Asymmetric Catalysis

A Highly Diastereo- and Enantioselective Reaction for Constructing Functionalized Cyclohexanes: Six Contiguous Stereocenters in One Step**

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Organic motifs with contiguous multiple stereocenters exist in numerous natural and unnatural products that exhibit important biological activity.^[1] The number of possible stereoisomers increases exponentially with the number of stereocenters, thus the highly stereoselective synthesis of chiral compounds with multiple stereocenters from simple starting materials is a challenge. Nature has developed many efficient ways to construct such structures from simple starting materials, as demonstrated by the production of chiral carbohydrates, proteins, and alkaloids. Inspired by nature, the asymmetric domino process, which generates more than one chemical bond concomitantly with the creation of multiple stereocenters in a one-pot fashion, has emerged as a promising way to achieve these aims.^[2] Despite the fact that a number of structurally diverse compounds with contiguous multiple stereocenters have been synthesized using this strategy, to the best of our knowledge, a domino process which generates six or more stereocenters by one intermolecular reaction of two simple compounds in an asymmetric fashion has not been reported.^[3,4]

The identification of a reactive species that triggers a domino process is a prerequisite for the successful establishment of an efficient tandem reaction. As active species, enolates are considered to be the most powerful and reliable cornerstones for establishing many classical transformations.^[5] α -Ketoesters could be recognized as latent enolates since the keto-to-enol tautomerization could easily take place in these compounds in the presence of suitable Lewis acids.^[6] With this in mind, we envisaged that the reactive enolate species derived from an α -ketoester would be useful to trigger a formal [2+2+2] cycloaddition through an asymmetric Michael^[7]/Michael/Henry^[8] tandem sequence with nitroal-kenes as electrophiles (Scheme 1). Mechanistically, a chiral Lewis acid catalyst would activate the α -ketoester to give rise to the intermediate enolate **A** which would then add to

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Scheme 1. Copper-catalyzed asymmetric tandem reaction for the construction of the functionalized cyclohexanes.

nitroalkene 2 by a conjugate addition to yield intermediate B. The intermediate **B** would further react with nitroalkene 2 to generate the intermediate C under appropriate reaction conditions. Ring closure through the Henry reaction would lead to the desired six-membered annulation product 3 with six stereogenic centers (Scheme 1). The challenge of designing such an efficient catalytic asymmetric strategy mainly depends on the necessity of stereoselectively generating the stable reactive species **B** and highly reactive intermediate **C** in situ. To address this challenge, we need to identify a chiral transition metal catalyst to generate the metal enolate A with stereodefined geometry, thus guaranteeing that the first conjugate Michael addition proceeds with high diastereoand enantioselectivity. A chiral Lewis acid catalyst with the appropriate steric and electronic properties is crucial for the successful implementation the above strategy. Given that a conformationally rigid structure would have good chiral induction abilities, we recently have designed and synthesized a series of rigid chiral diamines 5 and 6.^[9] We envisioned that these chiral diamine ligands, which have unusually rigid structures, would be useful for the construction of a well oriented chiral environment around the metal center, and the corresponding transition metal complexes derived from these chiral diamines could efficiently promote the proposed reaction. Herein, we report a novel copper-catalyzed asymmetric formal [2+2+2] cycloaddition between one equivalent of ketoester and two equivalents of nitroalkene for the synthesis of cyclohexanes with seven substituents.^[3a-c,e-k,l,10] These compounds are not only important building blocks in

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organic synthesis, but also represent a structural motif found in a number of important natural and synthetic bioactive products.^[11] It should be noted that this tandem reaction could be performed in the presence of 0.1 mol% of catalyst and delivered the chiral cyclohexane frameworks with complete diastereoselectivity and excellent enantioselectivity.

The tandem reaction of ketoester (1a) with nitrostyrene (2a) was performed in 2-PrOH at room temperature with 5 mol% of metal catalyst, which was prepared in situ from chiral diamine ligand (S,S)-5a and various transition metals (Table 1). A preliminary investigation indicated that the catalyst prepared with chiral ligand 5a was indeed effective for this reaction. The catalyst prepared with Cu(OAc)₂·H₂O and 5a afforded the annulation product 3aa with excellent yield (95%) and high enantioselectivity (95% ee) as well as absolute diastereoselectivity (Table 1, entry 1). This catalyst was highly chemically selective, and the linear conjugate addition by-product 4aa was not observed. Further screening of other copper precursors that have been efficient in different catalytic asymmetric reactions revealed that the counteranion played an important role in this reaction, and the copper salt containing the acetate anion gave good results in both of reactivity and selectivity. For example, the catalysts prepared from $Cu(OTf)_2$ and $CuBr_2$ did not catalyze the

Table 1: Screening of reaction conditions[a]



[a] Reaction conditions: 1a (0.2 mmol), 2a (0.6 mmol), MX_n (0.01 mmol), ligand (0.0105 mmol) in solvent (2.0 mL) at room temperature for 24 h, unless otherwise noted. [b] Yield of the isolated product. [c] Determined by ¹H NMR analysis of the crude products. [d] Determined by HPLC analysis using a chiral stationary phrase. [e] Using 1.0 mol% of Cu complex, 36 h. [f] Using 0.1 mol% of Cu complex and 10 mol% of Et₃N. [g] Using 0.033 mol% of Cu complex (S/C = 3000) and 10 mol% of Et₃N. acac = acetoacetonate. n.d. = not determined.

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obtained (Table 1, entries 3 and 4) with good stereoselectivity. Other transition metals, including nickel and zinc with various anions, were also evaluated under the identical screening reaction conditions and gave lower yield and stereoselectivity than the corresponding catalyst derived from $Cu(OAc)_2 \cdot H_2O$. Again, the basic acetate anion contained in the catalysts was essential to obtain high reactivity and selectivity (Table 1, entries 5-8). These results indicated that the basic acetate anion might serve as an endogenous base to generate the metal enolate and to facilitate the Michael addition in the first step.^[6d] Without a metal, the diamine ligand **5a** showed extremely lower activity and completely no selectivity (Table 1, entry 9). The effect of the solvent was next investigated (Table 1, entries 10-16), and it was found that the green solvent 2-PrOH was the best for this reaction. Other chiral diamine ligands (5b, 6a, and 6b; see Scheme 1) were also tested and we found the ligand 5a was the most suitable for this asymmetric reaction (Table 1, entries 17–19). The catalyst loading can be reduced to 1 mol% (Table 1, entry 20) without any reduction in yield and enantioselectivity, although a reaction time of 36 h was required to reach full conversion. Moreover, the addition of a catalytic amount of Et₃N was found to be effective and enabled the reaction to be

reaction at all, and only the undesired by-product 4aa was

performed in the presence of 0.1 mol% of Cu complex with only a slight loss of enantioselectivity (Table 1, entry 21). This loading of the Cu catalyst is two orders of magnitude lower than that commonly used in organocatalytic asymmetric tandem reactions.[3a-k] Furthermore, a high yield could still be obtained when the catalyst loading was further decreased to 0.033 mol% of Cu complex, but a loss in enantioselectivity was observed (Table 1, entry 22).

Having identified the optimal set of reaction conditions, we then investigated reactions with a variety of α -ketoesters **1**a-j, which contain R groups with different electronic and steric properties, and these results were summarized in Table 2. The reaction demonstrated a broad generality with respect to the α -ketoesters, and the nature of the R substitutents had a limited influence on the reactivities and stereoselectivities. In all cases, the reactions proceeded smoothly at room temperature under very mild reaction conditions, and the desired functionalized cyclohexanes (3aa-ja) were consistently obtained in good to excellent yields with complete diastereoselectivity and Table 2: Substrate scope of ketoesters.[a]

R I	CO ₂ tBu + Ph	(.NO ₂	Cu(OAc)₂·H₂O/ 5a (5 mol %) 2-PrOH, 20 ℃	HO_{R}	NO ₂ Ph NO ₂
Entry	R	Prod.	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	C ₆ H ₅ CH ₂	3 aa	95	> 20:1	95
2	4-MeC ₆ H ₄ CH ₂	3 ba	83	>20:1	94
3	3,4-diClC ₆ H ₃ CH ₂	3 ca	74	>20:1	94
4	$C_6H_5(CH_2)_3$	3 da	80	>20:1	95
5	CH ₃ CH ₂ CH ₂	3 ea	82	>20:1	94
6	$CH_3(CH_2)_4$	3 fa	81	>20:1	94
7	$CH_3(CH_2)_6$	3 ga	88	>20:1	94
8	$C_6H_5O(CH_2)_3$	3 ha	85	>20:1	95
9	$CH_2 = CH(CH_2)_2$	3 ia	80	>20:1	94
10	TMSC=C(CH ₂) ₂	3 ja	85	>20:1	93

[a] Reaction conditions: ketoester 1 (0.2 mmol), nitroalkene 2 (0.6 mmol), Cu(OAc)₂·H₂O (0.01 mmol), and (*S*,*S*)-**5** a (0.0105 mmol) in 2-PrOH (2.0 mL) at 20 °C for 24 h, unless otherwise noted. [b] Yield of the isolated product. [c] Determined by ¹H NMR analysis of the crude products. [d] Determined by HPLC analysis using a chiral stationary phase. TMS = trimethylsilyl.

excellent enantioselectivity (up to 95% *ee*). Notably, the formation of the alkene- and alkyne-containing adducts (**3ia** and **3ja**) is attractive because those functional groups could be easily converted into some important chiral compounds.

We also surveyed the scope of this new formal [2+2+2]tandem annulation process with respect to the nitroalkene. As summarized in Table 3, the annulation reaction of nitroalkenes with ketoesters catalyzed by the Cu- $(OAc)_2 \cdot H_2O/(S,S)$ -5a was found to be general with aromatic nitroalkenes bearing a variety of substituents. Several substituted aromatic nitroalkenes 2a-g, containing either electron-donating groups or electron-withdrawing groups in the para or meta position of the phenyl ring, were subjected to the reaction conditions. In all cases, high yield and excellent enantioselectivity with complete diastereoselectivity were obtained. Although nitroalkene 2i, derived from an orthosubstituted benzaldehyde, failed to deliver the annulation product when (S,S)-5a was used as the chiral ligand, the catalyst prepared with (S,S)-6a and Ni(OAc)₂·4H₂O led to a good yield for this substrate, but with a relatively lower enantioselectivity (3ai; Table 3, entry 9). This result may be due to a large steric hindrance between the substrate and the catalyst. As well as the substituted phenyl nitroalkenes, the naphthyl- and heteroaryl-substituted nitroalkenes are also compatible with the reaction conditions, thus generating the corresponding functionalized cyclohexanes (3ah and 3aj) in good yield with excellent stereoselectivity (Table 3, entries 8 and 10). Furthermore, the cinnamaldehyde-derived nitroalkene (2k) could also be used for this reaction to afford the desired annulation product with excellent stereoselectivity but only moderate yield (Table 3, entry 11). Unfortunately, the nitroalkene derived from an aliphatic aldehyde was not applicable in this reaction under the current reaction conditions. To test the practicality of the current catalytic reaction, the reaction of 1i with three equivalents of nitroalkene 2a in the presence of 0.1 mol% of CuTable 3: Substrate scope of nitroalkenes.^[a]

R	O CO ₂ <i>t</i> Bu	+ Ar NO ₂ -	Cu(OAc) ₂ (5 mo 2-PrOH	r [:] H ₂ O/ 5a t bl %) → I, 20 °C	BuO ₂ C HO R 3 ^{Ar}	Ar NO ₂
Entry	R	Ar	Prod.	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	C ₆ H₅CH₂	C ₆ H ₅	3 aa	95	>20:1	95
2	$C_6H_5CH_2$	4-ClC ₆ H₄	3 ab	92	>20:1	96
3	$C_6H_5CH_2$	$4-BrC_6H_4$	3 ac	70	>20:1	95
4 ^[e]	$C_6H_5CH_2$	$4-FC_6H_4$	3 ad	81	>20:1	94
5 ^[e]	$C_6H_5CH_2$	$4-MeC_6H_4$	3 ae	88	>20:1	96
6 ^[e]	$C_6H_5CH_2$	4-MeOC ₆ H ₄	3 af	80	>20:1	94
7	$C_6H_5CH_2$	3-ClC ₆ H₄	3 ag	83	>20:1	94
8	$C_6H_5CH_2$	1-naphthyl	3 ah	85	>20:1	94
9 ^[f]	$C_6H_5CH_2$	$2-MeOC_6H_4$	3 ai	76	>20:1	60
10	$C_6H_5CH_2$	2-furyl	3 aj	90	>20:1	98
11	$C_6H_5CH_2$	C ₆ H₅CH=CH	3 ak	42	>20:1	94
12	CH ₂ =CH- (CH ₂) ₂	2-furyl	3 al	80	>20:1	96

[a] Reaction conditions: ketoester 1 (0.2 mmol), nitroalkene 2 (0.6 mmol), Cu(OAc)₂·H₂O (0.01 mmol), and (*S*,*S*)-**5** a (0.0105 mmol) in 2-PrOH (2.0 mL) at 20 °C for 24 h, unless otherwise noted. [b] Yield of the isolated product. [c] Determined by ¹H NMR analysis of the crude products. [d] Determined by HPLC analysis using a chiral stationary phrase. [e] 10 mol% of Et₃N was added as co-catalyst. [f] With 5 mol% of Ni(OAc)₂·4 H₂O/**6** a and 10 mol% of Et₃N.

 $(OAc)_2$ ·H₂O/(*S*,*S*)-**5a** and 5 mol % of Et₃N was carried out on a 5 mmol scale of **1i**. The desired product **3ia** was obtained in gram scale with 77 % yield and 89 % *ee* as well as complete diastereoselectivity.

Although there is the possibility that $64(2^6)$ stereoisomers would be produced with the generation of six stereocenters in this cascade asymmetric reaction, we observed that in fact this asymmetric annulation was highly enantioselective, forming only one diastereomer, thus demonstrating the high efficiency of this protocol. The reason for the high stereoselectivity is that the chiral copper catalysts derived from the rigid chiral diamine guarantee the first Michael addition proceeds with high diastereo- and enantioselectivity, and the high stereoselectivity is kept or enhanced in the following Michael and Henry reactions. Crystal structures were obtained for annulation products 3ac and 3ia.^[12] The absolute configuration of products was the annulation determined to be 1R,2R,3R,4S,5R,6S from the single-crystal X-ray analysis of the bromo-containing product **3ac** (Figure 1). This indicated that the initial Michael reaction takes place from the Re face of the nitroalkene under the control of the catalyst. The absolute configurations of C4, C5, and C6 indicate that the second Michael addition takes place from the Si face of the nitroalkene and the final Henry reaction takes place from Re face of the carbonyl group, a result that suggests that the chiral catalyst is not involved in the formation of these two bonds.

In summary, a new enantioselective and diastereoselective transition-metal-catalyzed asymmetric formal [2+2+2] annulation between α -ketoesters and nitroalkenes has been established that gives rise to highly functionalized cyclohexane carboxylates with six stereogenic centers, including one quaternary stereocenter. A new copper complex consisting of



Figure 1. X-ray structure of the bromo-containing product 3 ac. Thermal ellipsoids are displayed at 20% probability.

a rigid chiral diamine has been identified as an efficient catalyst for delivering the cyclohexane carboxylates with excellent enantioselectivity and complete diastereoselectivity under mild and environmentally friendly reaction conditions. The excellent performance of the present tandem reaction represents an extremely simple and efficient way to synthesize highly functionalized cyclohexanes, which should find broad applications in synthetic organic chemistry.

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- For reviews, see: a) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* 2003, 551; b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* 2006, 118, 7292; *Angew. Chem. Int. Ed.* 2006, 45, 7134.
- [2] For reviews on tandem reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, Angew. Chem. 2007, 119, 1590; Angew. Chem. Int. Ed. 2007, 46, 1570; b) H.-C. Guo, J.-A. Ma, Angew. Chem. 2006, 118, 362; Angew. Chem. Int. Ed. 2006, 45, 354; c) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, Chem. Rev. 2005, 105, 1001; d) R. A. Bunce, Tetrahedron 1995, 51, 13103; e) L. F. Tietze, Chem. Rev. 1996, 96, 115; f) L.-F. Tietze, G. Brasche, K. M. Gericke, Domino reactions in organic synthesis, Wiley-VCH, Weinheim, 2006; g) T. J. J. Muller, Metal catalysed cascade reactions, Wiley-VCH, Weinheim, 2006; h) T.-L. Ho, Tandem organic reactions, Wiley, New York, 1992.
- [3] For selected examples of the stereocontrolled formation of more than three chiral centers by a one-pot reaction, see: a) B.-C. Hong, R. Y. Nimje, C.-W. Lin, J.-H. Liao, Org. Lett. 2011, 13, 1278; b) R. Imashiro, H. Uehara, C. F. Barbas, Org. Lett. 2010, 12, 5250; c) T. Urushima, D. Sakamoto, H. Ishikawa, Y. Hayashi, Org. Lett. 2010, 12, 4588; d) B. Tan, P. J. Chua, X. Zeng, M. Lu, G. Zhong, Org. Lett. 2008, 10, 3489; e) B. Tan, P. J. Chua, Y. Li, G. Zhong, Org. Lett. 2008, 10, 2437; f) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, Angew. Chem. 2007, 119, 9362; Angew. Chem. Int. Ed. 2007, 46, 9202; g) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, Angew. Chem. 2007, 119, 5010; Angew. Chem. Int. Ed. 2007, 46, 4922; h) A.

Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, Angew. Chem.
2007, 119, 1119; Angew. Chem. Int. Ed. 2007, 46, 1101; i) D.
Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, Nature 2006, 441, 861; j) M. Marigo, S. Bertelsen, A. Landa, K. A. Jørgensen, J. Am. Chem. Soc. 2006, 128, 5475; k) D. B. Ramachary, C. F.
Barbas, Chem. Eur. J. 2004, 10, 5323; l) S. Guo, Y. Xie, X. Hu, H.
Huang, Angew. Chem. 2010, 122, 2788; Angew. Chem. Int. Ed.
2010, 49, 2728; m) B. H. Lipshutz, B. Amorelli, J. B. Unger, J. Am. Chem. Soc. 2008, 130, 14378; n) T. Arai, N. Yokoyama, Angew. Chem. 2008, 120, 5067; Angew. Chem. Int. Ed. 2008, 47, 4989.

- [4] For an elegant method for the creation of eight stereogenic centers by two different reactions, see: a) D. Enders, M. R. M. Hüttl, J. Runsink, C. Raabe, B. Wendt, Angew. Chem. 2007, 119, 471; Angew. Chem. Int. Ed. 2007, 46, 467; b) For a recent closely related organocatalyzed asymmetric Michael/Michael/Henry sequence with 1,2-ketoamides, see: O. Baslé, W. Raimondi, M. M. Sanchez Duque, D. Bonne, T. Constantieux, J. Rodriguez, Org. Lett. 2010, 12, 5246.
- [5] For reviews see: a) D. A. Evans, Asymmetric Synthesis, Vol. 3, Academic Press, New York, 1984; b) C. H. Heathcock, Modern enolate chemistry: regio- and stereoselective formation of enolates and the consequence of enolate configuration on subsequent reactions, VCH, Weinheim, 1992; c) P. Arya, H. Qin, Tetrahedron 2000, 56, 917.
- [6] a) K. Juhl, K. A. Jørgensen, J. Am. Chem. Soc. 2002, 124, 2420;
 b) K. Juhl, N. Gathergood, K. A. Jørgensen, Angew. Chem. 2001, 113, 3083; Angew. Chem. Int. Ed. 2001, 40, 2995; c) G. Lu, H. Morimoto, S. Matsunaga, M. Shibasaki, Angew. Chem. 2008, 120, 6953; Angew. Chem. Int. Ed. 2008, 47, 6847; d) A. Nakamura, S. Lectard, D. Hashizume, Y. Hamashima, M. Sodeoka, J. Am. Chem. Soc. 2010, 132, 4036.
- [7] For reviews on Michael reactions, see: a) S. B. Tsogoeva, *Eur. J.* Org. Chem. 2007, 1701; b) D. Almaşi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* 2007, 18, 299; c) M. Koichi, M. Terada, M. Hiroshi, Angew. Chem. 2002, 114, 3704; Angew. Chem. Int. Ed. 2002, 41, 3554.
- [8] For reviews, see: a) C. Palomo, M. Oiarbide, A. Mielgo, Angew. Chem. 2004, 116, 5558; Angew. Chem. Int. Ed. 2004, 43, 5442;
 b) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, Tetrahedron: Asymmetry 2006, 17, 3315.
- [9] a) Q. Zhu, H. Huang, D. Shi, Z. Shen, C. Xia, Org. Lett. 2009, 11, 4536; b) Q. Zhu, D. Shi, C. Xia, H. Huang, Chem. Eur. J. 2011, 17, 7760.
- [10] For reviews on asymmetric catalytic reactions for the construction of chiral cyclohexanes, see: a) Comprehensive Asymmetric Catalysis I-III (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, 1999; b) Y. Hayashi in Cycloaddition reaction in Organic Synthesis (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, 2002, chap. 1. For selected examples: c) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, J. Am. Chem. Soc. 2000, 122, 4243; d) A. B. Northrup, D. W. C. MacMillan, J. Am. Chem. Soc. 2002, 124, 2458; e) K. Ishihara, K. Nakano, J. Am. Chem. Soc. 2005, 127, 10504; f) T. Kano, Y. Tanaka, K. Maruoka, Org. Lett. 2006, 8, 2687; g) S. Varga, G. Jakab, L. Drahos, T. Holczbauer, M. Czugler, T. Soós, Org. Lett. 2011, 13, 5416; h) Z.-J. Jia, Q. Zhou, Q.-Q. Zhou, P-Q. Chen, Y.-C. Chen, Angew. Chem. 2011, 123, 8797; Angew. Chem. Int. Ed. 2011, 50, 8638.
- [11] For reviews, see: a) A. G. Schultz, Acc. Chem. Res. 1990, 23, 207;
 b) B. Heasley, Eur. J. Org. Chem. 2009, 1477.
- [12] CCDC 844529 (3ac) and 844530 (3ia) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.