JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Enhanced Rate and Selectivity by Carboxylate Salt as a Basic Cocatalyst in Chiral N-Heterocyclic Carbene-Catalyzed Asymmetric Acylation of Secondary Alcohols

Satoru Kuwano, Shingo Harada, Bubwoong Kang, Raphaël Oriez, Yousuke Yamaoka, Kiyosei Takasu,* and Ken-ichi Yamada*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Supporting Information

ABSTRACT: The rate and enantioselectivity of chiral NHC-catalyzed asymmetric acylation of alcohols with an adjacent H-bond donor functionality are remarkably enhanced in the presence of a carboxylate cocatalyst. The degree of the enhancement is correlated with the basicity of the carboxylate. With a cocatalyst and a newly developed electron-deficient chiral NHC, kinetic resolution and desymmetrization of cyclic diols and amino alcohols were achieved with extremely high selectivity (up to s = 218 and 99% ee, respectively) at a low catalyst loading (0.5 mol %). This asymmetric acylation is characterized by a unique preference for alcohols over amines, which are not converted into amides under the reaction conditions.

Enzymes are biological catalysts that promote chemical transformations in living organisms under mild conditions. These transformations are achieved by cooperative functions of amino acid residues, which may be acidic, basic, or nucleophilic, located in proper positions. In artificial catalysis, achiral additives occasionally serve as cocatalysts that cooperatively function to assist the asymmetric catalysts and increase the efficiency.[1] N-Heterocyclic carbenes (NHCs) have recently emerged as useful organocatalysts. NHCs have been utilized in various transformations[2] as catalysts for umpolung of aldehydes,[3] generation of activated esters via redox of aldehydes,[4] and activation of alcohols as a general base.[5] Herein we report that carboxylate salts work as a Brønsted base cocatalyst and enhance the rate and selectivity of NHC-catalyzed asymmetric acylation of alcohols.

Kinetic resolution of racemic secondary alcohols via enantioselective acylation is an important process in synthetic chemistry.[6] Many artificial catalysts[7] and enzymatic methods[8] have been developed for this purpose. Although numerous methods to kinetically resolve alcohols via enantioselective acylation are already available, when we initiated this study, an efficient example of NHC-catalyzed redox acylation had yet to be reported.[9−12] To further extend our previous study,[13] we investigated the kinetic resolution of relatively unexplored important chiral building blocks, *trans*-cycloalkane-1,2-diols.[14,15]

A mixture of chiral NHC precursor **1a** (10 mol %), racemic *trans*-1,2-diol (±)-**2b**, and K_3PO_4 (1.1 equiv) in chloroform was stirred for 10 min at room temperature to generate the chiral NHC, and then α-chloro aldehyde **3a** (0.8 equiv) was added to the mixture. After 8 h, ester (+)-**4b** was produced in 46% yield with 80% ee, and enantiomerically enriched (−)-**2b** (68% ee) was recovered in 54% yield [selectivity factor (s)[16] = 18] (Table 1, entry 1). The independence of the s value from the conversion guaranteed its relevance in evaluating the selectivity [see the Supporting Information (SI)]. When α-bromo aldehyde **3b** was used in lieu of **3a**, the reaction proceeded slightly faster (54% conv. after 6 h) with a similar level of selectivity (s = 20) (entry 2). Surprisingly, using α-benzoyloxy aldehyde **3c** accelerated the reaction (51% conv. after 3 h) despite the inferior leaving-group ability of benzoate, and to our delight, the selectivity was also improved (s = 29) (entry 3).

We speculated that the liberated benzoate might be responsible for the observed improvement and therefore conducted the reaction with **3b** in the presence of potassium benzoate. The reaction was markedly accelerated. The selectivity was the same (s = 29), but the conversion reached 43% after only 15 min (entry 4). The same result was obtained when potassium benzoate was generated in situ from 1:1 benzoic acid/K_3PO_4 (entry 5). Consequently, benzoates with different basicities were tested with the in situ generation protocol. As shown in entries 5−7, the more basic the utilized benzoate,[17] the more enhanced the rate and selectivity. After only 2 min, 47% conversion was accomplished with high selectivity (s = 39) using 4-dimethylaminobenzoate (entry 7). These results indicate that the in situ-generated carboxylate acts as a base.

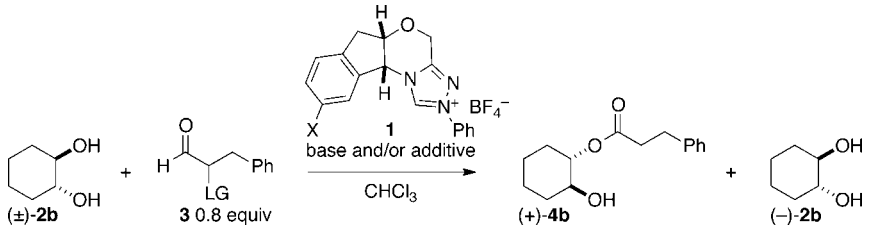
Modification of the chiral NHC further improved the selectivity. After screening NHCs (see the SI), we found that a new NHC derived from precursor **1b** bearing a Br atom on the indane moiety gave better results (40% conv. after 1 min, s = 62; entry 8). Finally, the NHC derived from **1c** bearing a nitro group gave the best result, and (±)-**2b** was resolved with a much higher selectivity (s = 85; entry 9). Although it is known that the steric and electronic properties of the *N*-aryl groups significantly influence the catalytic ability of NHCs,[18] to the best of our knowledge, this is the first example showing that the catalytic ability of chiral triazolylidene-type NHCs can be tuned by modifying the remote indane moiety.[19]

Among the tested bases (see the SI), 1,8-bis(dimethylamino)-naphthalene (proton sponge) was the best, providing sufficient selectivity (s = 115) with only 0.1 mol % **1c** and 0.1 equiv of the carboxylate additive (entry 10). Lowering the temperature

Received: June 4, 2013
Published: July 17, 2013

dx.doi.org/10.1021/ja4055838 | J. Am. Chem. Soc. 2013, 135, 11485−11488

Table 1. Optimization of the Reaction Conditions



entry	1/X (mol %)	3/LG	base and/or additive (equiv)	temp	time	conv. (%)[a]	*s*
1	**1a**/H (10)	**3a**/Cl	K_3PO_4 (1.1)	rt	8 h	46	18
2	**1a**/H (10)	**3b**/Br	K_3PO_4 (1.1)	rt	6 h	54	20
3	**1a**/H (10)	**3c**/OBz	K_3PO_4 (1.1)	rt	3 h	51	29
4	**1a**/H (10)	**3b**/Br	K_3PO_4 (1.1)/$C_6H_5CO_2K$ (1)	rt	15 min	43	29
5	**1a**/H (10)	**3b**/Br	K_3PO_4 (2.1)/$C_6H_5CO_2H$ (1)	rt	15 min	43	29
6	**1a**/H (10)	**3b**/Br	K_3PO_4 (2.1)/4-$NO_2C_6H_4CO_2H$ (1)	rt	20 min	34	14
7	**1a**/H (10)	**3b**/Br	K_3PO_4 (2.1)/4-$Me_2NC_6H_4CO_2H$ (1)	rt	2 min	47	39
8	**1b**/Br (10)	**3b**/Br	K_3PO_4 (2.1)/4-$Me_2NC_6H_4CO_2H$ (1)	rt	1 min	40	62
9	**1c**/NO_2 (10)	**3b**/Br	K_3PO_4 (2.1)/4-$Me_2NC_6H_4CO_2H$ (1)	rt	1 min	51	85
10	**1c**/NO_2 (0.1)	**3b**/Br	proton sponge (1.2)/4-$Me_2NC_6H_4CO_2H$ (0.1)	rt	4 h	28	115
11	**1c**/NO_2 (0.5)	**3b**/Br	proton sponge (1.2)/4-$Me_2NC_6H_4CO_2H$ (0.1)	0 °C	3 h	34	193
12	**1c**/NO_2 (1)	**3b**/Br	proton sponge (1.2)/4-$Me_2NC_6H_4CO_2H$ (0.1)	−20 °C	48 h	35	239

[a]Based on ee, determined by chiral-stationary-phase HPLC or GC, and confirmed by the isolated yield.

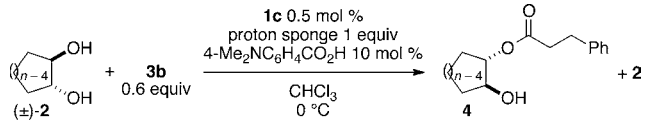
further improved the selectivity (s = 193 at 0 °C, s = 239 at −20 °C) at the cost of the catalyst loading (entries 11 and 12). Nevertheless, this high turnover number is a remarkable contrast to those of already-known organocatalyses, which typically require >1 mol % and sometimes 10−20 mol % catalyst.[20]

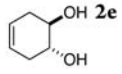
Next, other cyclic diols were applied to the reaction (Table 2). Six- to eight-membered cycloalkanediols (±)-**2b**−**d** were acylated with high selectivities (s = 149−218; entries 2−4). It is noteworthy that the highest selectivity to date (s = 18), although lower than for the other substrates, was observed in the resolution of cyclopentanediol (±)-**2a** (entry 1).[14f] Cyclohexene derivative (±)-**2e** was also resolved with high selectivity (s = 136; entry 5). Almost optically pure diols (−)-**2b**−**e** (>99% ee) were easily obtained when the reaction exceeded 50% conversion (entries 6−9). Because of the high selectivity, in addition to the alcohols, the esters (+)-**4**, which could be hydrolyzed to the antipodes of the recovered alcohols, were obtained with high optical purities (97−98% ee) in lower conversion (41−43%). It is noteworthy that the reaction quantitatively gave **2** and **4** without the formation of byproducts.

The utility of the reaction was highlighted by the multigram-scale availability of optically pure (−)-**2e**, which could be converted into **5**, a known intermediate[21] of antiflu drug oseltamivir (Scheme 1). The two hydroxy groups were replaced by azide groups through a triflate in 72% yield with inversion of the stereochemistry. Reduction of the azides followed by protection with Boc groups gave **5** in 69% yield without racemization.

It was reported that acylazoliums, the acylating intermediate in this reaction, strongly prefer acyl transfer to alcohols rather than amines, resulting in selective O-acylation in the presence of free amine.[13,22] To see whether the reaction can enjoy the benefits of this interesting selectivity, it was tested in the presence of dibenzylamine (Scheme 2). Although the pK_a values of the conjugate acids ($Bn_2NH_2^+$, 7.7; proton sponge·H^+, 12.1)[23]

Table 2. Kinetic Resolution of Diols 2



entry	2	time	4	recovered 2	*s*
1	**2a** n = 5	14 h	(−)-**4a** 39%, 82% ee	(−)-**2a** 60%, 54% ee	18
2	**2b** n = 6	8 h	(+)-**4b** 42%, 98% ee	(−)-**2b** 58%, 70% ee	218
3	**2c** n = 7	8 h	(+)-**4c** 43%, 97% ee	(−)-**2c** 55%, 77% ee	149
4	**2d** n = 8	8 h	(+)-**4d** 42%, 98% ee	(−)-**2d** 57%, 69% ee	196
5	 **2e**	8 h	(+)-**4e** 41%, 97% ee	(−)-**2e** 57%, 69% ee	136
6[a]	**2b**	17 h	(+)-**4b** 53%, 88% ee	(−)-**2b** 46%, >99% ee	
7[a]	**2c**	12 h	(+)-**4c** 53%, 85% ee	(−)-**2c** 46%, >99% ee	
8[a]	**2d**	14 h	(+)-**4d** 52%, 91% ee	(−)-**2d** 48%, >99% ee	
9[a,b]	**2e**	12 h	(+)-**4e** 54%, 83% ee	(−)-**2e** 44%, >99% ee	

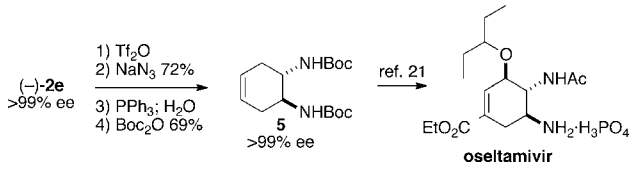
[a]0.7 equiv of **3b**. [b]5 g of (±)-**2e**.

indicated that the amine should mainly exist as the free amine, the reaction of (±)-**2b** proceeded without interference of the amine to give almost the same results (42% conv. after 8 h, s = 203) as in the absence of the amine (43% conv. after 8 h, s = 218; Table 2, entry 2) along with quantitative recovery of the amine.

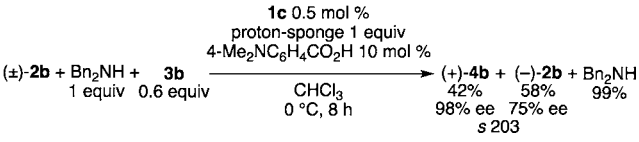
The following observations suggested that the carboxylate additive is involved in the stereodetermining transition state.

dx.doi.org/10.1021/ja4055838 | J. Am. Chem. Soc. 2013, 135, 11485−11488

Scheme 1. Formal Synthesis of Oseltamivir from (−)-2e



Scheme 2. Enantio- and Chemoselective O-Acylation in the Presence of Free Amine



When the reaction of Table 2, entry 2 was conducted without the addition of the carboxylic acid, both the rate and selectivity dramatically decreased (conv. after 8 h from 42% to 23%; s from 218 to 55). Furthermore, the absolute configuration of the chiral carboxylate additive influenced the enantioselectivity of the acylation. Relative to the reaction without an additive (s = 20; Table 1, entry 2), when potassium (*R*)- or (*S*)-*O*-methylmandelate was used in lieu of benzoate, the *S* enantiomer improved the selectivity (s = 26) while the antipode did not (s = 18).

On the basis of these results, the geometry of the possible transition state was calculated at the B3LYP/6-31G** level of theory (Figure 1). The carboxylate additive serves as a general

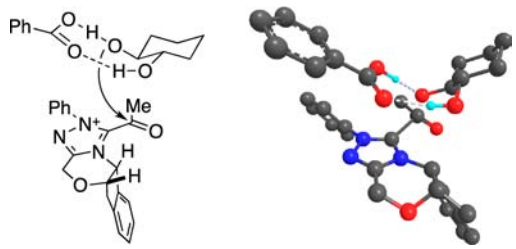
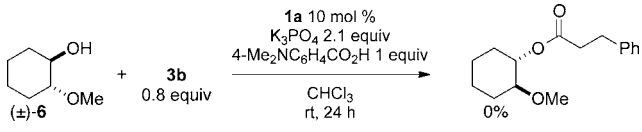


Figure 1. Perspective view of the calculated transition state for the fast-reacting enantiomer of **2b** (H atoms of the C−H bonds have been omitted for clarity).

base to deprotonate the hydroxyl group, creating a C−O bond. The other hydroxy group of the diol stabilizes the transition state by hydrogen bonding with the carboxylate (O···H−O = 1.853 Å). The acylation of racemic monomethyl ether (±)-**6** without an additional hydrogen-bond donor did not proceed, and (±)-**6** was recovered in 82% yield after 24 h (Scheme 3). The

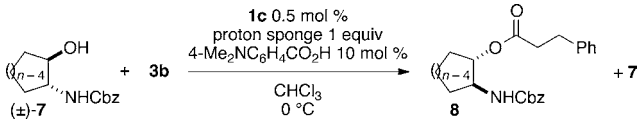
Scheme 3. Importance of the Adjacent H-Bond Donor



plausibility of this model was also supported by the reasonable free energy difference between the transition states of the fast- and slow-reacting enantiomers of **2b** ($\Delta\Delta G^{\ddagger}$ = 2.55 kcal/mol, corresponding to s = 73 at 25 °C). To the best of our knowledge, this is the first report where a carboxylate anion works as a Brønsted base cocatalyst to enhance the selectivity of asymmetric NHC catalysis.[24]

On the basis of the above speculation, we hypothesized that the reaction would work well with alcohols bearing an adjacent hydrogen-bond donor other than a hydroxyl group. Indeed, 2-aminocycloalkanols **7** were also good substrates.[25,26] The six- and seven-membered-ring substrates (±)-**7b** and -**7c** gave good yields (46−48%) of the corresponding esters (+)-**8b** and -**8c** with high selectivities (94−95% ee) and optically pure amino alcohols (−)-**7b** and (+)-**7c** (>99% ee), respectively, by modulation of the conversion (Table 3). Moreover, this methodology was applicable to the desymmetrization of *meso*-diol **9** to give optically pure **10** (>99% ee) in 98% yield even at ambient temperature (Scheme 4).

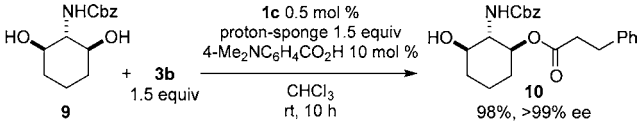
Table 3. Kinetic Resolution of Amino Alcohols 7



entry	7	time	8	recovered 7	s
1[a]	**7b** n = 6	8 h	(+)-**8b** 48%, 95% ee	(−)-**7b** 52%, 92% ee	117
2[b]	**7c** n = 7	18 h	(+)-**8c** 46%, 94% ee	(+)-**7c** 53%, 80% ee	82
3[b]	**7b**	12 h	(+)-**8b** 53%, 90% ee	(−)-**7b** 46%, >99% ee	
4[c]	**7c**	24 h	(+)-**8c** 55%, 79% ee	(+)-**7c** 45%, >99% ee	

[a]0.6 equiv of **3b**. [b]0.7 equiv of **3b**. [c]0.9 equiv of **3b**.

Scheme 4. Desymmetrization of *meso*-Amino Diol



In conclusion, we have developed highly enantioselective kinetic resolution and desymmetrization of secondary alcohols possessing an adjacent hydrogen-bond donor using a newly developed NHC bearing a nitro group on the indane moiety. The rate and selectivity are markedly enhanced by the presence of a carboxylate cocatalyst, which likely works as a base to facilitate the C−O bond-forming step. The compatibility with a free amino functionality is an amazing characteristic that distinguishes this asymmetric acylation from other methods. Details of the carboxylate effects are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

kay-t@pharm.kyoto-u.ac.jp; yamak@pharm.kyoto-u.ac.jp

Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/ja4055838 | *J. Am. Chem. Soc.* 2013, 135, 11485−11488

■ ACKNOWLEDGMENTS

We thank JSPS [Grant-in-Aid for Young Scientist (B)], MEXT (Platform for Drug Design, Discovery and Development), Uehara Memorial Foundation, and Takeda Science Foundation for financial support.

■ REFERENCES

(1) Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570.

(2) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

(3) Benzoin condensation: (a) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, *351*, 1749. (b) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628. Stetter reactions: (c) Li, Y.; Shi, F.-Q.; He, Q.-L.; You, S.-L. *Org. Lett.* **2009**, *11*, 3182. (d) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872. *β*-Umpolung of alkenals: (e) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (f) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370.

(4) External redox: (a) Tam, S. W.; Jimenez, L.; Diederich, F. *J. Am. Chem. Soc.* **1992**, *114*, 1503. (b) Miyashita, A.; Suzuki, Y.; Nagasaki, I.; Ishiguro, C.; Iwamoto, K.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 1254. (c) Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003. (d) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102. Internal redox: (e) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (f) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518.

(5) (a) Connor, E. F.; Nyce, G. W.; Myers, M.; Möck, A.; Hedrick, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 914. (b) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583. (c) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587. (d) Grasa, G. A.; Güveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *68*, 2812.

(6) (a) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613. (b) Müller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6012. (c) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570.

(7) Pioneering works: (a) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (b) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809. (c) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230. (d) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543. (e) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. (f) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (g) Iwasaki, F.; Maki, T.; Nakashima, W.; Onomura, O.; Matsumura, Y. *Org. Lett.* **1999**, *1*, 969. (h) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. Recent examples: (i) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226. (j) Mandai, H.; Murota, K.; Mitsudo, K.; Suga, S. *Org. Lett.* **2012**, *14*, 3486. (k) Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15149.

(8) (a) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769. (b) Hanefeld, U. *Org. Biomol. Chem.* **2003**, *1*, 2405. (c) Ghanem, A.; Aboul-Enein, H. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3331.

(9) (a) De Sarkar, S.; Biswas, A.; Song, C. H.; Studer, A. *Synthesis* **2011**, 1974. (b) Iwahana, S.; Iida, H.; Yashima, E. *Chem.—Eur. J.* **2011**, *17*, 8009. Also see ref 4f.

(10) Transesterification approach: (a) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770. (b) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347.

(11) Recently, kinetic resolution of 3-hydroxy-3-substituted oxindoles was reported. See: Lu, S.; Poh, S. B.; Siau, W.-Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1731.

(12) Desymmetrization of *meso*-diols: Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371. Also see ref 4f.

(13) Kuwano, S.; Harada, S.; Oriez, R.; Yamada, K. *Chem. Commun.* **2012**, *48*, 145.

(14) Previous results: Enzymatic: (a) Seemayer, R.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1991**, 49 (no *s* calculated because of diacylation). (b) Naemura, K.; Fukuda, R.; Murata, M.; Konishi, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2385 (**2b**, *s* = 7). Nonenzymatic: (c) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052 (**2b**, *s* = 14; **2c**, *s* = 28). (d) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325 (**2b**, *s* = 22; **2c**, *s* = 21). (e) Mazet, C.; Roseblade, S.; Köhler, V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879 (**2b**, *s* = 21). (f) Müller, C. E.; Wanka, L.; Jewell, K.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6180. (g) Hrdina, R.; Müller, C. E.; Schreiner, P. R. *Chem. Commun.* **2010**, *46*, 2689. (h) Hrdina, R.; Müller, C. E.; Wende, R. C.; Wanka, L.; Schreiner, P. R. *Chem. Commun.* **2012**, *48*, 2498 (**2a**, *s* = 11; **2b**−**d**, *s* > 50).

(15) Enzymatic resolution of related substrates: Tanaka, M.; Demizu, Y.; Nagano, M.; Hama, M.; Yoshida, Y.; Kurihara, M.; Suemune, H. *J. Org. Chem.* **2007**, *72*, 7750 and references therein.

(16) To express the enantioselectivity in kinetic resolution, *s* is defined as the ratio of reaction rate constants for the fast- and slow-reacting enantiomers of the starting material. In simple first-order kinetics, $s = k_{fast}/k_{slow} = \ln[(1 - C)(1 - ee')]/\ln[(1 - C)(1 + ee')] = \ln[1 - C(1 + ee)]/\ln[1 - C(1 - ee)]$, where $C = ee'/(ee' + ee)$ is the conversion and ee and ee′ are the enantiomeric excesses of the product and recovered starting material, respectively. See: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

(17) pK_a values: (a) 4-Nitrobenzoic acid, 3.41: de Bettencourt-Dias, A.; Viswanathan, S. *Dalton Trans.* **2006**, 4093. (b) Benzoic acid, 4.01: Vulpius, D.; Geipel, G.; Baraniak, L.; Bernhard, G. *Spectrochim. Acta, Part A* **2006**, *63*, 603. (c) 4-Dimethylaminobenzoic acid, 4.92: Smiataczowa, K.; Wawrzynow, A.; Korewa, R. *Pol. J. Chem.* **1995**, *69*, 1306.

(18) (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (b) Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 2713. (c) Rovis, T. *Chem. Lett.* **2008**, *37*, 2. (d) Liu, F.; Bugaut, X.; Schedler, M.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 12626.

(19) Hsieh, S.-Y.; Binanzer, M.; Kreituss, I.; Bode, J. W. *Chem. Commun.* **2012**, *48*, 8892.

(20) *Asymmetric Organocatalysis 1 & 2*; List, B., Maruoka, K., Eds.; Science of Synthesis; Thieme: Stuttgart, Germany, 2011.

(21) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

(22) (a) Bruice, T. C.; Kundu, N. G. *J. Am. Chem. Soc.* **1966**, *88*, 4097. (b) Owen, T. C.; Richards, A. *J. Am. Chem. Soc.* **1987**, *109*, 2520.

(23) (a) Yang, D.; Zuccarello, G.; Mattes, B. R. *Macromolecules* **2002**, *35*, 5304. (b) Hibbert, F.; Hunte, K. P. P. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1895.

(24) The presence of a weak Brønsted acid cocatalyst (e.g., acetic acid, catechol) has been reported to accelerate NHC-catalyzed reactions of aldehydes by the following: (a) Activation of electrophiles via protonation: Zhao, X.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466. (b) Facilitation of rate-determining proton transfer of intermediates: DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402.

(25) Previous results: (a) Enzymatic: Maestro, A.; Astorga, C.; Gotor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3153 (**7b**, 33% conv. after 6 days, *s* > 100). (b) Non-enzymatic: Reference 7h (*N*-acetyl analogues of **7b**, *s* = 51; **7c**, *s* = 17).

(26) The reaction of the unprotected 2-aminocyclohexanol gave a complex mixture, probably as a result of enamine formation with **3b**.