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Organocatalytic Asymmetric Addition of Alcohols and Thiols to Activated Electrophiles: Efficient Dynamic Kinetic Resolution and Desymmetrization Protocols

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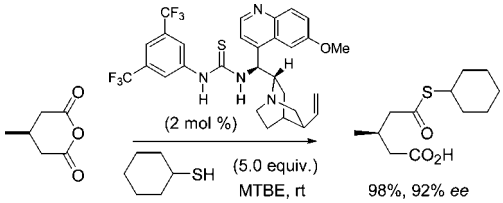

Bifunctional urea-based cinchona alkaloid derivatives have been shown to promote highly efficient DKR reactions of azalactones using an alcohol nucleophile. The optimum catalyst is remarkably insensitive to the steric bulk of the amino acid residue, allowing alanine-, methionine-, and phenylalanine-derived azalactones to undergo DKR with unprecedented levels of enantioselectivity using a synthetic catalyst. The first DKR of these substrates by thiols and the highly enantioselective desymmetrization of a *meso*-glutaric anhydride by thiolysis are also reported.

The catalytic dynamic kinetic resolution (DKR)[1] of α-substituted azalactones by alcoholysis is a potentially useful route to the facile, enantioselective synthesis of orthogonally protected α-amino acid derivatives. While principally a kinetic resolution process in which one enantiomer of the racemic starting material reacts perferentially with an alcohol nucleophile in the presence of a chiral catalyst, the acidity of the α-hydrogen of the azalactone (pK_a = ca. 9, H_2O, 25 °C)[2] allows a maximum theoretical yield of almost 100% through the continuous regeneration of the fast-reacting antipode if the catalyst is of sufficient basicity to ensure that the racemization rate is considerably greater than that of the alcoholysis of the slow reacting enantiomer (i.e. $k_{fast} \gg k_{slow}$ and $k_{rac} \gg k_{slow}$, Figure 1). Several strategies involving de novo designed catalysts[3] have been employed to bring about the selective DKR of azalactone substrates including the use of Ti-based complexes,[4] cyclic

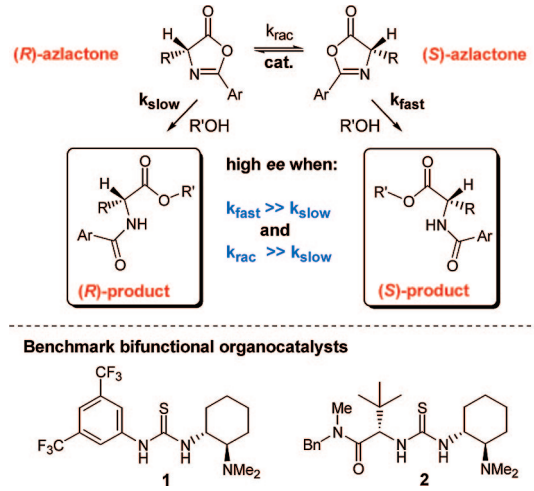

FIGURE 1. Catalytic DKR of azalactones by alcoholysis.

dipeptides,[5] and chiral 4-*N,N*-dialkylaminopyridine nucleophilic catalysts.[6] While some of these methodologies allowed the synthesis of the ring-opened adducts with high levels of product enantiomeric excess (>80% ee), in general, their applicability is mitigated by narrow substrate scope and/or low activity leading to long reaction times.

Recently, Berkessel[7] has exploited the hydrogen-bonding ability of (thio)urea derivatives[8] in the use of a suite of bifunctional catalysts—of which Takemoto's catalyst **1**[9] and an improved second-generation promoter **2** (Figure 1) are representative—which promote the enantioselective addition of allyl alcohol to azalactones. It was proposed that the catalysts operate via the simultaneous activation of the reaction's electrophilic and nucleophilic components by hydrogen bonding and general base catalysis, respectively. Excellent levels of enantioselectivity (>90% ee) were obtained using hindered valine and (in particular) *tert*-leucine-derived azalactones at the expense of

(1) (a) Faber, K. *Chem. Eur. J.* **2001**, *7*, 5004. (b) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291.

(2) De Jersey, J.; Zerner, B. *Biochemistry* **1969**, *8*, 1967.

(3) For examples of the use of enzymes (which are generally only selective at temperatures of 37 °C or above, depending on the particular enzyme) to asymmetrically ring-open azalactones with high levels of enantioselectivity, see: (a) S. A. Brown, S. A.; Parker, M.-C.; Turner, N. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1687. (b) Crich, J. Z.; Brieva, R.; Marquant, P.; Gu, R. L.; Flemming, S.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 3252. (c) Gu, R. L.; Lee, I.-S.; Sih, C. J. *Tetrahedron Lett.* **1992**, *33*, 1953.

(4) (a) Seebach, D.; Jaeschke, G.; Gottwald, K.; Mastsuda, K.; Formisano, R.; Chaplin, D. A. *Tetrahedron* **1997**, *53*, 7539. (b) Gottwald, K.; Seebach, D. *Tetrahedron* **1999**, *55*, 723.

(5) Xie, L.; Hua, W.; Chan, A. S. C.; Leung, Y.-C. *Tetrahedron: Asymmetry* **1999**, *10*, 4715.

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(7) (a) Berkessel, A.; Cleeman, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem.* **2005**, *44*, 807. (b) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898. (c) Berkessel, A.; Mukherjee, S.; Müller, T. N.; Cleeman, F.; Roland, K.; Brandenburg, M.; Neudörfl, J.-M.; Lex, J. *Org. Biomol. Chem.* **2006**, *4*, 4319.

(8) For selected recent reviews on the use of hydrogen bonding in catalysis, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (e) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909. (f) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (g) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (h) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

(9) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

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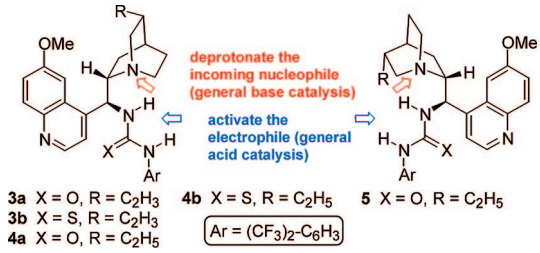


FIGURE 2. Bifunctional alkaloid-derived catalysts.

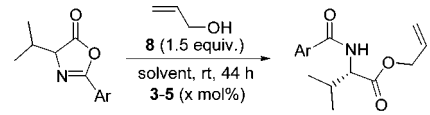
product yield, whereas electrophiles with a lower steric requirement underwent smooth ring-opening with reduced[10] (yet still on a par with previous benchmarks[4–6]) enantiopurity.

While remarkable progress toward the development of a general catalytic asymmetric system for these potentially useful transformations has been made, some challenges remain—in particular, the need to address the sensitivity of the methodology to substrate steric bulk and the expansion of the reaction scope to include nonalcoholic nucleophiles. We therefore became interested in the evaluation of the cinchona alkaloid-derived urea- and thiourea-based catalysts (Figure 2) in this reaction. These bifunctional materials promote a variety of asymmetric addition reactions of acidic pronucleophiles to hydrogen-bond accepting electrophiles,[11,12] and in particular, we were encouraged by recently finding that they are capable of mediating highly efficient and enantioselective additions of alcohols to *meso*-anhydrides.[13]

Our investigation began with the DKR of valine-derived azalactones **6a**–**c** with allyl alcohol in the presence of the urea-based catalyst **3a** at ambient temperature (Table 1).[14] These initial experiments revealed that **3a** is an active catalyst capable of promoting both racemization and enantioselective (>80% ee) ring opening of these substrates (no reaction was observed in the absence of the catalyst) at loadings of 5 mol %. As expected, the more activated azalactone **6c** underwent faster and slightly less selective DKR than either **6a** or **6b** (entries 1–4). The influence of concentration and nucleophile loading was next examined—either 1.5 or 2.0 equiv of allyl alcohol at 0.2 M reaction concentration provided a convenient balance between rate and enantioselectivity (entries 5–11). Dichloromethane was determined to be superior to either ethereal solvents or toluene (entries 6 and 12–15), while carrying out the reaction at −20 °C resulted in a small improvement in enantioselectivity (87% ee), albeit with reduced conversion even after extended reaction time (entry 16). Interestingly, urea derivative **3a** is a better catalyst under these conditions than its thiourea analogue **3b**,[15] while the corresponding dihydroquinine-derived (thio)urea derivatives **4a**,**b** possesses similar selectivity but better activity profiles than their quinine-derived counterparts **3a**,**b** (entries 17–20). Thus, **4a** (at 5 mol % levels) emerged from these initial optimization studies as a readily prepared, active catalyst capable of the highly enantioselective (85% ee), almost quantitative conversion of the hindered substrate **6a** to **7a** at ambient temperature.

Having established **4a** as the optimum catalyst, we next turned to the determination of the substrate scope (Table 2). We were pleased to find **4a** to be relatively insensitive to the steric bulk of the azalactone alkyl substituent: both unhindered azalactones (entries 1–4) and more bulky analogues (entries 5–7) underwent enantioselective DKR to furnish orthogonally protected amino acids with very good enantioselectivity. To the best of our knowledge, this represents the most selective DKR of azalactones **8**–**10** by alcoholysis with a synthetic catalyst to date.

TABLE 1. Initial Catalyst Screening



6a Ar = C_6H_5
6b Ar = 4-OMe-C_6H_4
6c Ar = 4-CF_3-C_6H_4

7a Ar = C_6H_5
7b Ar = 4-OMe-C_6H_4
7c Ar = 4-CF_3-C_6H_4

entry	lactone	cat.	*x*	solvent	conc[a] (M)	conv[b] (%)	ee[c] (%)
1	**6a**	none		CH_2Cl_2	0.4	0	n.d.
2	**6a**	**3a**	5	CH_2Cl_2	0.4	92	82
3	**6b**	**3a**	5	CH_2Cl_2	0.4	79	81
4	**6c**	**3a**	5	CH_2Cl_2	0.4	92	78
5	**6a**	**3a**	5	CH_2Cl_2	1.0	>98	62
6	**6a**	**3a**	5	CH_2Cl_2	0.2	75	83
7[d]	**6a**	**3a**	5	CH_2Cl_2	0.2	62	84
8[e]	**6a**	**3a**	5	CH_2Cl_2	0.2	83	83
9	**6a**	**3a**	10	CH_2Cl_2	0.4	95	82
10	**6a**	**3a**	10	CH_2Cl_2	0.2	89	84
11	**6a**	**3a**	10	CH_2Cl_2	0.1	78	85
12	**6a**	**3a**	5	MTBE	0.2	26	83
13	**6a**	**3a**	5	THF	0.2	2	n.d.
14	**6a**	**3a**	5	Et_2O	0.2	31	n.d.
15	**6a**	**3a**	5	PhMe	0.2	71	77
16[f]	**6a**	**3a**	10	CH_2Cl_2	0.2	52	87
17[g]	**6a**	**3b**	5	CH_2Cl_2	0.2	100	67
18[h]	**6a**	**4a**	5	CH_2Cl_2	0.2	99	85
19[i]	**6a**	**4a**	10	CH_2Cl_2	0.2	94	84
20[g]	**6a**	**4b**	5	CH_2Cl_2	0.2	100	77
21[j]	**6a**	**5**	5	CH_2Cl_2	0.2	47	n.d.

[a] Refers to the concentration of the azalactone. [b] Conversion: determined by ^{1}H NMR spectroscopy. [c] Enantioselectivity (% ee, determined by CSP-HPLC; see the Supporting Information). [d] 1.0 equiv of **8**. [e] 2.0 equiv of **8**. [f] 2.0 equiv of **7**, at −20 °C, conversion after 72 h. [g] 2.0 equiv of **8**, conversion after 65 h. [h] 2.0 equiv of **8**, conversion after 34 h. [i] 2.0 equiv of **8**, at −20 °C, conversion after 72 h. [j] 2.0 equiv of **8**, conversion after 24 h.

(10) For example, the levels of enantiomeric excess obtained with alanine and phenylalanine-derived substrates using catalyst **2** and allyl alcohol was 80 and 78% ee, respectively[7b]).

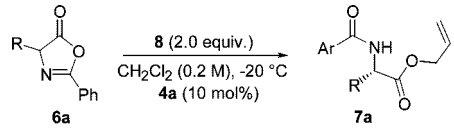
(11) For a review of the applications of this class of catalyst, see: Connon, S. J. *Chem. Commun.* **2008**, 2499.

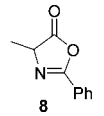
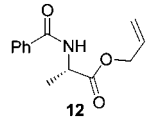
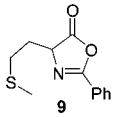
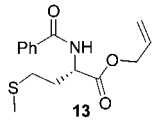
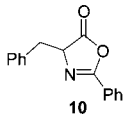
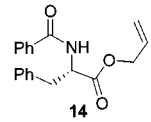
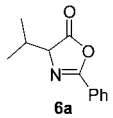
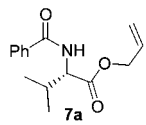
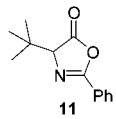
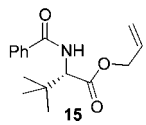
(12) (a) Li, B.-J.; Jang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (c) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (d) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (e) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (f) McCooey, S. H.; McCabe, T.; Connon, S. J. *J. Org. Chem.* **2006**, *71*, 7494. (g) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932. (h) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652. (i) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (j) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (k) Bode, C. M.; Ting, A.; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499. (l) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151. (m) Liu, T.-Y.; Li, R.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Eur. J.* **2007**, *13*, 319. (n) Amere, M.; Lasne, M.-C.; Rouden, J. *Org. Lett.* **2007**, *9*, 2621. (o) Hynes, P. S.; Stranges, D.; Stupple, P. A.; Guarna, A.; Dixon, D. A. *Org. Lett.* **2007**, *9*, 2107. (p) Liu, T.-Y.; Cui, H.-Lei.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Commun.* **2007**, 2228. (q) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830. (r) Gu, C.-L.; Liu, L.; Sui, Y.; Zhao, J.-L.; Wang, D.; Chen, Y. J. *Tetrahedron: Asymmetry* **2007**, *18*, 455. (s) Song, J.; Shih, H.-W.; Deng, L. *Org. Lett.* **2007**, *9*, 603. (t) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (u) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (v) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mazzanti, A.; Sambri, L.; Melchiorre, P. *Chem. Commun.* **2007**, 722.

(13) Peschiulli, A.; Gun'ko, Y.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 2454.

(14) Allyl alcohol proved the optimum alcohol nucleophile; for example, use of the more acidic 2,2,2-trichloroethanol under conditions otherwise identical to those in Table 1, entry 6, furnished the product with 85% conversion and 33% ee after 24 h. Phenol was a similarly unsuitable nucleophile.

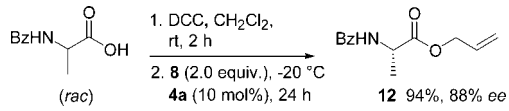
TABLE 2. Investigation of Substrate Scope



entry	azalactone	product	t (h)	yield (%)[a]	*ee* (%)[b]
1	 8	 12	28	98	88
2[c]			24	99	82
3	 9	 13	30	97	79
4	 10	 14	28	98	78
5[c]	 6a	 7a	34	99	85
6			72	94	84
7[c]	 11	 15	48	93	85

[a] Isolated yield. [b] Enantioselectivity (% ee, determined by CSP-HPLC; see the Supporting Information). [c] Reaction at rt with 5 mol % catalyst.

SCHEME 1. One-Pot DKR from a *N*-Benzoylamino Acid



The robust nature of catalyst **4a** also allowed us to develop a convenient, organocatalyzed one-pot DKR protocol starting from N-protected racemic alanine which gives the corresponding enantioenriched allyl ester in excellent isolated yield and enantioselectivity (Scheme 1).

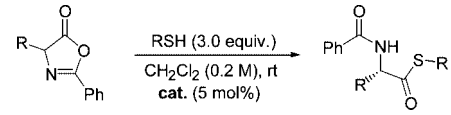
The broad applicability of catalyst **4a** in these reactions prompted us to investigate the use of thiol nucleophiles in these processes for the first time. Such a DKR process would be particularly attractive synthetically as it could allow the direct synthesis of enantioenriched unnatural amino acid thioesters for use in native chemical ligation (NCL),[16] a powerful coupling tool in contemporary chemical biology.[17]

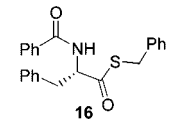
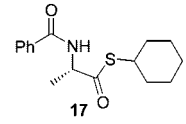
(15) This superiority of urea over thiourea derivatives is unusual but not unprecedented; for other examples, see: (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (b) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259. (c) Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301. (d) Kavanagh, S. A.; Piccinini, A.; Fleming, E. M.; Connon, S. J. *Org. Biomol. Chem.* **2008**, *6*, 1339. (e) Fleming, E. M.; Quigley, C.; Rozas, I.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 948.

(16) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. *Science* **1994**, *266*, 776.

(17) Macmillan, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7668.

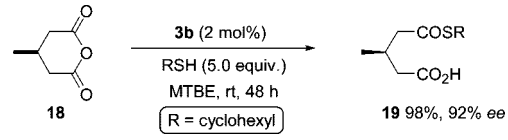
TABLE 3. Catalytic DKR Using Thiol Nucleophiles



entry	cat.	product	t (h)	yield (%)[a]	*ee* (%)[b]
1	**3a**	 16	20	99[c]	30
2	**3a**		24	92	49
3	**3b**	 17	24	96	38
4	**4a**		24	98	50
5[d]	**4a**		24	90	64

[a] Isolated yield. [b] Enantioselectivity (% ee, determined by CSP-HPLC). [c] Refers to conversion. [d] At −30 °C with 10 mol % of **4a**.

SCHEME 2. Desymmetrization of a *meso*-Anhydride by Thiolysis



Gratifyingly, preliminary experiments revealed that while the unhindered benzyl mercaptan provided the thioester product with low enantioselectivity, use of the more hindered cyclohexyl thiol[18] resulted in more selective desymmetrization (Table 3, entries 1−4). Under optimum conditions using catalyst **4a**, the challenging unhindered racemic azalactone substrate **8** could be converted to thioesters **16** and **17** with moderate/good levels of enantiomeric excess (entry 5).

Finally, the compatibility of thiols with catalyst **4a** led us to postulate that these cinchona alkaloid derivatives could promote the efficient desymmetrization of *meso*-anhydrides by thiolysis.[19] Treatment of *meso*-glutaric anhydride **18** with cyclohexyl thiol in the presence of thiourea **3b** (1 mol%) afforded the synthetically useful hemithioester **19** in excellent yield and >90% ee (Scheme 2).[20] This represents the most selective organocatalytic thiolysis of this electrophile to date.

In summary, readily synthesized bifunctional cinchona alkaloid derived catalysts promote the highly efficient DKR of azalactones with allyl alcohol. Urea derivatives are superior to their thiourea analogues in these reactions, and most usefully, the catalysts are insensitive to the steric bulk of the amino acid residue, allowing alanine-, methionine-, and phenylalanine-derived azalactones to undergo DKR with unprecedented levels of enantioselectivity using a synthetic catalyst. The compatibility of these catalysts with thiol nucleophiles was exploited in the first enantioselective catalytic DKR of azalactones by thiolysis to furnish enantioenriched amino acid thioesters of potential use

(18) Use of *t*ert-butyl thiol did not result in further improvements.

(19) Only one such protocol has been reported: Honjo, T.; Sano, S.; Shiro, M.; Nagao, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5838.

(20) Early experiments indicate that succinic anhydrides are inferior substrates in these reactions.

in NCL processes. Further experimentation revealed that this catalysis mode could be extended to the ambient-temperature efficient desymmetrization of a *meso*-glutaric anhydride by thiolysis with excellent enantioselectivity using a little as 2 mol % of catalyst. Experiments to further develop the wide scope of these catalysts in DKR and desymmetrization reactions are underway.

Experimental Section

One-Pot DKR from *N*-Benzoylalanine. A 5 mL reaction vial containing a stirring bar was charged with *N*-benzoylalanine (58.0 mg, 0.3 mmol), flushed with argon, and fitted with a septum. CH_2Cl_2 (0.5 mL) was added followed by a solution of DCC (65.0 mg, 0.315 mmol) in CH_2Cl_2 (0.5 mL) via syringe, and the mixture was stirred at room temperature for 2 h. **4a** (17.4 mg, 0.03 mmol) was added as a solution in CH_2Cl_2 (0.5 mL), and the resulting mixture was cooled to −20 °C. Allyl alcohol (41 μL, 0.6 mmol) was then added in a dropwise manner via syringe, and the reaction was stirred at −20 °C for 24 h. After filtration of the white dicyclohexylurea precipitate, the product was purified by flash chromatography and obtained as a white solid (66.0 mg, 94%, 88% ee). For characterization data, see the Supporting Information.

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Supporting Information Available: General experimental procedures, ^1H and ^{13}C NMR spectra, characterization data, and HPLC assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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