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Enantioselective Acylation of Secondary Alcohols Catalyzed by Chiral *N*-Heterocyclic Carbenes

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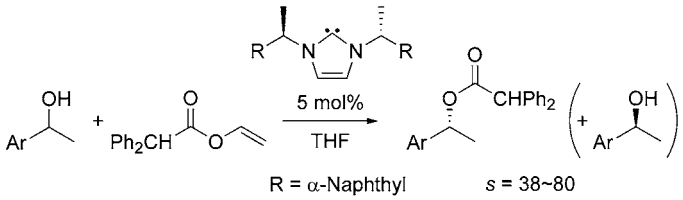
ABSTRACT



The synthetic utility of chiral *N*-heterocyclic carbenes, which have been used mainly in transition metal-catalyzed reactions as a ligand, was demonstrated by the enantioselective acylation of secondary alcohols.

Efficient organocatalytic transformations that are catalyzed by small organic molecules have been intensely investigated in the past few years.[1] In this area, thiazolium salts and triazolium salts have long been known to catalyze the benzoin condensation[2] and the Stetter reaction[3] under basic conditions, and a number of asymmetric variants of these reactions have been developed recently.[1d] In these transformations, actual species as active catalysts are proposed to be nucleophilic heterocyclic carbenes which are generated by the deprotonation of thiazolium salts or triazolium salts. On the other hand, nucleophilic *N*-heterocyclic carbenes prepared from imidazolium salts are used mainly in transition metal-catalyzed reactions as ligands,[4,5] and only a few organocatalytic transformations with such carbenes have been reported to date.[6−8] Although Hedrick and Nolan independently found that the nonchiral nucleophilic *N*-heterocyclic carbenes generated from imidazolium salts could catalyze transesterification reaction between esters and alcohols,[6,9] there have been only a few reports on the application of the chiral

(1) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3727. (b) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (c) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (d) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.

(2) (a) Sheehan, J. C.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196. (b) Tagaki, W.; Tamura, Y.; Yano, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478. (c) Zhao, C.; Chen, S.; Wu, P.; Wen, Z. *Huaxue Xuebao* **1988**, *46*, 784. (d) Martí, J.; Castells, J.; López-Calahorra, F. *Tetrahedron Lett.* **1993**, *34*, 521. (e) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217. (f) Gerhard, A. U.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3615. (g) Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925. (h) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891. (i) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743.

(3) (a) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (c) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934. (d) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876.

(4) For reviews, see: (a) Herrmann, W. A.; Ofele, K.; von Preysing, D.; Schneider, S. K. *J. Organomet. Chem.* **2003**, *687*, 229. (b) Yong, B. S.; Nolan, S. P. *Chemtracts* **2003**, *16*, 205.

(5) Chiral imidazolium salts **1** and **2** can be readily prepared from commercially available chiral amines **3** and **4** according to the reported procedure, See: (a) Herrmann, W. A.; Goossen, L. J.; Artus, G. R.; Kocher, C. *Organometallics* **1997**, *16*, 2472. (b) Sato, Y.; Yoshino, T.; Mori, M. *Org. Lett.* **2003**, *5*, 31. (c) Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345.

(6) (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. (e) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209. (f) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971.

(7) *N*-heterocyclic carbene-catalyzed direct annulations of enals and aldehydes: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205.

(8) Suzuki, Y.; Toyota, T.; Imada, F.; Sato, M.; Miyashita, A. *Chem. Commun.* **2003**, 1314.

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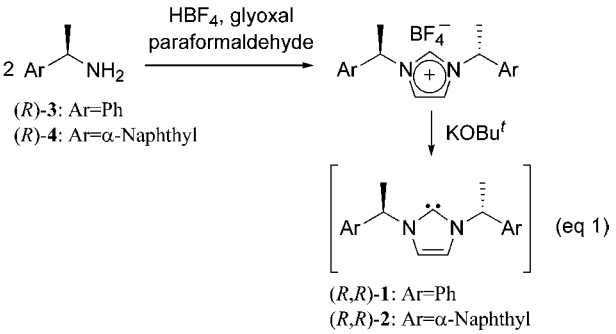
carbenes generated from the imidazolium salts to asymmetric organocatalytic transformations. In this context, we are interested in the possibility of using the chiral *N*-heterocyclic carbenes **1** and **2** in asymmetric organocatalytic transformations. Very recently, Suzuki reported the initial study of nonenzymatic enantioselective acylation of secondary alcohols catalyzed by chiral nucleophilic *N*-heterocyclic carbenes[10] and the report prompted us to disclose our own result on the synthetic utility of chiral carbenes to a useful level.[11−17]

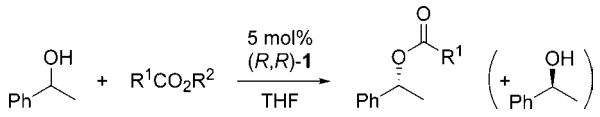
The requisite chiral carbene catalysts (*R*,*R*)-**1** and (*R*,*R*)-**2** were generated in situ by treatment of corresponding chiral imidazolium salts with potassium *tert*-butoxide (eq 1).[5] We



first attempted to apply the chiral carbene (*R*,*R*)-**1** catalyzed transesterification reaction to the enantioselective acylation of secondary alcohols. Unfortunately, the reaction of 1-phenylethanol with a large excess of methyl acetate proceeded slowly at low temperature in the presence of 5 mol % of (*R*,*R*)-**1**, and the resulting ester was found to be totally racemic (Table 1, entry 1). We then investigated the use of more reactive acylating agents such as vinyl esters, which are often used in lipase-catalyzed kinetic resolution. Thus, acetylation of 1-phenylethanol with vinyl acetate proceeded smoothly to give the ester in 36% yield with an ee of 29% (entry 2). This result encouraged us to explore the more sterically hindered acylating agents. In fact, increasing the steric bulk of vinyl esters could improve the enantioselectivities of the resulting esters in the enantioselective acylation of 1-phenylethanol catalyzed by (*R*,*R*)-**1** (entries 3 and 4). Finally, the reaction with vinyl diphenylacetate indicated satisfactory selectivity (entry 5).[18,19]

With vinyl diphenylacetate at hand, we then tested the enantioselective acylation of various secondary alcohols, and the results are summarized in Table 2. In general, use of chiral carbene catalyst (*R*,*R*)-**2** gave a slightly higher ee value at the expense of the reaction rate (entries 2, 5, and 8). Similar high levels of enantioselectivity were obtained when

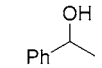
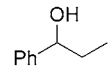
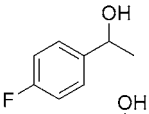
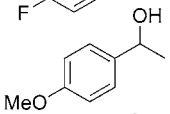
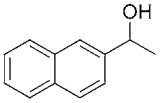
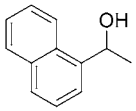
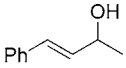
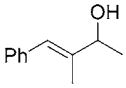
Table 1. Enantioselective Acylation of 1-Phenylethanol with Chiral Carbene Catalyst (*R*,*R*)-**1**[a]



entry	$R^1CO_2R^2$	equiv	conditions [°C, h]	ester [% ee[b] (% yield[c])]	*s*
1[d]	$MeCO_2Me$	10.5	−78 to −20, 5; 0, 2	0 (61)	1.0
2	$MeCO_2$(vinyl)	0.5	−78, 1	29 (36)	2.2
3	*i*-$PrCO_2$(vinyl)	0.5	−78, 1	67 (37)	7.8
4	*t*-$BuCO_2$(vinyl)	1.5	−78, 1	76 (40)	12
5	Ph_2CHCO_2(vinyl)	0.75	−78, 3	93 (33)	46

[a] Unless otherwise specified, 1-phenylethanol (0.6 mmol) was treated with 0.5−10.5 equiv of acylating agents in the presence of 5 mol % of catalyst (*R*,*R*)-**1** in 2 mL of THF under the given reaction conditions under argon atmosphere. Yield and enantiopurity of the remaining alcohol are described in the Supporting Information. [b] Enantiopurity of the resulting esters was determined by HPLC or GC analysis with use of chiral columns (Daicel Chiralcel AD-H or Astec Chiraldex B-DM). Absolute configuration was determined by the comparison of the HPLC retention time of the recovered alcohol with literature data. See the Supporting Information for more detail. [c] Isolated yield. [d] The reaction was carried out in the presence of molecular sieves 4 Å.

Table 2. Enantioselective Acylation of *sec*-Alcohols with Chiral Carbene Catalysts (*R*,*R*)-**1** and -**2**[a]

entry	substrate	catalyst	conditions [°C, h]	ester [% ee[b] (% yield[c])]	*s*
1		(*R*,*R*)-**1**	-78, 3	93 (33)	46
2		(*R*,*R*)-**2**	-78, 3	96 (32)	80
3[d]		(*R*,*R*)-**2**	-78, 0.5; -20, 3.5	92 (33)	38
4		(*R*,*R*)-**1**	-78, 3	90 (35)	33
5[d]		(*R*,*R*)-**2**	-78, 4	91 (39)	42
6[d]		(*R*,*R*)-**2**	-78, 2; -40, 3	94 (30)	48
7		(*R*,*R*)-**1**	-78, 1.5	93 (35)	46
8[d]		(*R*,*R*)-**2**	-78, 6	95 (27)	56
9[d]		(*R*,*R*)-**2**	-78, 4; -40, 0.5	94 (29)	47
10		(*R*,*R*)-**1**	-78, 3.5	84 (27)	16
11		(*R*,*R*)-**1**	-78, 1; -40, 2	87 (33)	22

[a] Unless otherwise specified, secondary alcohols (0.6 mmol) were treated with 0.75 equiv of vinyl diphenylacetate in the presence of 5 mol % of catalyst (*R*,*R*)-**1** or -**2** in 2 mL of THF under the given reaction conditions under argon atmosphere. Yield and enantiopurity of the remaining alcohol are described in the Supporting Information. [b] Enantiopurity of the resulting esters was determined by HPLC analysis with use of chiral columns. Absolute configuration was determined by the comparison of the HPLC retention time of the recovered alcohol with literature data. See the Supporting Information for more detail. [c] Isolated yield. [d] 1.5 equiv of vinyl diphenylacetate was used.

(9) Esterification reactions catalyzed by carbenes generated from thiazolium and triazolium salts, see: (a) Chow, K. Y. K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (b) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518.

(10) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770.

1-phenylpropanol was used (entry 3). Neither the electron-donating nor the electron-withdrawing groups on the aromatic ring of secondary alcohols affected the enantioselectivity of the reaction (entries 4−6). The chiral carbene catalyst could discriminate between the enantiomers of allylic alcohols with slightly lower enantioselectivity than arylalkyl carbinols (entries 10 and 11).

In contrast to the enantioselective acylation of secondary alcohols catalyzed by nucleophilic organic compounds (e.g., DMAP derivatives) with acid chlorides or acid anhydrides, the present reaction proceeds via transesterification and can be performed without a stoichiometric amount of base. While an analogous reaction is known to be catalyzed by enzymes, our results represent a rare example of the highly enantioselective transesterification of secondary alcohols with vinyl esters mediated by artificial molecular catalysts.[10,20]

In summary, we have established that chiral *N*-heterocyclic carbenes (*R*,*R*)-**1** and (*R*,*R*)-**2** serve as a new class of catalysts for the nonenzymatic enantioselective acylation of racemic secondary alcohols with vinyl diphenylacetate. An important feature of this catalyst system is that the C_2-symmetric chiral imidazolium salts, the precursor of these chiral carbene catalysts, can be readily synthesized from commercially available chiral amines, paraformaldehyde, glyoxal, and tetrafluoroboric acid in one step. Further investigations into the precise mechanism of this reaction as well as the use of chiral carbenes as organocatalysts in other asymmetric reactions are currently underway in our laboratory.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Nonenzymatic enantioselective acylation of secondary alcohols is known to be catalyzed by various small organic compounds such as chiral 4-aminopyridines, diamines, peptides, and phosphines with high efficiency and enantioselectivity: see refs 12−17.

(12) 4-Aminopyridine: (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (b) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. (c) Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, *68*, 7379. (d) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844.

(13) Diamine: Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265.

(14) Peptide: (a) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. (b) Fierman, M. B.; O'Leary, D. J.; Steinmetz, W. E.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 696.

(15) Phosphine: (a) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166.

(16) For reviews, see: (a) Spivey, A. C.; Maddaford, A.; Redgrave, A. J. *Org. Prep. Proc. Int.* **2000**, *32*, 331. (b) Jarvo, E. R.; Miller, S. J. Asymmetric Acylation. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 2004; Chapter 43.

(17) Chiral 2,3-dihydroimidazo[1,2-*a*]pyridines as a new class of acyl transfer catalysts: Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226.

(18) Vinyl diphenylacetate is readily prepared from diphenylacetic acid and vinyl acetate. See the Supporting Information for details.

(19) The resulting 1-phenylethyl diphenylacetate is readily hydrolyzed with aqueous NaOH to 1-phenylethanol without loss of enantiopurity.

(20) Yttrium-salen complexe-catalyzed enantioselective transesterification: Lin, M.-H.; RajanBabu, T. V. *Org. Lett.* **2002**, *4*, 1607.