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Phase-Transfer-Catalyzed Enantioselective α-Hydroxylation of Acyclic and Cyclic Ketones with Oxygen

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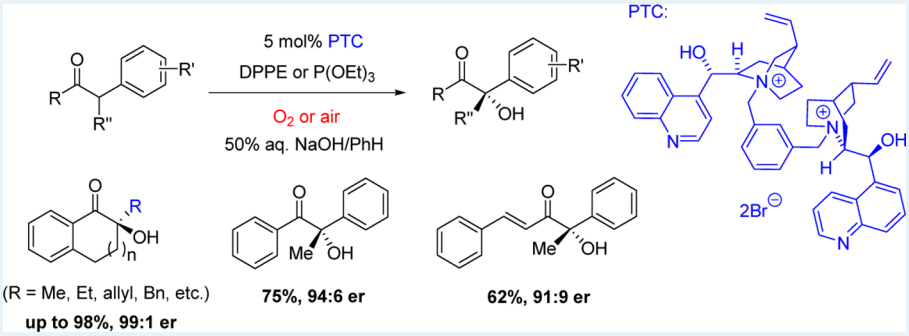
Supporting Information



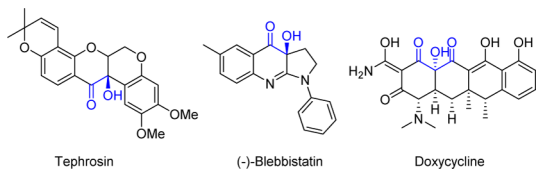
ABSTRACT: An efficient and enantioselective α-hydroxylation of acyclic as well as cyclic ketones using molecular oxygen has been developed. This simple catalytic procedure uses a readily available phase-transfer catalyst and produces a wide range of valuable tertiary α-hydroxy ketones in good to excellent enantiopurity.

KEYWORDS: *phase transfer catalysis, hydroxylation, α-hydroxy ketone, oxygen, cinchona alkaloid, enantioselectivity*

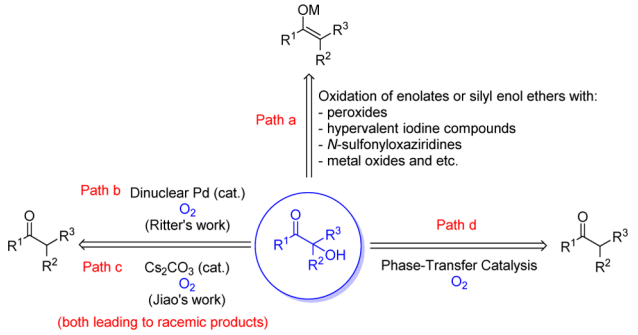
The tertiary α-hydroxy carbonyl functionality is found in many biologically active natural products as well as synthetic drugs such as tephrosin,[1a] (−)-blebbistatin,[1b] and doxycycline[1c] (Scheme 1). Also, enantiomerically enriched α-hydroxy carbonyl compounds are useful building blocks in the synthesis of complex molecules,[2] and they can act as stereodirecting groups.[3] Therefore, the development of methods for the synthesis of this class of compounds is an actively pursued area of research.[4]

The most direct method to access tertiary α-hydroxy carbonyl compounds would be the introduction of a hydroxyl moiety α to the readily available carbonyl group. Although α-hydroxylation of aldehydes and ketones by enamine catalysis to form secondary alcohols is well-established,[5] the corresponding transformation to produce tertiary alcohols, and in particular the asymmetric variant, has proven to be quite challenging. Indeed, catalytic systems utilizing the preformed enolates or silyl enol ethers have been extensively studied in the past few decades, and enantioselective variants have also been reported

Scheme 1. Biologically Active Compounds Possessing Tertiary α-Hydroxy Carbonyl Moiety



Scheme 2. Methods To Access α-hydroxy Carbonyl Compounds Starting from Carbonyl Compounds



(path a, Scheme 2). Along these lines, various oxidants such as *N*-sulfonyloxaziridines, peroxides, hypervalent iodine compounds, and metal oxides have been utilized.[4] However, in addition to the necessity of prior generation of the enolates or enol ethers from ketones, these methodologies generally need to be carried out under stringent conditions because the reagents used are typically moisture-sensitive. In addition, each reaction step generates a stoichiometric amount of byproduct.

More recently, the Ritter group reported a palladium-catalyzed aerobic hydroxylation of ketones (path b, Scheme

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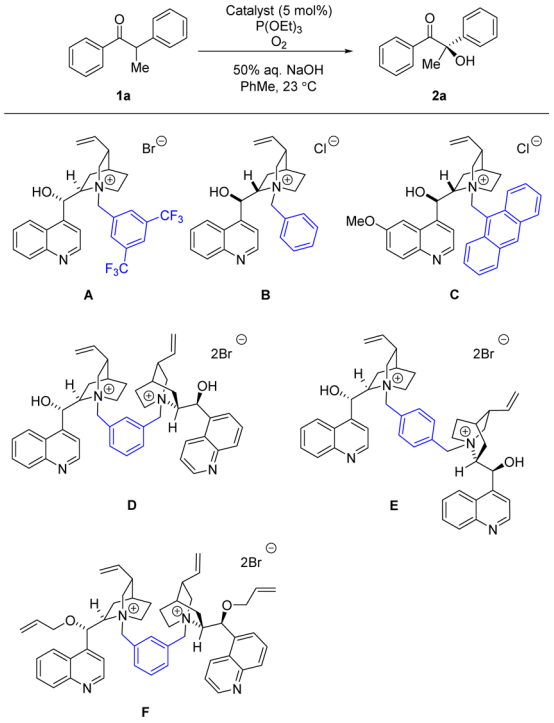
Table 1. Screening of Catalysts[a]



entry	catalyst	time (h)	yield (%)[b]	er[c]
1	**A**	48[d]	30	66:34
2	**B**	48[d]	25	48:52
3	**C**	48	trace	n.d.
4	**D**	24	51	92:8
5	**E**	48[d]	37	77:23
6	**F**	48[d]	20	54:46

[a]General conditions: **1a** (0.1 mmol), catalyst (5 mol %), $P(OEt)_3$ (0.1 mmol), 50% aq NaOH (0.25 mL), PhMe (0.1 M) at room temperature. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Conversion of the starting material was not complete, but the reaction was stopped as there was no improvement in conversion.

Scheme 3. Formation of Side Products during the Reaction

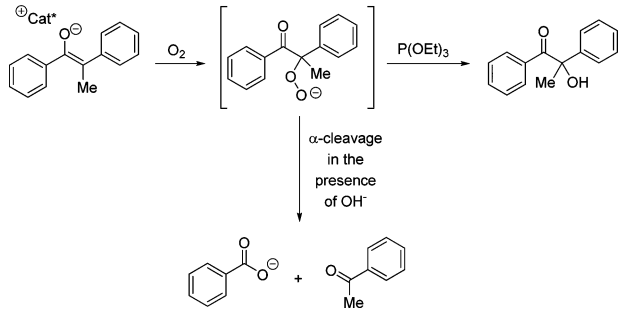
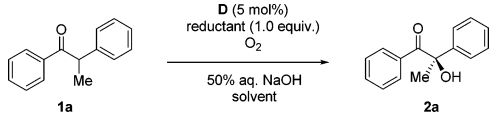


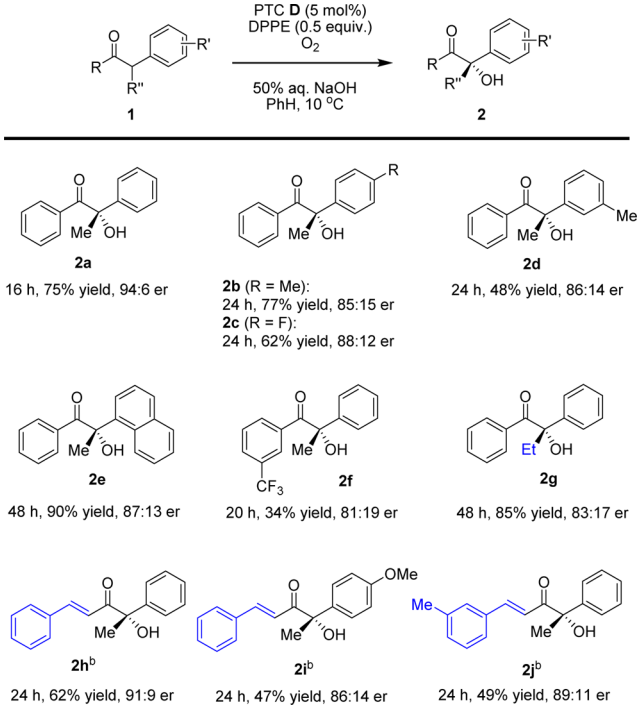
Table 2. Optimization of Reaction Conditions[a]



entry	solvent	reductant	time (h)	yield (%)[b]	er[c]
1	Et_2O	$P(OEt)_3$	72	43	81:19
2	CH_2Cl_2	$P(OEt)_3$	72	35	60:40
3	PhH	$P(OEt)_3$	8	54	93:7
4	PhH	$P(O^iPr)_3$	8	19	88:12
5	PhH	PPh_3	8	40	88:12
6	PhH	$P(n\text{-octyl})_3$	8	71	80:20
7	PhH	DPPE[d]	8	83	82:18
8	PhH	DPPE (0.5 equiv)	8	76	93:7
9[e]	PhH	DPPE (0.5 equiv)	16	75	94:6
10[f]	PhH	DPPE (0.5 equiv)	48	56	92:8

[a]General conditions: **1a** (0.1 mmol), **D** (5 mol %), reductant (0.1 mmol), 50% aq NaOH (0.25 mL), solvent (0.1 M) at room temperature. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]DPPE: 1,2-bis(diphenylphosphino)ethane. [e]Reaction performed at 10 °C. [f]Reaction performed at 10 °C in air instead of using O_2.

Scheme 4. Scope of Acyclic Ketones[a]



[a]General Conditions: **1** (0.1 mmol), **D** (5 mol %), DPPE (0.05 mmol), 50% aq NaOH (0.25 mL), PhH (0.1 M) at 10 °C. [b]Reaction performed with $P(OEt)_3$ (0.1 mmol) in PhH (0.2 M).

2).[6a] The ketone was directly used as the substrate, and the inexpensive and environmentally benign oxygen gas was used as the oxidant. The group of Jiao also developed an interesting Cs_2CO_3-catalyzed α-hydroxylation of ketones using oxygen gas (path c, Scheme 2).[6b] In these two systems, both cyclic as well as acyclic α-hydroxy ketones were obtained in good yields, although they represent racemic syntheses of these valuable compounds. From both an economical as well as an environmental viewpoint, the low cost, abundance, and benign nature of molecular oxygen makes it an ideal candidate to serve as an oxidant or as a source of O atom in organic synthesis,[7] especially in asymmetric catalysis.

The α-hydroxylation of carbonyl compounds with oxygen has also been achieved by phase-transfer catalysis, with the use of chiral phase-transfer catalysts (PTCs) leading to enantioenriched products (path d, Scheme 2).[8] However, the examples reported along these lines were restricted to cyclic ketones[9a−d] and oxindoles,[9e,f] whereas access to acyclic tertiary α-hydroxy

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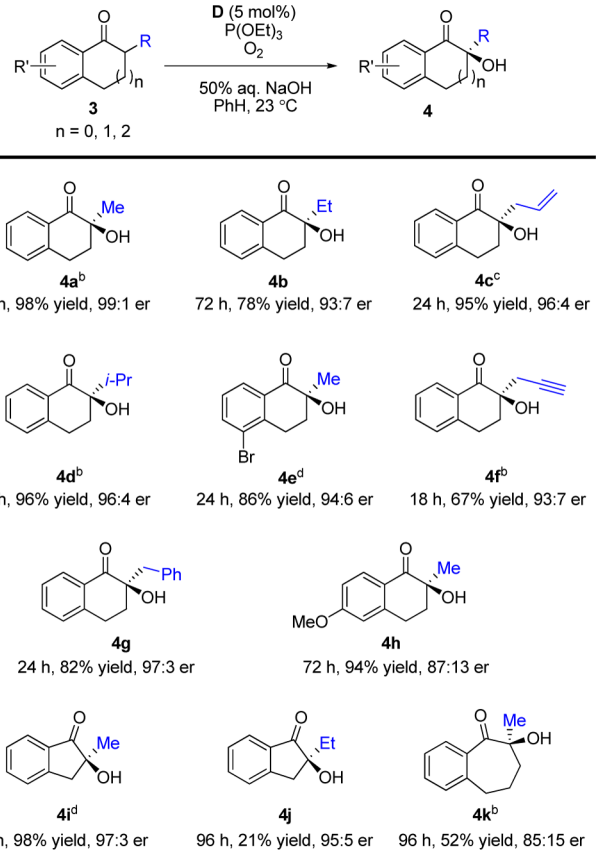
Scheme 5. Scope of Cyclic Ketones[a]



[a]General conditions: **3** (0.1 mmol), **D** (5 mol %), $P(OEt)_3$ (0.1 mmol), 50% aq NaOH (0.25 mL), PhH (0.1 M) at room temperature. [b]Reaction performed in PhH (0.2 M). [c]Reaction performed in PhH (0.067 M) and 50% aq NaOH (0.30 mL). [d]Reaction using **D** (10 mol %), 50% aq NaOH (0.30 mL) in PhH (0.067 M).

carbonyl compounds remained elusive. Herein we report our recent discovery of an efficient and operationally simple method for the synthesis of enantioenriched acyclic and cyclic α-hydroxy ketones using oxygen. A cinchona alkaloid-derived dimeric phase-transfer catalyst that can be easily prepared in one step proved to be highly efficient and enantioselective.

We initiated our studies using acyclic ketone **1a** as the model substrate (Table 1), which was previously used by the Davis group in their studies on enantioselective α-hydroxylation using chiral *N*-sulfonyloxaziridines.[10] Cinchona alkaloid-based PTCs **A** to **C** that have found wide application in asymmetric phase-transfer catalysis were screened, but they proved to be disappointing because they gave the product **2a** in low yields and enantiomeric ratios (entries 1−3). We then turned to catalyst **D**, which was originally reported by Park and Jew.[11] It can be easily synthesized in high yields in a single step from commercially available starting materials. To our delight, use of just 5 mol % of **D** afforded the product in good enantiomeric ratio (92:8 er) albeit with a modest isolated yield of 51% (Table 1, entry 4). Encouraged by this result, we screened catalyst **E**, which is a variant of **D** but has a para-substitution pattern on the linker as well as **F**, in which the hydroxyl groups on the cinchona alkaloids were allylated. Both these modifications failed to improve the yield or enantiomeric ratio of the product (Table 1, entries 5 and 6). Thus, PTC **D** was chosen as the catalyst for further optimization of the hydroxylation reaction.

It is noteworthy that alkylation of the hydroxyl groups in catalyst **F** led to a drastic decrease in enantioselectivity, which implies that the hydroxyl groups play an important role in controlling the enantioselectivity, possibly through hydrogen bonding with the enolate intermediate.[9a]

During the course of the catalyst screening, we observed the formation of side products in the reaction, which led to low yield of the desired product, even when there was complete consumption of **1a**. Isolation and characterization of the side products revealed that they were acetophenone and benzoate salt. In fact, a closely related transformation was studied in detail by Ogata and co-workers, who proposed the mechanism of α-cleavage of the peroxide intermediate in the presence of base (Scheme 3).[12] Hence, we set about optimizing the reaction conditions to minimize the side product formation and to increase the yield of the desired α-hydroxy ketone.

With PTC **D** as the optimal catalyst, different solvents were screened, and it was found that reaction in benzene gave slightly better enantioselectivity compared to toluene (Table 2, entry 3), while poorer results were obtained with diethyl ether and dichloromethane (Table 2, entries 1 and 2). Even though triethyl phosphite is normally used for reducing the peroxide intermediate to the product,[13] we decided to screen other reductants in hopes of increasing product yield. It was found that phosphines could also be used for this role,[13a] and 1,2-bis(diphenylphosphino)ethane (DPPE) was able to furnish the product in good yield, although with diminished enantioselectivity (Table 2, entry 7). Gratifyingly, by decreasing the amount of DPPE used to 0.5 equiv, we were able to obtain the product with an improved yield and no compromise in enantioselectivity compared to using $P(OEt)_3$ (Table 2, entry 8 vs entry 3). Lowering the reaction temperature to 10 °C further improved the enantiomeric ratio (Table 2, entry 9). Very importantly, the reaction can also be conducted in air in place of O_2, although a lower yield and slightly diminished enantioselectivity were obtained (Table 2, entry 10).

With the optimized conditions in hand, we explored the substrate scope of the α-hydroxylation reaction (Scheme 4). Substitution on the phenyl ring generally decreased the enantioselectivity of the products (**2a**−**2e**). Those bearing electron-withdrawing substituents could also be accessed, albeit with lower yield (**2c** and **2f**) due to more facile α-cleavage of the intermediate. On the other hand, it was observed that increasing the steric bulk on the α-carbon led to improved yields of the products (**2e, 2g**), probably due to the decreased rate of α-cleavage of the intermediate. We were pleased to find that the α-hydroxylation reaction can also be applied to enones, yielding the synthetically versatile products with good enantiomeric ratios, although the yields were modest (**2h**−**2j**). Substrates bearing dialkyl substitutions at the α-position were also examined. The level of efficiency and selectivity were unfortunately much lower (results not shown).

Encouraged by the results obtained with acyclic substrates, we applied dimeric catalyst **D** to the α-hydroxylation of cyclic ketones, in particular α-substituted tetralones (Scheme 5). To our great delight, the hydroxylated products were obtained with good to excellent enantioselectivities and generally good yields even when the reactions were performed at room temperature using only 5 mol % of catalyst and triethyl phosphite as the reductant. A variety of alkyl substituents at the α-position were well tolerated (**4a-4d, 4f, 4g**), whereas substitutions on the aromatic ring decreased the enantiomeric ratios slightly (**4e, 4h**). Although indanones can also be hydroxylated with good

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enantioselectivities (**4i, 4j**), an increase in the ring size of the ketone diminished the yield and enantiomeric ratio (**4k**). Nevertheless, these results constituted a significant improvement in enantioselectivities and substrate scope over previous reports on phase-transfer-catalyzed asymmetric α-hydroxylation of cyclic ketones.[9a−c]

In summary, we have developed an operationally simple and economical method for the asymmetric α-hydroxylation of ketones using phase-transfer catalysis with relatively low catalyst loadings. Synthetically valuable acyclic ketones can be hydroxylated in modest to good yields with good enantioselectivities, whereas a wide range of cyclic α-hydroxy ketones can be obtained with excellent yields and enantiopurity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00583.

Experimental procedures and characterization data for all the products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Matsuda, H.; Yoshida, K.; Miyagawa, K.; Asao, Y.; Takayama, S.; Nakashima, S.; Xu, F.; Yoshikawa, M. *Bioorg. Med. Chem.* **2007**, *15*, 1539−1546. (b) Lucas-Lopez, C.; Patterson, S.; Blum, T.; Straight, A. F.; Toth, J.; Slawin, A. M. Z.; Mitchison, T. J.; Sellers, J. R.; Westwood, N. J. *Eur. J. Org. Chem.* **2005**, *2005*, 1736−1740. (c) Olack, G.; Morrison, H. *J. Org. Chem.* **1991**, *56*, 4969−4971.

(2) Hannessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983; pp 7−19.

(3) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876−889. (c) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629−631. (d) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629−4630. (e) Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986**, *27*, 799−802. (f) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569.

(4) See: Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. In *Organic Reactions*; Overman, L. E., Ed. Wiley: New York, 2003; Vol. *62*, pp 1−356 and references therein.

(5) For selected examples, see: (a) Ramachary, D. B.; Barbas, C. F. *Org. Lett.* **2005**, *7*, 1577−1580. (b) Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2007**, *9*, 1943−1946.

(6) (a) Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 1760−1762. (b) Liang, Y.-F.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 548−552.

(7) For selected reviews, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (b) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362−367. (c) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329−2363. (d) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612−6615. (e) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221−229. (f) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318−5365. (g) Piera, J.; Backvall, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506−3523. (h) Stahl, S. S. *Science* **2005**, *309*, 1824−1826. (i) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227−8241. (j) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736−1748. (k) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381−3430.

(8) For selected reviews on asymmetric phase-transfer catalysis, see: (a) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222−4266. (b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656−5682. (c) Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312−4348.

(9) (a) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835−2838. (b) de Vries, E. F. J.; Ploeg, L.; Colao, M.; Brussee, J.; van der Gen, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1123−1132. (c) Dehmlow, E. V.; Wagner, S.; Müller, A. *Tetrahedron* **1999**, *55*, 6335−6346. (d) Lian, M.; Li, Z.; Cai, Y.; Meng, Q.; Gao, Z. *Chem. - Asian J.* **2012**, *7*, 2019−2023. (e) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593−1595. (f) Yang, Y.; Moinodeen, F.; Chin, W.; Ma, T.; Jiang, Z.; Tan, C.-H. *Org. Lett.* **2012**, *14*, 4762−4765.

(10) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679−6690.

(11) (a) Jew, S.-S.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-G. *Chem. Commun.* **2001**, 1244−1245. (b) Park, H.-G.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-K.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036−3038. (c) Park, H.-G.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-S.; Kim, M. G.; Jew, S.-S. *Tetrahedron Lett.* **2003**, *44*, 3497−3500.

(12) Sawaki, Y.; Ogata, Y. *J. Am. Chem. Soc.* **1975**, *97*, 6983−6989.

(13) (a) Denney, D. B.; Goodyear, W. F.; Goldstein, B. *J. Am. Chem. Soc.* **1960**, *82*, 1393−1395. (b) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294−3297.

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