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Direct Asymmetric Benzoyloxylation of Aldehydes Catalyzed by 2-Tritylpyrrolidine

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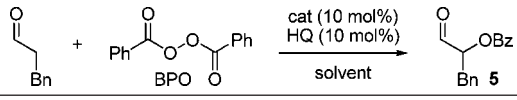
α-Oxygenated carbonyl compounds are common structural motifs in a wide range of natural products and are important chiral building blocks in the synthesis of biologically active compounds. To date, a number of asymmetric α-oxygenation reactions of carbonyl compounds, including epoxidation,[1] dihydroxylation,[2] and aminoxylation[3] of preformed enol ethers, enolates, and enamines have been developed.[4] Recently, some organocatalytic direct asymmetric oxygenations of aldehydes and ketones through enamine intermediates were reported; however, the available oxygen functionalities were limited to aminoxy and hydroxy groups. [5−8] In this context, we have been interested in the development of an asymmetric acyloxylation of aldehydes, which introduces a useful oxygen functionality. Although a number of acyloxylations have been reported,[9−12] to the best of our knowledge, the catalytic direct asymmetric acyloxylation of aldehydes has not been realized, despite the potential for application of the resulting α-acyloxyaldehydes in organic synthesis. Herein we report a direct asymmetric benzoyloxylation of aldehydes catalyzed by (*S*)-2-tritylpyrrolidine [(*S*)-**2a**].

(*S*)-**1a** (Ar = Ph) (*S*)-**2a** (Ar = Ph)
(*S*)-**1b** (Ar = 3,5-$(CF_3)_2C_6H_3$) (*S*)-**2b** (Ar = 3,5-xylyl)

We first investigated α-benzoyloxylation of 3-phenylpropanal with benzoyl peroxide (BPO)[13] in THF in the presence of various pyrrolidine-type catalysts (10 mol %), and the results are shown in Table 1. The use of pyrrolidine as a catalyst afforded the

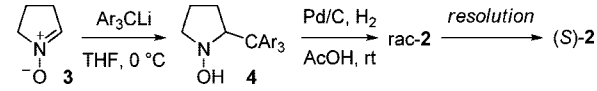
Table 1. Benzoyloxylation of 3-Phenylpropanal with BPO[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1[d]	pyrrolidine	THF	rt	3	10	−
2	pyrrolidine	THF	rt	3	46	−
3	(*S*)-**1a**	THF	0	6	45	93
4	(*S*)-**1b**	THF	0	6	18	90
5	(*S*)-**2a**	THF	0	6	68	94
6	(*S*)-**2a**	THF	rt	2	72	93
7	(*S*)-**2b**	THF	0	3	36	98
8	(*S*)-**2a**	dioxane	0	1.3	67	91
9	(*S*)-**2a**	DMF	0	6	39	91
10	(*S*)-**2a**	CH_2Cl_2	0	6	18	90
11	(*S*)-**2a**	toluene	0	6	16	82

[a] The reaction of 3-phenylpropanal (0.1 mmol) and BPO (0.11 mmol) was carried out in a solvent (0.5 mL) in the presence of a catalyst (0.01 mmol) and HQ (0.01 mmol). [b] Isolated yield. [c] The ee of the product was determined by HPLC analysis using a chiral column after conversion to the corresponding primary alcohol. [d] In the absence of HQ.

Scheme 1



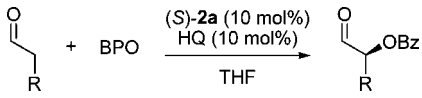
α-benzoyloxyaldehyde **5** in low yield (entry 1). When 10 mol % hydroquinone (HQ) was employed as an additive, an increase in yield was observed (entry 2). The reaction catalyzed by chiral pyrrolidine (*S*)-**1a**[14] at 0 °C gave **5** in moderate yield, albeit with high enantioselectivity (entry 3). Use of commercially available (*S*)-**1b**[14a] resulted in lower yield and enantioselectivity (entry 4). Since substantial amounts of 3-phenylpropanal remained unreacted, we assumed that the catalyst might be deactivated through benzoyloxylation of the catalyst nitrogen atom by BPO.[15] With the expectation of suppressing such undesired catalyst deactivation by changing the steric and electronic environment of the siloxydiarylmethyl moiety in (*S*)-**1**, we thought about the possibility of using chiral pyrrolidines (*S*)-**2** having a C_3-symmetric triarylmethyl group.[16] Accordingly, a general approach for the preparation of (*S*)-**2** starting from nitrone **3** was developed (Scheme 1). To our delight, the reaction using (*S*)-**2a** proceeded smoothly to give the desired product **5** in improved yield without loss of enantioselectivity (entry 5). The reaction performed at room temperature gave **5** in similar yield and enantioselectivity in a shorter reaction time (entry 6). In addition, while the enantioselectivity was improved by using (*S*)-**2b**, which has a tris(3,5-xylyl)methyl group instead of a trityl group (entry 7), (*S*)-**2a** was chosen for further study because of the catalyst turnover and its easier availability. With (*S*)-**2a**, reactions were conducted in various solvents, and THF was found to be the optimal solvent in terms of both yield and enantioselectivity (entries 5 and 8−11).

The direct asymmetric α-benzoyloxylation reactions of several other aldehydes with BPO in the presence of 10 mol % (*S*)-**2a** and HQ were examined, and the results are shown in Table 2. In general, these direct asymmetric α-benzoyloxylation reactions gave the corresponding α-benzoyloxyaldehydes with good enantioselectivity. The reaction with a lower catalyst loading (5 mol %) gave the identical result with slightly longer reaction time (entry 5 vs entry 4). By comparison of optical rotation of the product obtained in entry 2 with the literature value,[17] the absolute configuration of the product was determined to be *S*.

The obtained α-benzoyloxyaldehydes were useful intermediates in organic synthesis that were readily converted to the corresponding diols and monoprotected diols (Scheme 2). When a mixuture of **5** in MeOH was treated with $NaBH_4$ at 0 °C and then heated to 50 °C, diol **6** was obtained in excellent yield with almost complete retention of stereochemistry. On the other hand, reduction of **5** with $NaBH_4$ at 0 °C rapidly formed a monoprotected diol **7** in quantitative yield without loss of optical purity. The benzoyl group of **7** migrated to the primary hydroxyl group in the presence of DBU to give the other monoprotected diol **8**.

10.1021/ja809963s CCC: $40.75

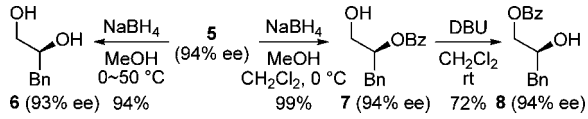
Table 2. Benzoyloxylation of Various Aldehydes with BPO[a]



entry	R	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	Me	0	2	62	94
2	Et	0	4	73	93
3	Bu	0	5	70	94
4	Bn	rt	2	72	93
5[d]	Bn	rt	3	71	93
6	allyl	rt	1.5	62	92
7	*i*-Pr	rt	5	64	92
8	Cy	rt	6	65	94

[a] Unless otherwise specified, the reaction between an aldehyde (0.1 mmol) and BPO (0.11 mmol) was carried out in THF (0.5 mL) in the presence of (*S*)-**2a** (0.01 mmol) and HQ (0.01 mmol). [b] Isolated yield. [c] The ee of the product was determined by HPLC analysis using a chiral column after conversion to the corresponding primary alcohol. [d] (*S*)-**2a** (5 mol %), HQ (5 mol %).

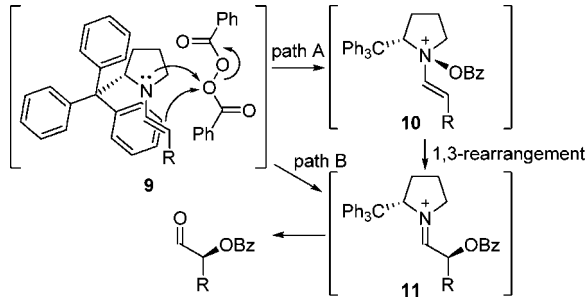
Scheme 2



In the absence of HQ, the reaction of 3-phenylpropanal with BPO catalyzed by (*S*)-**2a** gave **5** in low yield (30%). While low yields of **5** were obtained by addition of phenol (38%), $MeSO_2NH_2$ (35%), and $(CF_3)_2CHOH$ (30%), which have Brønsted acidities similar to that of HQ, the reaction using TEMPO, which is a typical radical scavenger, gave a better yield (52%). On the basis of these observations, HQ may play a role in the inhibition of undesired radical reactions.

The radical initiator BPO is known to be stable at room temperature,[18] and the present benzoyloxylation takes place in the presence of the radical scavenger HQ. On the basis of these observations, we speculated that this process would proceed through the ionic pathway as shown in Scheme 3, although other plausible mechanisms via radical intermediates cannot be ruled out at this point. We considered the following two plausible mechanisms for the ionic pathway: (1) The enamine intermediate **9** reacts at nitrogen, giving an *N*-benzoyloxy adduct **10** that undergoes a 1,3-rearrangement to the α-benzoyloxyiminium intermediate **11** (Scheme 3, path A). (2) The enamine intermediate **9** reacts at carbon to give the α-benzoyloxyiminium intermediate **11** directly (Scheme 3, path B). In both cases, BPO would approach s-trans enamine **9**, whose one face is shielded by the trityl group of catalyst (*S*)-**2a**. Hence, the reaction of an aldehyde with BPO catalyzed by (*S*)-**2a** provides the *S* isomer predominantly.

Scheme 3



In summary, we have developed a direct asymmetric benzoyloxylation of aldehydes with BPO catalyzed by the novel pyrrolidine-type catalyst (*S*)-**2a**. This method represents the first example of the catalytic and highly enantioselective synthesis of optically active α-acyloxyaldehydes, which could be readily converted to synthetically useful and important chiral building blocks such as non- or monoprotected diols.

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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.

References

(1) For reviews, see: (a) Adam, W.; Fell, R. T.; Stegmann, V. R.; Saha-Möller, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 708. (b) Adam, W.; Fell, R. T.; Saha-Möller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1998**, *9*, 397. (c) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. (d) Koprowski, M.; Łuczak, J.; Krawczyk, E. *Tetrahedron* **2006**, *62*, 12363.
(2) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463.
(3) (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038. (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080. (c) Kawasaki, M.; Li, P.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3795.
(4) (a) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835. (b) Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007**, 538. (c) Adam, W.; Lazarus, M.; Saha-Möller, C. R.; Schreier, P. *Acc. Chem. Res.* **1999**, *32*, 837. (d) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679. (e) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (f) Hirt, U. H.; Springler, B.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 7674. (g) Lohray, B. B.; Enders, D. *Helv. Chim. Acta* **1989**, *72*, 980.
(5) (a) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293.
(6) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124.
(7) (a) Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914. (b) Ibrahem, I.; Zhao, G.-L.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 4659.
(8) Engqvist, M.; Casas, J.; Sundén, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 2053.
(9) (a) Rawilson, D. J.; Sosnovsky, G. *Synthesis* **1973**, 567. (b) Williams, G. J.; Hunter, N. R. *Can. J. Chem.* **1976**, *54*, 3830. (c) Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839. (d) Demir, A. S.; Reis, Ö.; Igdir, A. C. *Tetrahedron* **2004**, *60*, 3427. (e) Reitsema, R. H. *J. Am. Chem. Soc.* **1957**, *79*, 4465. (f) Kuehne, M. E.; Giacobbe, T. *J. Org. Chem.* **1968**, *33*, 3359. (g) Lee, J. C.; Jin, Y. S.; Choi, J.-H. *Chem. Commun.* **2001**, 956. (h) Lemaire, M.; Imbert, G. D.; Guetté, J.-P. *J. Chem. Soc., Chem. Commun.* **1986**, 741. (i) Pan, Z.-L.; Liu, X.-Y.; Liang, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 4101.
(10) (a) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O. *Org. Lett.* **2005**, *7*, 5729. (b) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, T. C.; Parry, R. T.; Thomas, S. P.; Tomkinson, N. C. O. *Chem. Commun.* **2005**, 1478.
(11) (a) Augustine, R. L. *J. Org. Chem.* **1963**, *28*, 581. (b) Greene, A. E.; Muller, J.-C.; Ourisson, G. *Tetrahedron Lett.* **1972**, *13*, 3375. (c) Lee, J.; Oya, S.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5899.
(12) Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700.
(13) With lauroyl peroxide instead of BPO, the corresponding product was obtained in only 9% yield under conditions similar to those described in entry 2 of Table 1.
(14) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.
(15) Denney, D. B.; Denney, D. Z. *J. Am. Chem. Soc.* **1960**, *82*, 1389.
(16) Klumpp, D. A.; Aguirre, S. L.; Sanchez, G. V., Jr.; de Leon, S. J. *Org. Lett.* **2001**, *3*, 2781. Also see the Supporting Information for details.
(17) Abate, A.; Brenna, E.; Fuganti, C.; Malpezzi, L.; Serra, S. *Tetrahedron: Asymmetry* **2007**, *18*, 1145.
(18) Walling, C. *Tetrahedron* **1985**, *41*, 3887.

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