Organic LETTERS

Letter

pubs.acs.org/OrgLett

Asymmetric α-Benzoyloxylation of β-Ketocarbonyls by a Chiral Primary Amine Catalyst

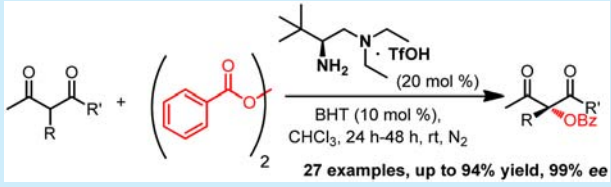
Dehong Wang,[†] Changming Xu,[†] Long Zhang,[†,‡] and Sanzhong Luo*[,†,‡]

[†]Beijing National Laboratory for Molecular Sciences (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin, 300071, China

Supporting Information

ABSTRACT: The direct asymmetric α-benzoyloxylation of β-ketocarbonyls catalyzed by a chiral primary amine is described herein. This protocol demonstrates excellent enantioselectivity for a broad range of substrates, which allows convenient access to highly enantioenriched α-hydroxy-β-ketocarbonyls.



α-Hydroxy-β-dicarbonyl is a prominent structural feature in biologically relevant molecules and drug candidates,[1] such as Kjellmanianone, Hamigeran A, and Doxycycline (Figure 1).[2]

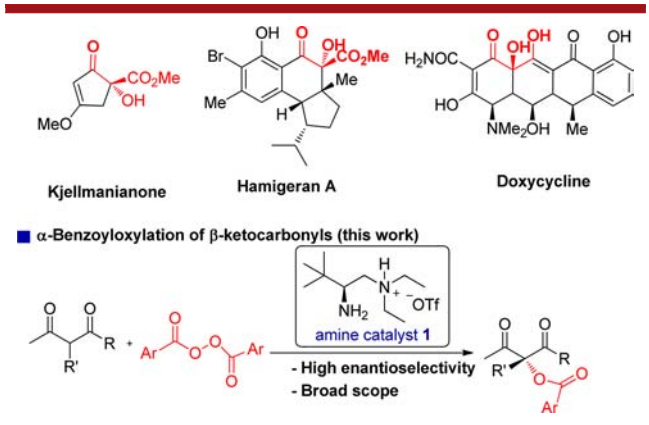


Figure 1. Direct benzoyloxylation for the synthesis of α-hydroxy-β-dicarbonyls.

Such a functional unit can also serve as a versatile chiral synthon in many multistep reaction sequences.[3] Hence, asymmetric synthesis of α-hydroxy-β-dicarbonyls via enantioselective α-hydroxylation of β-dicarbonyls, the most straightforward approach, has been much explored.[4−6] Davis and co-workers developed the first enantioselective α-hydroxylation of β-ketoesters employing stoichiometric amounts of enantiopure *N*-sulfonyloxaziridines three decades ago.[4] Recently, Togni and co-workers reported Ti-catalyzed α-hydroxylation of both cyclic and acyclic β-ketoesters. However, enantioselectivities were rather poor in the cases with acyclic ketoesters.[5b] Yamamoto and co-workers described an elegant asymmetric *O*-nitrosocarbonyl aldol reaction of acyclic β-ketothioesters with *N*-Boc-hydroxylamine as the nitrosocarbonyl precursor. The reactions require a sterically demanding ester group for optimal stereocontrols.[7] Despite these advances, a general catalytic asymmetric protocol for α-hydroxylation of β-dicarbonyls with high enantioselectivities for a broad scope, to include dicarbonyls other than β-ketoesters such as 1,3-diketones and β-ketoamides, remains to be developed.

α-Benzoyloxylation is a powerful approach for the direct asymmetric α-oxygenation of carbonyl compounds. Recently, the groups of Maruoka,[8] List,[9] and others[10] have reported the catalytic direct asymmetric α-benzoyloxylation of aldehydes and cyclic ketones employing benzoyl peroxide (BPO) as a readily available and inexpensive hydroxylation reagent. In this regard, asymmetric α-benzoyloxylation of α-branched ketones such as β-ketocarbonyls has not been achieved so far. In fact, α-branched aldehydes and ketones remain challenging substrates for this reaction. In a single previous report, the reaction with α-branched aldehydes has been attempted, affording poor enantioselectivity.[9b]

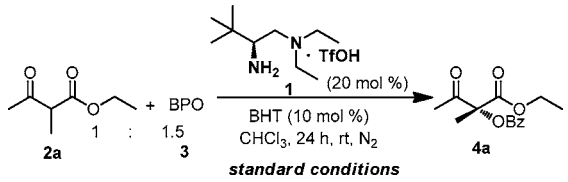
Very recently, we have developed chiral primary amines, e.g. primary amine **1**, as viable catalysts for enamine-based transformations of β-ketocarbonyls.[11] In the process of further explorations of this catalysis, it was realized that the asymmetric α-benzoyloxylation of β-ketocarbonyls remained an unsolved issue, in particular with acyclic ketocarbonyls where the construction of acyclic chiral quaternary carbons is involved. Herein we report a chiral primary amine catalyzed direct asymmetric α-benzoyloxylation of β-ketocarbonyls with broad scopes and high enantioselectivity (Figure 1).

In the model reaction between acetoacetate **2a** and benzoyl peroxide (BPO), the desired α-benzoyloxylated product **4a** was obtained in 83% yield and 96% *ee* under the optimized conditions (Table 1, entry 1). Among the solvents examined, $CHCl_3$ was found to be the optimal solvent in terms of both yield and enantioselectivity (Table 1, entries 2−5). The use of a higher concentration was found to be favorable for the product yield (Table 1, entry 5 vs 1). It was found that 1.5 equiv of **3**

Received: December 14, 2014
Published: January 15, 2015

DOI: 10.1021/ol503592n
Org. Lett. 2015, 17, 576−579

Table 1. Screening and Optimization[a]



entry	variation from standard conditions	yield (%)[b]	*ee* (%)[c]
1	none	83	96
2[d]	THF	65	27
3[d]	toluene	53	73
4[d]	1,4-dioxane	trace	–
5[d]	$CHCl_3$	62	95
6	**2a**:**3a** = 2:1	72	96
7	**2a**:**3a** = 1.5:1	68	96
8	**2a**:**3a** = 1:1.2	70	96
9	without BHT	76	96
10	under air	57	96

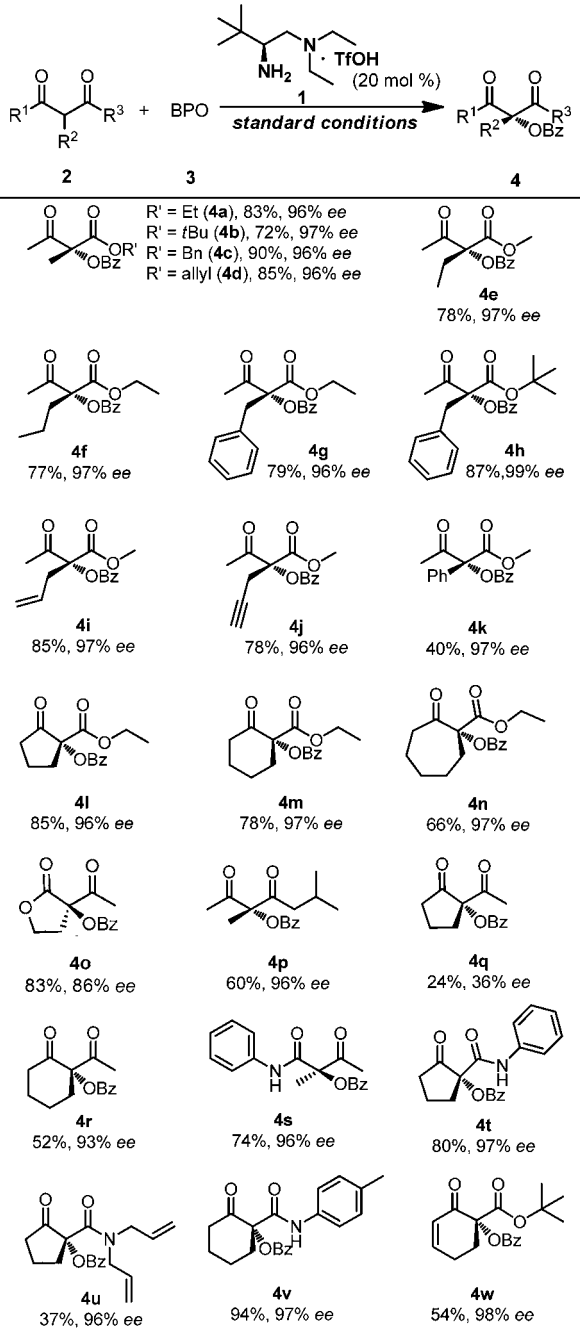
[a]Reactions were performed at rt in 0.25 mL of $CHCl_3$ with **2a** (0.20 mol), **3** (0.3 mol), **1** (20 mol %), BHT (10 mol %) under N_2, 24 h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]These reactions were performed at a concentration of 0.2 M. BPO: benzoyl peroxide; BHT: butylated hydroxytoluene.

was optimal, and larger or smaller ratios of **2a**/**3** all led to a decreased yield (Table 1, entries 6–8). Butylated hydroxytoluene (BHT), as a radical inhibitor, was previously employed to avoid possible benzoyl radical side reactions.[9] In our cases, the use of 10 mol % BHT furnished a slightly better yield (Table 1, entry 9 vs 1). Finally, the reaction worked more cleanly under N_2 with a higher yield than under aerobic atmosphere (Table 1, entry 10); thus, all the reactions were conducted under N_2.

With the optimized conditions in hand, we first investigated the scope of acyclic ketoesters. As shown in Scheme 1, acyclic acetoacetates bearing various ester moieties (R^3 position), including those with sterically bulky *tert*-butyl ester, benzyl, and allyl ester groups, afforded the desired α-benzoyloxylation products in high yields and excellent enantioselectivities (Scheme 1, **4a**–**d**). The reactions also tolerated a range of α-substituents on acetoacetates (R^2 position, **4e**–**k**). In particular, the reaction with acetoacetates bearing either an α-allyl or a propargyl substituent proceeded smoothly to deliver the corresponding α-benzoyloxylation products with high yields and enantioselectivities (**4i** and **4j**), and no oxidation of the unsaturated bonds was observed. Delightfully, **2k** (R^2 = Ph) is also a workable substrate, delivering the corresponding adduct (**4k**) in acceptable yield and good *ee*. The use of α-unsubstituted acetoacetate (R^2 = H) and phenyl ketoester (R^1 = Ph) gave racemic adducts (data not shown), suggesting these reactions are mainly background enol processes escaping catalyst control.

The current catalysis worked extremely well with cyclic β-ketoesters to give the desired α-benzoyloxylation products with high yields and excellent enantioselectivities (**4l**–**n**). The relatively unstable α-acetybutyrolactone was also amenable to the mild catalytic conditions, furnishing an 83% yield and 86% *ee* (**4o**). Most delightfully, both cyclic and acyclic 1,3-diketones are workable substrates under the current conditions. Heptane-2,4-dione and 2-acetyl-1-cyclohexanone reacted smoothly to give the desired α-benzoyloxylation products with moderate yields and excellent enantioselectivities (**4p** and **4r**). In

Scheme 1. Scope of the Asymmetric α-Benzoyloxylation of β-Ketocarbonyls[a]



[a]All the reactions were performed at rt in 0.25 mL $CHCl_3$ with **2** (0.2 mmol), **3** (0.3 mmol), **1** (20 mol %), BHT (10 mol %) under N_2, 24–48 h. Yields shown are of isolated products.

contrast, 2-acetyl-1-cyclopentanone was a poor substrate for the reaction producing a low yield and poor enantioselectivity (**4q**); presumably, the two keto moieties in this setting are less differentiable for the catalyst with coformation of enamine regioisomers, thus leading to poor chiral induction.

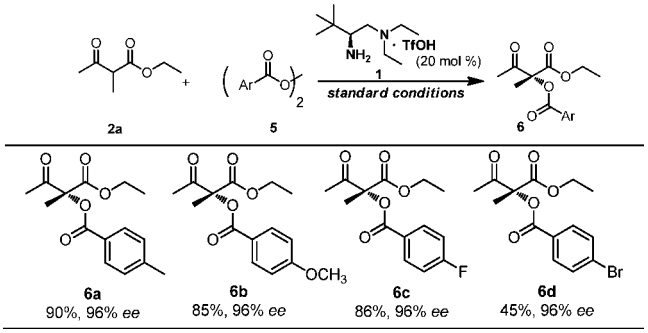
To further explore the synthetic utility of the current α-benzoyloxylation reaction, β-ketoamides were also examined in the reactions. As shown in Scheme 1, β-ketoamides with or without a free N–H bond all worked well in the reaction to cleanly give α-benzoyloxylation products. Both acyclic and

DOI: 10.1021/ol503592n
Org. Lett. 2015, 17, 576–579

cyclic *N*-phenyl *β*-ketoamides reacted to furnish the expected *α*-benzoyloxylation with high yields and excellent enantioselectivities (**4s**, **4t**, and **4v**). *N*-Allyl *β*-ketoamide was also workable with excellent enantioselectivity albeit in a reduced yield (**4u**). Notably, a cyclohexenone derived ketoester can also be applied in the reaction to afford the desired benzoyloxylation adduct **4w** in 54% yield and 98% *ee* (Scheme 1). Unfortunately, the reaction with the cyclopentenone derivative, a direct access to Kjellmanianone, did not work under our conditions.

Other aryl acylperoxides have also been examined under the reaction conditions, showing comparable performance with high yields and excellent enantioselectivities (**6a**–**6d**) (Scheme 2). The yield of **6d** was relatively low due to the poor solubility of bis(*p*-bromobenzoyl) peroxide.

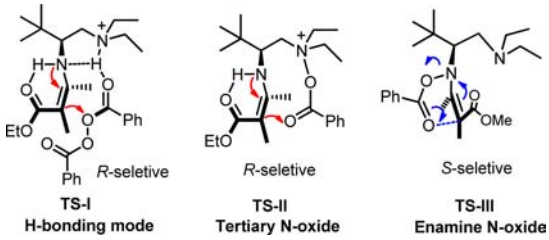
Scheme 2. Scope of Other Aryl Acylperoxides[a]



[a]All the reactions were performed at rt in 0.25 mL of $CHCl_3$, with **2a** (0.2 mmol), **5** (0.3 mmol), **1** (20 mol %), BHT (10 mol %) under N_2, 24–48 h. Yields shown are of isolated products.

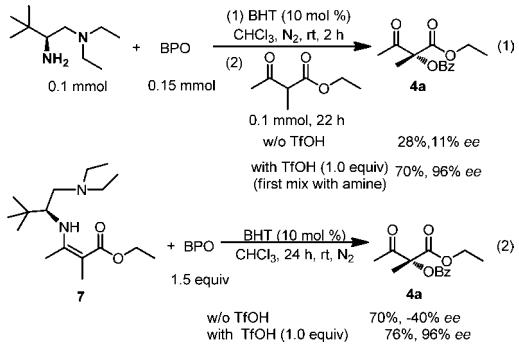
The absolute configuration of the hydroxylated adduct was determined to be *R* by comparison of the optical rotation of **4h** with the literature value.[12] Based on our previous studies, an H-bonding transition state was proposed to account for the observed *R*-selectivity (Scheme 3, **TS-I**). Similar H-bonding **TS**

Scheme 3. Proposed Transition States



has also recently been proposed in previous studies.[9a] Since amines are known to undergo facile *N*-oxidation in the presence of BPO,[13] the reaction may also occur *via* a *N*-oxide addition pathway to give the major enantiomer (Scheme 3, **TS-II**). To further look into this issue, we have carried out stoichiometric experiments with catalyst **1**. When the free amine catalyst was first treated with BPO in the absence of TfOH, the hydroxylation barely proceeded with rather low enantioselectivity due to the oxidation of the aminocatalyst[14] (Scheme 4, eq 1), while the same reaction sequence in the presence of TfOH occurred smoothly to give the desired adduct with maintained outcomes. The critical role of TfOH in tuning both activity and selectivity can be further verified in the stoichiometric reaction of preformed enamine **7**. In this case,

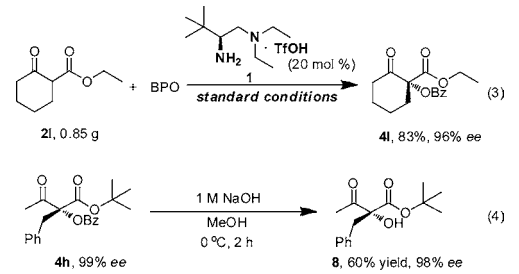
Scheme 4. Stoichiometric Experiments



enamine **7** could react with BPO to give product **4a** in 70% yield and 40% *ee*; however, the product was obtained in an opposite *S*-configuration, indicating an alternative reaction pathway. In this context, an *S*-selective enamine *N*-oxide pathway may be invoked (Scheme 3, **TS-III**). The stereoinduction can be restored to *R*-selective control with 96% *ee* upon the addition of TfOH (Scheme 4, eq 2). Taken together, these observations suggest that the *N*-oxide pathways (Scheme 3, modes **II** and **III**), though not completely ruled out, should be minor and can be largely disfavored in the presence of acid additive TfOH and that H-bonding directed addition would be the major productive pathway under the current conditions.

To probe the utility of our method in preparative synthesis, a gram-scale reaction of *β*-ketoesters **2l** was performed, delivering the desired product **4l** with a good yield (83%) and excellent enantioselectivity (96% *ee*) (Scheme 5, eq 3). Furthermore, *O*-

Scheme 5. Gram Scale Reaction and Synthetic Transformations



deprotection of *α*-benzoyloxylated products is smooth and facile, e.g. **4h** (Scheme 5, eq 4). Treatment with 1 M NaOH afforded *α*-hydroxy-*β*-ketoester **8** in good yield with maintained stereoselectivity.

In summary, we have developed a highly enantioselective *α*-benzoyloxylation of *β*-ketocarbonyls with benzoyl peroxide under mild conditions by using a simple chiral primary amine. The reactions enable the constructions of *α*-hydroxylated quaternary *β*-ketocarbonyls with excellent enantioselectivity and encompass a wide range of substrates including the elusive 1,3-diketones and *β*-ketoamides. The current reaction provides a straightforward access to synthetically useful and important chiral building blocks and can be scaled up without loss of yield and enantioselectivity.

DOI: 10.1021/ol503592n
Org. Lett. 2015, 17, 576–579

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

* E-mail: luosz@iccas.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Natural Science Foundation of China (21390400, 21025208, and 21202171) and the National Basic Research Program of China (2011CB808600) for financial support. S.L. is supported by the National Program of Top-notch Young Professionals and CAS Youth Innovation Promotion Association.

■ REFERENCES

(1) Christoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143.

(2) (a) Nakayama, M.; Fukuoka, Y.; Nozaki, H.; Matsuo, A.; Hayashi, S. *Chem. Lett.* **1980**, 1243. (b) Zhu, J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron. Lett.* **1994**, *35*, 2787. (c) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79. (d) Olack, G.; Morrison, H. *J. Org. Chem.* **1991**, *56*, 4969.

(3) Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299.

(4) (a) Boschelli, D.; Smith, A. B., III.; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. *Tetrahedron Lett.* **1981**, *22*, 4385. (b) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919.

(5) (a) Bonaccorsi, C.; Althaus, M.; Becker, C.; Togni, A.; Mezzetti, A. *Pure Appl. Chem.* **2006**, *78*, 391. (b) Toullec, P. Y.; Banaccorsi, C.; Mezzetti, A.; Togni, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5810. (c) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488. (d) Smith, A. M. R.; Billen, D.; Hii, K. K. *Chem. Commun.* **2009**, 3925. (e) Takechi, S.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2011**, *52*, 2140. (f) Li, J.; Chen, G.; Wang, Z.; Zhang, R.; Zhang, X.; Ding, K. *Chem. Sci.* **2011**, *2*, 1141. (g) Yin, C.; Cao, W.; Lin, L.; Liu, X.; Feng, X. *Adv. Synth. Catal.* **2013**, *355*, 1924. (h) Gu, X.; Zhang, Y.; Xu, Z.-J.; Che, C.-M. *Chem. Commun.* **2014**, *50*, 7870.

(6) For an organocatalytic approach, see: (a) Acocella, M. R.; Mancheno, O. G.; Bella, M.; Jørgensen, K. R. *J. Org. Chem.* **2004**, *69*, 8165. (b) Lu, M.; Zhu, D.; Lu, Y.; Zeng, X.; Tan, B.; Xu, Z.; Zhong, G. *J. Am. Chem. Soc.* **2009**, *131*, 4562. (c) Lian, M.; Li, Z.; Cai, Y.; Meng, Q.; Gao, Z. *Chem.—Asian J.* **2012**, *7*, 2019. (d) Yao, H.; Lian, M.; Li, Z.; Wang, Y.; Meng, Q. *J. Org. Chem.* **2012**, *77*, 9601. (e) Zou, L.; Wang, B.; Mu, H.; Zhang, H.; Song, Y.; Qu, J. *Org. Lett.* **2013**, *15*, 3106. (f) Fusco, C. D.; Meninno, S.; Tedesco, C.; Lattanzi, A. *Org. Biomol. Chem.* **2013**, *11*, 896.

(7) Baidya, M.; Griffin, K. A.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 18566.

(8) Kano, T.; Mii, H.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 3450.

(9) (a) Lifchits, O.; Demoulin, N.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9680. (b) Demoulin, N.; Lifchits, O.; List, B. *Tetrahedron* **2012**, *68*, 7568.

(10) (a) Gotoha, H.; Hayashi, Y. *Chem. Commun.* **2009**, 3083. (b) Vaismaa, M. J. P.; Yau, S. C.; Tomkinson, N. C. O. *Tetrahedron Lett.* **2009**, *50*, 3625. (c) Jadhav, M. S.; Righi, P.; Marcantoni, E.; Bencivenni, G. *J. Org. Chem.* **2012**, *77*, 2667.

(11) (a) Xu, C.; Zhang, L.; Luo, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 4149. (b) Zhu, Y.; Zhang, L.; Luo, S. *J. Am. Chem. Soc.* **2014**, *136*, 14642. (c) Xu, C.; Zhang, L.; Luo, S. *J. Org. Chem.* **2014**, *79*, 11517. (d) Zhang, L.; Xu, C.; Mi, X.; Luo, S. *Chem.—Asian J.* **2014**, *9*, 3565.

(12) Hashimoto, T.; Sasaki, K.; Fukumoto, K.; Murase, Y.; Abe, N.; Ooi, T.; Maruoka, K. *Chem.—Asian J.* **2010**, *5*, 562.

(13) (a) Denney, D. B.; Denney, D. Z. *J. Am. Chem. Soc.* **1960**, *82*, 1389. (b) Hasegawa, S.; Kashino, S.; Mukahi, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 69. (c) Buckley, D.; Dunstan, S.; Henbest, H. B. *J. Chem. Soc.* **1957**, 4901.

(14) ESI-MS clearly indicated the complete conversion of the aminocatalyst; one oxidized form is *O*-benzoyl-*N*-oxide. However, we were unable to differentiate between the tertiary and primary *N*-oxide. In the presence of TfOH, the oxidation of the aminocatalyst has been found to be minor as also verified by the control experiments (Scheme 4).

DOI: 10.1021/ol503592n
Org. Lett. 2015, 17, 576–579