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Construction of Highly Functional Quaternary Carbon Stereocenters *via* an Organocatalytic Tandem Cyanation–Allylic Alkylation Reaction

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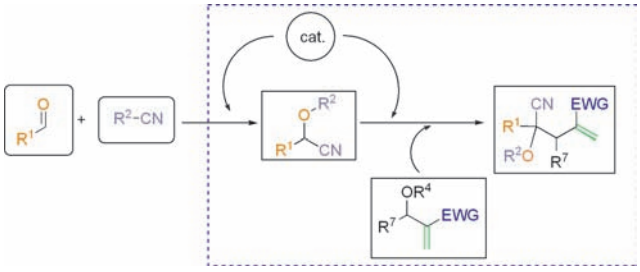
ABSTRACT



The first tertiary amine-catalyzed tandem cyanation–allyic alkylation (CAA) reaction of aldehydes, appropriate cyanide sources, and Morita–Baylis–Hillman (MBH) adducts has been developed, which provides a facile access to densely functionalized products containing *O*-substituted quaternary centers.

Catalytic multistep processes, whereby one or more catalysts promote two or more distinct chemical transformations in a single flask, have received growing attention due to their high efficiency and economy to access valuable molecular constructs.[1] Several successful synthetic strategies based on this concept have been developed to enable the construction of diverse molecular architectures *via* organocatalysis.[2] As a fundamentally important chemical transformation, to construct molecules with tetrasubstituted carbon stereocenters represents a stimulating challenge in modern organic synthesis.[3] Although significant progress has been made toward this target, utilization of novel catalytic multistep processes, especially *via* organocatalytic tandem pathways to access densely functionalized products containing *O*-substituted quaternary stereocenters, is still required.[4]

The addition of cyanide to carbonyl compounds is one of the oldest known C–C bond-forming reactions, and cyanohydrins have demonstrated considerable synthetic potential as useful building blocks.[5]Although cyanohydrins

(1) For selected recent reviews on multicatalysis, see: (a) Enders, D.; Grondal, C.; Huettl, M. R. M. *Angew. Chem., Int. Ed* **2007**, *46*, 1570. (b) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477. (c) Ramachary, D. B.; Jain, S. *Org. Biomol. Chem* **2011**, *9*, 1277. (d) Zhou, J. *Chem.—Asian J.* **2010**, *5*, 422. (e) Ambrosini, L. M.; Lambert, T. H. *ChemCatChem* **2010**, *2*, 1373.

(2) For selected recent examples: (a) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (b) Reyes, E.; Talavera, G.; Vicario, J. L.; Badia, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 5701. (c) Brandau, S.; Maerten, E.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (d) Enders, D.; Huettl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem., Int. Ed* **2007**, *46*, 467. (e) Zhao, G.-L.; Rios, R.; Vesely, J.; Eriksson, L.; Cordova, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8468. (f) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349. For recent reviews, see: (g) Enders, D.; Grondal, C.; Huettl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.

(3) For selected recent reviews of catalytic asymmetric reactions, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (d) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (e) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. (f) Bella, M.; Gasperi, T. *Synthesis* **2009**, *10*, 1583.

(4) For examples of organocatalytic domino synthesis of tertiary alcohols, see: (a) Halland, N.; Aburel, P. S.; Jorgensen, K. A. *Angew. Chem.* **2004**, *116*, 1292. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272. (b) Zhao, G.-L.; Vesely, J.; Rios, R.; Ibrahem, I.; Sundén, H.; Córdova, A. *Adv. Synth. Catal* **2008**, *350*, 237.

(5) For reviews, see: (a) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147. (b) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. (c) Brunel, J.-M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752. (d) North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146. (e) Wang, W. T.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Eur. J. Org. Chem.* **2010**, *25*, 4751.

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containing an acidic proton which can be employed as nucleophilic reagents have been applied in organic synthesis,[6] to the best of our knowledge, organocatalytic synthesis of tertiary alcohols based on cyanohydrins, which have potential utility in organic synthesis C−C bond formations, has been undeveloped.[7]

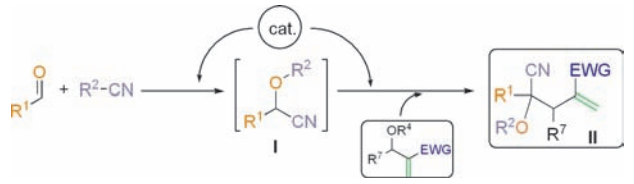


Figure 1. Strategy of tandem cyanation−allylic alkylation reaction.

Recently, the metal-free Lewis base catalyzed substitution of MBH adducts has emerged as a powerful tool for preparing multifunctional compounds.[8] This approach normally relies on a tandem S_N2'/S_N2'substitution sequence to access allylic product. We envisioned that these two distinct chemical transformations could be triggered by one or more organocatalysts, therefore creating a new C−C bond formation in a sequential way which may deliver substantial increases in molecular complexity *via* single-pot operations without the need for intermediate workups or purifications, since they share similar or the same catalysts and reaction environment. As outlined in Figure 1, initial *O*-substituted cyanohydrins **I** from aldehydes would be generated by an organocatalyst *in situ*. Subsequently, the deprotonation of the acidic CH group of cyanohydrins by the oxygen-based anion generated *in situ* would occur, and selective allylic alkylation would follow to deliver valuable densely functionalized products **II**, which contain a tertiary alcohol moiety, as well as cyanide and allylic functional groups.

Here, we report the first CAA reaction with MBH adducts, providing a useful protocol to prepare highly functionalized cyanohydrins.

To assess the feasibility of an organocatalytic tandem CAA reaction, an initial investigation was examined with MBH carbonate **2a** and preformed cyanohydrins **1a** which were prepared readily from benzaldehyde and ethyl cyanoformate in the presence of organic Lewis base catalysts.[9,10] Gratifyingly, this reaction proceeded well in toluene with a catalytic amount of DABCO (1,4-diazabicyclo[2.2.2]octane) (Table 1, entry 1). Under these optimized conditions, intermolecular catalytic allylic alkylation of MBH adducts with a spectrum of prochiral cyanohydrins derived from aldehydes was surveyed to explore the generality of this transformation. The results are summarized in Table 1. For the cyanohydrins prepared from aromatic aldehydes with electron-withdrawing or -donating substituents, the corresponding allylic alkylation products **3a**−**3d, 3g** were obtained in good to excellent yields. When cyanohydrins with ortho-substituents at the aryl group (**1e** and **1f**) were employed, low transformations and long reaction times were observed (72 h, 17% for **3e**; 30 h, 42% for **3f**), presumably due to a steric hindrance effect. However, submitting this reaction in acetonitrile provided **3e** and **3f** in moderate to high yields (Table 1, entries 5, 6). The allylic alkylation of MBH acetate **2c** with cyanohydrins **1a** failed to give desired product **3a**. In contrast to aromatic analogue **1a**, cyanohydrin **1l** possessing two electron-withdrawing groups can smoothly react with MBH acetate **2c** to provide **3l** with 95% yield (Table 1, entries 13, 14), which reveals a dramatic dependence on the ΔpK_a between the conjugate acid of the leaving group and the pronucleophile. The subsititution of MBH carbonate **2a** with heteroaromatic substituted cyanohydrins **1h** also gave rise to desired product **3h** in 71% yield. MBH adduct **2d** which would allow the generation of vicinal quaternary and tertiary carbon centers was investigated. Cyanohydrins **1a** reacted with **2d** to furnish desired product **3r** in high yield with low diastereoselectivity (dr: 1/1, Table 1, entry 15). Furthermore, *O*-protected derivatives such as *O*-acetyl, *O*-benzoyl, and *O*-trimethylsilyl cyanohydrins have been investigated. *O*-Acetyl and *O*-benzoyl cyanohydrins readily reacted with MBH carbonate **2a** to afford desired products (Table 1, entries 10, 11), while *O*-TMS cyanohydrin **1k** did not provided any desired product under standard reaction conditions (Table 1, entry 12).

As a further demonstration of the scope of this reaction, catalytic allylic alkylation of MBH adducts **2** with

(6) For reviews, see: (a) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207. For selected examples in organic synthesis, see: (b) Moritani, Y.; Fukushima, C.; Ukita, T.; Miyagishima, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 6922. (c) Katritzky, A. R.; Zhang, G.; Jiang, J. *J. Org. Chem.* **1995**, *60*, 7589.

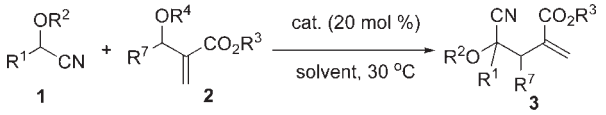
(7) Pd-catalyzed allylic alkylation of prochiral cyanohydrins: Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523.

(8) For selected examples, see: (a) Cho, C.-W.; Krische, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689. (b) Du, Y.; Han, X.; Lu, X. *Tetrahedron Lett.* **2004**, *45*, 4967. (c) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337. (d) van Steenis, D. J. V. C.; Marcelli, T.; Lutz, M.; Spek, A. L.; van Maarseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal.* **2007**, *349*, 281. (e) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202. (f) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737. (g) Cui, H.-L.; Peng, J.; Feng, X.; Du, W.; Jiang, K.; Chen, Y.-C. *Chem.—Eur. J.* **2009**, *15*, 1574. (h) Jiang, K.; Peng, J.; Cui, H.-L.; Chen, Y.-C. *Chem. Commun.* **2009**, 3955. (i) Feng, X.; Yuan, Y.-Q.; Cui, H.-L.; Jiang, K.; Chen, Y.-C. *Org. Biomol. Chem.* **2009**, *7*, 3660. (j) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720. (k) Huang, J.-R.; Cui, H.-L.; Lei, J.; Sun, X.-H.; Chen, Y.-C. *Chem. Commun.* **2011**, 4784. (l) Hong, L.; Sun, W. S.; Liu, C. X.; Zhao, D. P.; Wang, R. *Chem. Commun.* **2010**, *46*, 2856. (m) Sun, W. S.; Hong, L.; Liu, C. X.; Wang, R. *Org. Lett.* **2010**, *12*, 3914. (n) Jiang, L.; Lei, Q.; Huang, X.; Cui, H. L.; Zhou, X.; Chen, Y.-C. *Chem.—Eur. J.* **2011**, *17*, 9489. (o) Yang, W.; Wei, X.; Pan, Y.; Lee, R.; Zhu, B.; Liu, H.; Yan, L.; Huang, K. W.; Jiang, Z.; Tan, C. H. *Chem.—Eur. J.* **2011**, *17*, 8066.

(9) For examples of synthesis of racemic *O*-carbonylated cyanohydrins using nonchiral tertiary amines, see: (a) Hoffmann, H. M. R.; Ismail, Z. M.; Hollweg, R.; Zein, A. R. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1807. (b) Poirier, D.; Berthiaume, D.; Boivin, R. P. *Synlett* **1999**, 1423. (c) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995. (d) Deardorff, D. R.; Taniguchi, C. M.; Tafti, S. A.; Kim, H. Y.; Choi, S. Y.; Downey, K. J.; Nguyen, T. V. *J. Org. Chem.* **2001**, *66*, 7191. (e) Aoki, S.; Kotani, S.; Sugiura, M.; Nakajima, M. *Tetrahedron Lett.* **2010**, *51*, 3547. (f) Baeza, A.; Najera, C.; Retamosa, M. G.; Sansano, J. M. *Synthesis* **2005**, *16*, 2787.

(10) See Supporting Information for details.

Table 1. Direct Allylic Alkylation of *O*-Protected Cyanohydrins with MBH Adducts **2**[a]



2a: R^7 = H; R^4 = Boc; R^3 = Me; **2b**: R^7 = H; R^4 = Boc; R^3 = Et;
2c: R^7 = H; R^4 = Ac; R^3 = Me; **2d**: R^7 = Ph; R^4 = Boc; R^3 = Me;

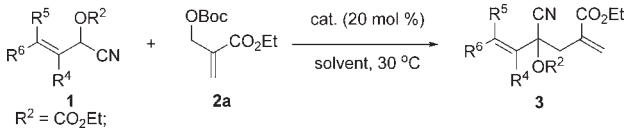
entry	**1**	R^1	R^2	**2**	**3**	*t* (h)	yield (%)[b]
1	**1a**	Ph	CO_2Et	**2a**	**3a**	12	98
2	**1b**	4-ClC_6H_4	CO_2Et	**2a**	**3b**	12	96
3	**1c**	4-$MeOC_6H_4$	CO_2Et	**2a**	**3c**	21	78
4	**1d**	3-$MeOC_6H_4$	CO_2Et	**2a**	**3d**	12	86
5[c]	**1e**	2-$MeOC_6H_4$	CO_2Et	**2a**	**3e**	24	58
6[c]	**1f**	2-BrC_6H_4	CO_2Et	**2a**	**3f**	12	89
7	**1g**	2-naphyl	CO_2Et	**2a**	**3g**	15	99
8	**1h**	2-furyl	CO_2Et	**2a**	**3h**	9	71
9	**1a**	Ph	CO_2Et	**2b**	**3q**	12	97
10	**1i**	Ph	COMe	**2a**	**3i**	12	84
11	**1j**	Ph	COPh	**2a**	**3j**	24	83
12	**1k**	Ph	TMS	**2a**	**3k**	12	–[d]
13[e]	**1l**	CO_2Et	COMe	**2a**	**3l**	2	92
14[f]	**1l**	CO_2Et	COMe	**2c**	**3l**	2	95
15	**1a**	Ph	CO_2Et	**2d**	**3r**	12	88[g]

[a] Unless otherwise noted, reactions were performed with 0.3 mmol of **1a**, 0.6 mmol of **2a**, 0.15 mmol of $(Boc)_2O$, and 20 mol % of DABCO in 3.0 mL of toluene at 30 °C. [b] Isolated yield. [c] The reactions was performed in CH_3CN. [d] No desired product was detected. [e] The reactions was performed at 0 °C . [f] The reactions was performed at 18 °C . [g] Mixture of diastereomers. dr: 1/1 (determined by ^1H NMR).

α,β-unsaturated cyanohydrins **1** prepared from α,β-unsaturated aldehydes was attempted, which would provide more synthetic useful allylic and vinyl substituted cyanohydrin derivatives. In contrast to the palladium-catalyzed allylation, in which acylated α,β-unsaturated cyanohydrins are used to generate (π-allyl) palladium complexes and subsequently react with nucleophiles,[9d] cyanohydrins **1** acted as nucleophiles and attacked activated MBH adducts to furnish **3** (Table 2). Gratifyingly, whether upon exposure of the β-alkyl (Table 2, entries 1, 2), or β-aryl, α,β-substituted cyanohydrin carbonates (Table 2, entries 3, 4) and MBH carbonate **2a** to modified reaction conditions, efficient conversions to the corresponding allylic products **3** were observed.

We next focused our attention on the development of a catalytic cascade version of the CAA reaction. Recently, much effort has been focused toward achieving a facile and environmentally friendly procedure for the synthesis of *O*-substituted cyanohydrins from aldehydes.[9] In particular, solvent-free synthesis makes cyanation of carbonyl compounds more attractive due to its environmental, safety, and economical benefits.[9e,f] Interestingly, simple treatment of benzaldehyde and ethyl cyanoformate with catalyst DABCO (20%) in the absence of solvent and subsequent addition of MBH adducts furnished the expected products **3a** in 92% yield (Table 3, entry 1). Under

Table 2. Direct Allylic Alkylation of *O*-Protected Allylic Cyanohydrin **1** with MBH Adducts **2**[a]

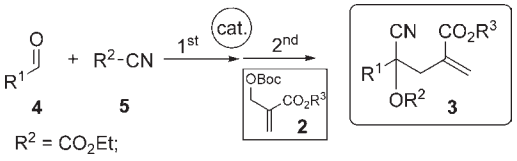


entry	**1**	R^4	R^5	R^6	**3**	*t* (h)	yield (%)[b]
1	**1m**	H	H	Me	**3m**	6	71
2	**1n**	H	H	n-C_3H_7	**3n**	9	81
3	**1o**	Me	H	Ph	**3o**	15	73
4	**1p**	H	Me	Ph	**3p**	3	81

[a] Reactions were performed with **1** (0.4 mmol), **2a** (0.2 mmol), $(Boc)_2O$ (0.2 mmol), and 20 mol % of DABCO in CH_3CN at 30 °C. [b] Isolated yield.

this solvent-free condition, a variety of above-mentioned allylic substituted cyanohydrins with *O*-substituted quaternary centers can been readily and rapidly prepared from commercially available aldehydes and cyanoformates by using this tandem cyanation–allylic alkyation reaction.[10]

Table 3. Tandem Cyanation–Allylic Alkylation Reaction with MBH Adducts[a]

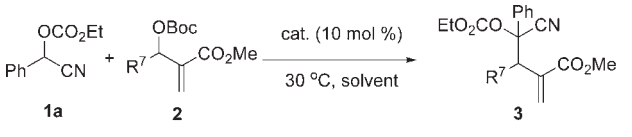


entry	R^1	**2**	R^3	**3**	*t* (1st/2nd, h/h) [b]	yield (%)[c]
1	Ph	**2a**	Me	**3a**	0.5/2	92
2	2-BrC_6H_4	**2a**	Me	**3f**	1/2	70
3[d]	2-naphthyl	**2a**	Me	**3g**	0.5/3	91
4[e]	2-furyl	**2a**	Me	**3h**	1/3	81
5[f]	(*E*)-CH_3CH=CH	**2b**	Et	**3m**	1/2	67
6[f]	(*E*)-$CH_3(CH_2)_2CH$=CH	**2b**	Et	**3n**	1/2	67
7[f]	(*E*)-Ph(CH_3)CH=CH	**2b**	Et	**3p**	1/1	61
8[f]	(*E*)-PhCH=CH(CH_3)	**2b**	Et	**3o**	1/1	49

[a] Reaction was performed with **4** (0.3 mmol), ethyl cyanoformate **5** (0.33 mmol), and 20 mol % of DABCO in neat at 30 °C during 1st step; **2** (0.6 mmol) and $(BOC)_2O$ (0.15 mmol) were added during the 2nd step. [b] 1st/2nd = the 1st step time/the 2nd step time. [c] Isolated yield. [d] The reaction was performed in CH_3CN (0.1 mL). [e] During the 2nd step, CH_3CN (3.0 mL) was added. [f] Aldehyde **4** (0.40 mmol), cyanoformate **5** (0.44 mmol), and NEt_3 (20%) were employed during the 1st step; **2** (0.2 mmol), $(BOC)_2O$ (0.2 mmol), and 20 mol % of DABCO were added during the 2nd step.

Investigation of asymmetric CAA reactions of MBH adducts were carried out by employing various chiral

Scheme 1. Asymmetric Allylic Alkylation Reactions of *O*-Protected Cyanohydrin **1** with MBH Adducts



2a (R^7 = H): $(DHQD)_2PHAL$(10%),Toluene, 72h; trace (**3a**);
$(DHQD)_2PHAL$(10%), CH_3CN, 12h; Yield: 89% (**3a**); ee: 4%;
2d (R^7 = Ph): $(DHQD)_2PHAL$(10%), Toluene, 120h; Yield: 15% (**3q**);
dr: 1/1.4 ; ee: 75% / 81%;
$(DHQD)_2PHAL$(10%), CH_3CN, 24h, Yield: 66% (*ent*-**3q**);
dr: 1/3; ee: 17% / 56%;

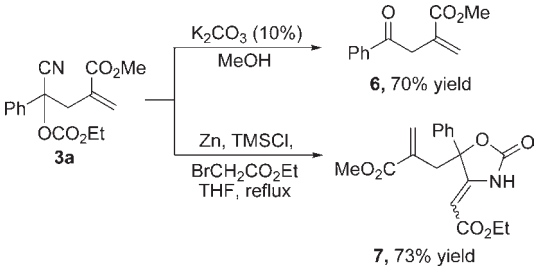
tertiary amines. $(DHQD)_2PHAL$ gave the best enantioselectivity (Scheme 1).[10] When the simple MBH adduct **2a** was employed, almost racemic products were obtained in 89% yield with 4% ee. Although the substitution of MBH carbonate **2d** with **1a** afforded desired product **3q** with moderate stereoselectivity (dr: 1/1.4, ee: 75%/81%), the low yield was obtained probably due to the lower activity of the catalyst.

Finally, the synthetic utilities of CAA products were illustrated. The treatment of **3a** with a K_2CO_3 (20%) in MeOH/H_2O solution afforded the corresponding ketone **6** in 70% yield.[9c] The nitrile functionality of products can also serve as an effective handle for further elaboration. For example, the reaction of a Reformatsky reagent, derived from ethyl α-bromoacetate and zinc, with **3a** resulted in highly functionalized 2-oxazolidinones **7** in 73% yield (Scheme 2).[11]

In conclusion, we have demonstrated an organocatalytic cyanation−allylic alkylation reaction with aldehydes, cyanoformate, and MBH adducts, which provided an efficient synthetic route for the preparation of densely functionalized products bearing an *O*-substituted quaternary centers. A number of aromatic or

(11) Syed, J.; Forster, S.; Effenberger, F. *Tetrahedron: Asymmetry* **1998**, *9*, 805.

Scheme 2. Synthetic Applications of the CAA Substitution Adducts



α,β-unsaturated aldehydes could be successfully applied to give multifunctional desired products which have potential utilities in organic synthesis. An asymmetric version of this reaction has also been demonstrated and displayed a moderate stereoselectivity. Furthermore, the first organocatalytic tandem CAA reaction has been applied on solvent-free conditions which makes it more environmentally friendly and economical. Further studies on synthetic applications and asymmetric catalysis are ongoing in our laboratories and will be reported in due course.

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Supporting Information Available. General procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.