monitoring the conversion of *anti*-7 to *endo*-8. For a previous asymmetric organocatalyst approach to *endo*-8 with 46–65% ee, see: Xue, M.-X.; Zhang, X.-M.; Gong, L.-Z. *Synlett* **2008**, 691.