

Brønsted Base/Lewis Acid Cooperative Catalysis in the Enantioselective Conia-Ene Reaction

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Cooperative catalysis is a powerful tool in asymmetric synthesis, allowing access to new chemical reactivity and high stereocontrol in a wide range of reactions.¹ By mutual activation and organization of reagents, this concept has been applied widely² via combinations of Lewis and Brønsted acids and bases distributed around a chiral scaffold.

The idea we wanted to investigate was that of using ligand/metal-ion dynamic equilibria obtained by combining different metal-ion sources with precatalyst structures bearing basic sites and hydrogen-bond donors. We envisioned that such an approach could allow the discovery of new reaction pathways by joining acid/base activation of substrates with transition-metal-ion-catalyzed processes. This would differ strategically from other cooperative systems in which full ligation of the metal ion is normally imposed prior to the addition of the starting materials. Although this approach is conceptually simple, for it to be effective in asymmetric catalysis, a nonligated background reaction must not compete in the enantiodetermining step. We reasoned that cinchona-derived bifunctional catalysts such as **1**, introduced by our group³ and others,^{1a,b} could act as the desired precatalysts (Figure 1).

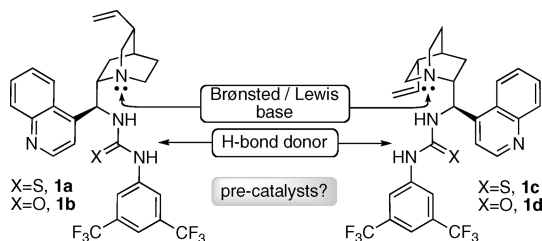


Figure 1. Pseudoenantiomeric cinchona-derived potential precatalysts to Brønsted base/Lewis acid cooperative catalysts.

These compounds are effective in generating enolates of β -ketoesters,^{1a} and we postulated that these intermediates, in the presence of metal ions, could be reactive toward alkyne functionalities. We chose to examine the asymmetric Conia-ene reaction of β -ketoesters **2**,⁴ recently developed by Toste,⁵ as a platform for this cooperative catalysis concept.

Preliminary studies to assess reactivity and stereoinduction were performed using readily prepared β -ketoester **2a**. Initially, thiourea **1a** and urea **1b** derived from a 9-amino-9-deoxyepicinchonidine scaffold were screened in combination with a range of “soft” transition-metal ions⁶ (Table 1). When thiourea **1a** was employed as the precatalyst, no conversion to the desired cycloisomerized product **3a** was observed in any experiment.⁷ Use of urea **1b** in the presence of Au(PPh₃)Cl or Ag(OTf) also gave no conversion. Pleasingly, however, the analogous experiment with Zn(OTf) gave 31% conversion to (*R*)-**3a** with 6% ee. In the presence of NiCl₂(dppe) complex, 68% conversion with 30% ee in favor of the *S* enantiomer was obtained. However, with copper(I)

Table 1. Catalyst Identification Studies

entry	precat	[M]	time (h)	conv. (%)	ee (%)
1	1a	Au(PPh ₃)Cl/AgOTf	18	0	—
2	1a	AgOTf	18	0	—
3	1a	Zn(OTf) ₂	18	0	—
4	1a	NiCl ₂ (dppe)	18	0	—
5	1a	CuOTf·1/2C ₆ H ₆	18	0	—
6	1b	Au(PPh ₃)Cl/AgOTf	18	0	—
7	1b	AgOTf	18	0	—
8	1b	Zn(OTf) ₂	18	31	+6
9	1b	NiCl ₂ (dppe)	18	68	−30
10	1b	CuOTf·1/2C ₆ H ₆	18	79	+92
11	1b	—	16	0	—
12	—	CuOTf·1/2C ₆ H ₆	16	0	—

triflate, good reactivity (79% conversion) with excellent enantiocontrol (92% ee) was observed.

Control experiments (entries 11 and 12) confirmed that both the precatalyst and the CuOTf were required for catalytic activity; no background reaction was observed with either independently.

A series of experiments (Table 2) measuring conversion against relative loadings of precatalyst and Cu(I) revealed that the optimal **1b**/CuOTf molar ratio was between 20:5 and 20:2.5. Interestingly, at both low (entry 2) and high (entries 1, 6, and 7) copper loadings, the reaction rates were noticeably lower while the enantiocontrol remained essentially constant.⁸

With optimal reactivity and enantiocontrol established, the scope of the reaction was surveyed using 20 mol % **1b** or **1d** as the precatalyst and 5 mol % copper(I)triflate in dichloromethane at room temperature. A range of pentynyl β -ketoesters incorporating significant structural and electronic changes to both the ester and ketone groups were investigated, and the results are presented in Table 3. The reaction was general for aliphatic and electron-rich or -poor aromatic β -ketoester substrates. The steric demand of the ester group had little effect on the reaction enantioselectivity (entries 1–3).

Similarly, aryl amide **2r** was also a good substrate in the process. Reaction times reflected in part the acidity of the substrates, with the

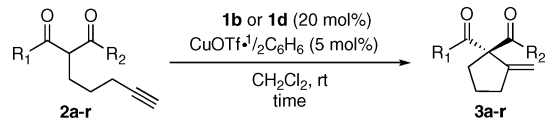
Table 2. Studies of Copper Loading versus Conversion

entry	1b (mol %)	CuOTf·1/2C ₆ H ₆ (mol %)	conv. (%)	ee (%)
1	20	0	0	—
2	20	1	56	92
3	20	2.5	67	92
4	20	5	68	92
5	20	10	56	92
6	20	20	16	92
7	20	40	6	90

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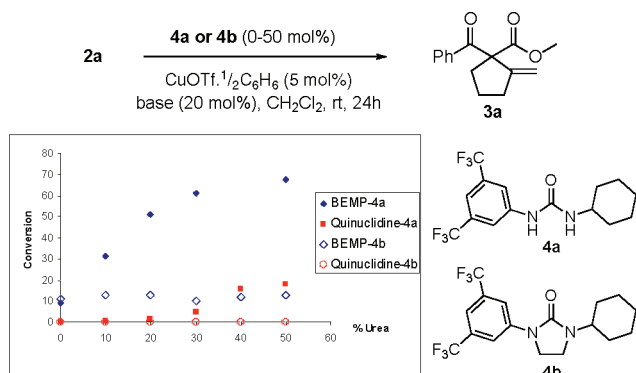
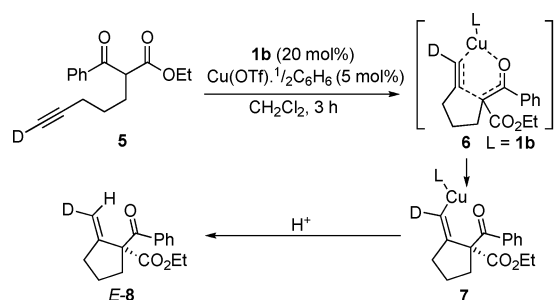
Table 3. Scope of the Catalytic Asymmetric Conia-Ene Reaction


entry	product	R ₁	R ₂	catalyst	time (days)	yield (%)	ee (%)
1	(R)- 3a	Ph	OMe	1b	1.5	98	92
2	(R)- 3b	Ph	OEt	1b	1.5	82	91
3	(R)- 3c	Ph	OBn	1b	1.5	95	89
4	(R)- 3d	4-MeC ₆ H ₄	OMe	1b	3	97	92
5	(R)- 3e	3-MeC ₆ H ₄	OMe	1b	2	99	92
6	(R)- 3f	2-MeC ₆ H ₄	OMe	1b	1	67	87
7	(R)- 3g	4-MeOC ₆ H ₄	OMe	1b	10	91	91
8	(R)- 3h	3-MeOC ₆ H ₄	OMe	1b	1.5	96	93
9	(R)- 3i	4-FC ₆ H ₄	OMe	1b	4	74	92
10	(R)- 3j	2-FC ₆ H ₄	OMe	1b	1	77	89
11 ^a	(R)- 3k	4-BrC ₆ H ₄	OMe	1b	1	87	93
12	(R)- 3 L	3,4-Cl ₂ C ₆ H ₃	OMe	1b	1	83	92
13	(R)- 3m	4-PhC ₆ H ₄	OMe	1b	1	89	89
14	(R)- 3n	2-naphthyl	OMe	1b	2	84	91
15 ^a	(R)- 3o	Me	OEt	1b	1.5	85	83
16 ^a	(R)- 3p	Me	OBn	1b	1.5	67	80
17	(R)- 3q	Et	OMe	1b	3.5	77	79
18	(R)- 3r	Ph	NHPh	1b	5	85	83
19	(S)- 3a	OMe	Ph	1d	2	92	89
20	(S)- 3o	OEt	Me	1d	2	90	74

^a For proof of the absolute stereochemical configuration, see the Supporting Information.

fastest finishing after 1 day and the slowest after 10 days. Enantiomeric excesses ranged from 79 to 93%, with the highest arising from aryl ketone substrates. The substitution of **1b** for pseudoenantiomeric precatalyst **1d** in the cyclization reaction of **2a** afforded (S)-**3a** in good yield and enantiocontrol (entry 19, 92% yield, 89% ee); **2o** yielded (S)-**3o** in an improved yield but with a slightly diminished ee of 74% (entry 20 vs entry 15).

To ascertain the possible contributions of the functional groups of the precatalysts to the observed reactivity, **1b** and **1d** were replaced by combinations of Brønsted bases and ureas **4a/4b**. Conversion versus loading experiments were performed. Two experimental series, one employing 20 mol % quinuclidine and the other 20 mol % 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) were performed on **2a** with 5 mol % copper(I) triflate, and conversion was measured against a variable quantity of urea **4a** (Scheme 1). In both series, a significant rate acceleration effect due to the urea was observed. When both experiments were repeated using cyclic urea **4b**, no rate acceleration was observed. These results indicate the importance of the urea N–H bonds in the rate-determining step and point to a potential ligand acceleration effect arising from the urea group. Further mechanistic insight was gained by repeating the reaction with the deuterated substrate **5**. At low conversion,⁹ the predominant monodeuterated product was (E)-**8**. This is consistent with the intermediacy of a ligated copper enolate that undergoes an enantioselective syn carbocupration^{6a} (Scheme 2).

Scheme 1. Studies of Conversion versus Urea Loading**Scheme 2.** Proposed Mechanistic Pathway via a Copper Enolate

These data are suggestive of a cooperative mechanism where the copper ion, the amine, and the N–H urea are all essential for the observed reactivity. Although further mechanistic studies are required, we postulate that the precatalyst has two distinct roles: (1) as a Brønsted base in the deprotonation of the β -ketoester, and (2) as an effective ligand for the copper enolate, which imparts high levels of enantiocontrol. This hypothesis is also consistent with data in Table 2, which illustrates that an excess of precatalyst compared to CuOTf is required for optimal reactivity.

In summary, a combination of copper(I) triflate and bifunctional 9-amino-9-deoxyepicinchona-derived urea compounds has proven to be an effective catalytic system in the enantioselective Conia-ene reaction. Further investigations in this field of catalysis are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data for compounds **3** and **4**, assignments of absolute stereochemistry, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Recent reviews: (a) Connon, S. J. *Chem. Commun.* **2008**, 2499. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393. (d) Muñiz, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6622. (e) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Pure Appl. Chem.* **2005**, *77*, 2047. (f) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491. (g) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566.
- (2) Selected examples: (a) Hasegawa, Y.; Watanabe, M.; Gridnev, I. D.; Ikariya, T. *J. Am. Chem. Soc.* **2008**, *130*, 2158. (b) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222. (c) Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2447. (d) Almási, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nagel, Y.; Nájera, C. *Eur. J. Org. Chem.* **2007**, 2328. (e) Lin, Y. M.; Boucay, J.; Li, Z.; Casarotto, V.; Lin, J.; Nguyen, A. N.; Ehrmantraut, J. *Org. Lett.* **2007**, *9*, 567. (f) Zeng, B.; Zhou, X.; Liu, X.; Feng, X. *Tetrahedron* **2007**, *63*, 5129. (g) Ma, K.; You, J. *Chem.—Eur. J.* **2007**, *13*, 1863. (h) Xiong, Y.; Huang, X.; Gou, S.; Huang, J.; Wen, Y.; Feng, X. *Adv. Synth. Catal.* **2006**, *348*, 538. (i) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206. (j) Jones, S.; Northen, J.; Rolfe, A. *Chem. Commun.* **2005**, 3832. (k) Sojome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643. (l) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232.
- (3) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.
- (4) Conia, J. M.; Le Perche, P. *Synthesis* **1975**, 1.
- (5) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168.
- (6) Metal-catalyzed Conia-ene reactions: (a) Au: Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Ni: Gao, Q.; Zheng, B.-F.; Li, J.-H.; Yang, D. *Org. Lett.* **2005**, *7*, 2185. (c) Cu: Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297.
- (7) We postulate that the Lewis acidity of the metal-ion complex was poisoned by strong ligation to the thiourea.
- (8) At high copper(I) loadings, saturation of the bridgehead nitrogen presumably reduces the amount of Brønsted base required for enolate formation.
- (9) The reaction was quenched and analyzed after 3 h (25% conversion, E/Z = 94:6) to minimize the extent of Cu(I)-promoted H/D exchange processes in **5** prior to cyclization.

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