Organic LETTERS

Letter

pubs.acs.org/OrgLett

Direct Transformation of Ethylarenes into Primary Aromatic Amides with *N*-Bromosuccinimide and I_2–Aqueous NH_3

Shohei Shimokawa,[†] Yuhsuke Kawagoe,[†] Katsuhiko Moriyama,[†,‡] and Hideo Togo*[,†]

[†]Graduate School of Science, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522, Japan

[‡]Molecular Chirality Research Center, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522, Japan

Supporting Information

ABSTRACT: A variety of ethylarenes were converted into the corresponding primary aromatic amides in good yields via treatment with *N*-bromosuccinimide in the presence of a catalytic amount of 2,2′-azobis(isobutyronitrile) in a mixture of ethyl acetate and water, acetonitrile and water, or chloroform and water, followed by reaction with molecular iodine and aq NH_3 in one pot. It was found that aryl α-bromomethyl ketones and/or aryl methyl ketones were formed at the first reaction step and their iodoform-type reaction occurred at the second reaction step to provide primary aromatic amides. The present reaction is a useful and practical transition-metal-free method for the preparation of primary aromatic amides from ethylarenes.

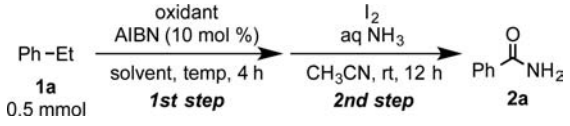
Primary aromatic amides are valuable compounds that are used as pharmaceuticals[1] and intermediates for the synthesis of aromatic nitriles, carboxylic acids, and heterocyclic compounds, such as oxazoles. As typical conventional methods for the preparation of primary aromatic amides, the treatment of aroyl chlorides with aqueous ammonia (Schotten–Baumann reaction), the dehydration of arenecarboxylic acids and ammonia, and the hydration of aromatic nitriles are known.[2] The amidation of electron-rich aromatics with $EtOCONH_2$ and $AlCl_3$ was also reported.[3] On the other hand, the Lieben iodoform reaction is useful for the preparation of primary amides, particularly primary aromatic amides, from aryl methyl ketones or α-arylethanols with molecular iodine and aq NH_3 under transition-metal-free and low-toxicity conditions.[4] The reaction of aryl trichloromethyl ketones with primary amines was reported to give secondary aromatic amides.[5] Recently, the tetrabutylammonium iodide mediated transformation of aryl methyl ketones with *tert*-butyl hydrogen peroxide (TBHP) and aq NH_3 at 100 °C into primary aromatic amides[6a] and the I_2-mediated transformation of aryl methyl ketones with primary amines and TBHP at 0 °C into secondary aromatic amides[6b] were reported. Moreover, the reaction of aryl methyl ketones and α-arylethanols with molecular iodine and aq NH_3 at 60 °C was reported to provide the corresponding primary aromatic amides.[7] Recently, we reported the one-pot transformation of methylarenes into aromatic nitriles, which involved the treatment with *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and a catalytic amount of 2,2′-azobis(isobutyronitrile) (AIBN) or benzoyl peroxide (BPO) under warming conditions or irradiation with a tungsten lamp, followed by reaction with molecular iodine and aq NH_3 at 60 °C,[8a] and treatment with aq H_2O_2 and aq HBr under warming conditions or irradiation with a tungsten lamp, followed by reaction with molecular iodine and aq NH_3 at 60 °C.[8b] Here, as part of our study of molecular iodine for organic synthesis,[9] we report a one-pot transformation of ethylarenes into primary aromatic amides by treatment with NBS followed by the reaction with molecular iodine and aq NH_3. In the course of our present study, a one-pot conversion of ethylarenes into primary aromatic amides with molecular iodine and TBHP in aq NH_3 at 100 °C for 3 h was reported.[10] As the reaction looked highly useful and attractive, we checked its applicability to the one-pot preparation of primary aromatic amides from ethylbenzene and *p*-bromoethylbenzene with molecular iodine, TBHP, and aq NH_3 under the same reaction conditions.[10] However, we question the veracity of the report; although we performed the above reaction carefully on the basis of the reported reaction conditions, we obtained only 6% of benzamide and 7% of *p*-bromobenzamide, together with starting ethylarenes and complicated reaction mixtures. Thus, we found that the reaction is not reproducible. Here, we report a practical one-pot transformation of ethylarenes into primary aromatic amides by treatment with NBS, followed by the reaction with molecular iodine and aq NH_3.

Treatment of ethylbenzene **1a** (0.5 mmol) with NBS (2.5 equiv) in the presence of AIBN (10 mol %) in a mixture of chloroform and H_2O (10 equiv) at 60 °C for 4 h followed by reaction with molecular iodine (3.0 equiv) and aq NH_3 (28–30%) at room temperature for 12 h gave benzamide **2a** in 5% yield (Table 1, entry 1). To improve the yield of benzamide **2a**, optimization of the reaction conditions by changing the solvent, namely mixtures of chloroform and water (9:1), carbon tetrachloride and water (9:1), *tert*-butyl methyl ether (TBME) and water (9:1), ethyl acetate and water (9:1), and acetonitrile and water (9:1), was carried out, and it was found that the mixture of ethyl acetate and water was the best choice, giving benzamide **2a** in 63% yield (Table 1, entries 2–6). Finally, we found that treatment of ethylbenzene **1a** with NBS (3.5 equiv) in the presence of AIBN in a mixture of ethyl acetate and water (5:1) at 60 °C for 4 h, followed by the reaction with molecular iodine and aq NH_3 (28% ∼ 30%) at

Received: January 6, 2016
Published: January 27, 2016

DOI: 10.1021/acs.orglett.6b00048
Org. Lett. 2016, 18, 784–787

Table 1. Optimization of Reaction Conditions with Ethylbenzene

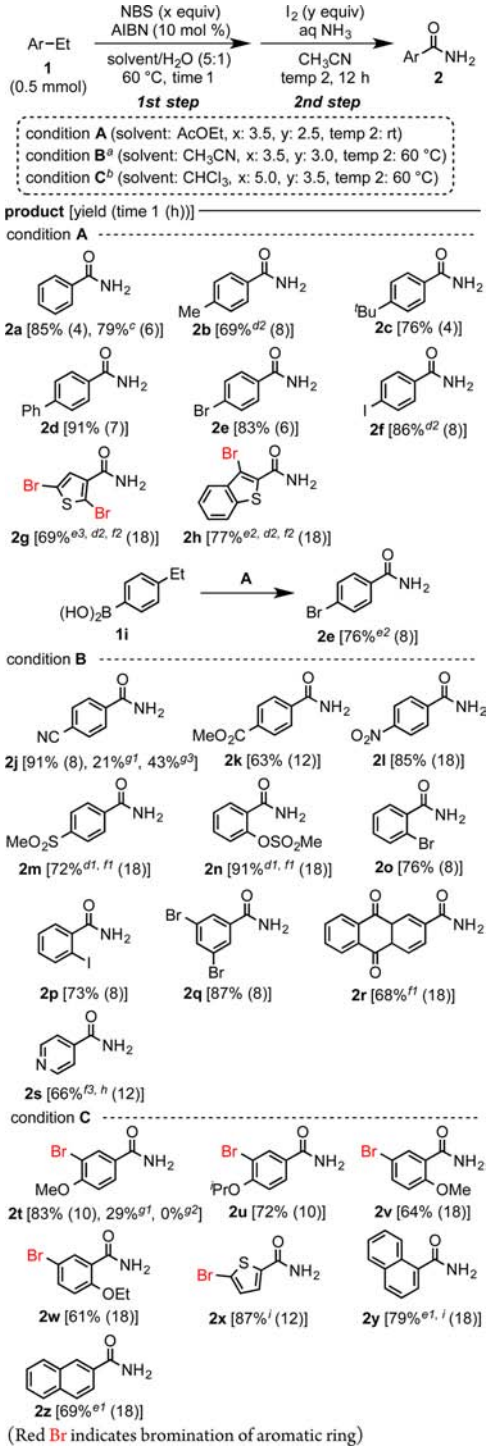


	first step			second step	
entry	oxidant (equiv)	solvent	temp (°C)	I_2 (equiv)	yield (%)
1[a]	NBS (2.5)	$CHCl_3$	60	3.0	5
2	NBS (2.5)	$CHCl_3/H_2O$ (9:1)	60	3.0	7
3	NBS (2.5)	CCl_4/H_2O (9:1)	60	3.0	0
4	NBS (2.5)	TBME/H_2O (9:1)	60	3.0	16
5	NBS (2.5)	AcOEt/H_2O (9:1)	60	3.0	63
6	NBS (2.5)	CH_3CN/H_2O (9:1)	60	3.0	43
7	NBS (3.5)	AcOEt/H_2O (9:1)	60	2.5	80
8	NBS (3.5)	AcOEt/H_2O (5:1)	60	2.5	85
9	DBDMH (1.75)	AcOEt/H_2O (5:1)	60	2.5	82
10	NBA (3.5)	AcOEt/H_2O (5:1)	60	2.5	20
11	BrNPhth (3.5)	AcOEt/H_2O (5:1)	60	2.5	81
12	NBS (3.5)	AcOEt/H_2O (5:1)	40	2.5	0
13	NIS (3.5)	AcOEt/H_2O (5:1)	60	2.5	0

[a]H_2O (10 equiv) was added at the first reaction step.

room temperature for 12 h gave benzamide **2a** in 85% yield (Table 1, entry 8). Here, α-bromoacetophenone was the major product in the reaction with NBS in a mixture of ethyl acetate and water at 60 °C for 4 h (the first reaction step), and the yield was in 81% yield. *N*-Iodosuccinimide (NIS) was not effective at all (Table 1, entry 13). Treatment of ethylbenzene **1a** with DBDMH or *N*-bromophthalimide (BrNPhth) instead of NBS under the same procedure and conditions gave benzamide **2a** in 82% and 81% yields, respectively, whereas the yield of benzamide **2a** was low when *N*-bromobenzamide (NBA) was used under the same conditions (Table 1, entries 9−11). Lowering the temperature of the first reaction step was also detrimental to the present reaction, even if NBS was used in a mixture of ethyl acetate and water (5:1) (Table 1, entry 12). On the basis of these results, various ethylarenes **1** were treated with NBS (3.5 equiv) in the presence of AIBN (10 mol %) in a mixture of ethyl acetate and water (5:1) at 60 °C for the indicated time, followed by the reaction with molecular iodine (2.5 equiv) and aq NH_3 (28−30%) at room temperature for 12 h to give primary aromatic amides, as shown in Table 2 (conditions A). At first, the semilarge-scale treatment of ethylbenzene **1a** (10 mmol) under the same procedure and conditions gave benzamide **2a** in 79% yield. Treatment of ethylarenes **1**, such as 4-methyl-1-ethylbenzene **1b**, 4-*tert*-butyl-1-ethylbenzene **1c**, 4-phenyl-1-ethylbenzene **1d**, 4-bromo-1-ethylbenzene **1e**, and 4-iodo-1-ethylbenzene **1f** under the same procedure and conditions provided the corresponding primary aromatic amides **2b**, **2c**, **2d**, **2e**, and **2f** in good yields. When ethylarenes **1**, such as 3-ethylthiophene **1g** and 2-ethylbenzothiophene **1h**, were treated under the same procedure and conditions with 6.0 and 5.0 equiv of NBS, respectively, at the first reaction step, brominated amides 2,5-dibromothiophene-3-carboxamide **2g** and 3-bromobenzothiophene-2-carboxamide **2h** were obtained in good yields. When 4-ethylphenylboronic acid **1i** was reacted with 5.0 equiv of

Table 2. Transformation of Ethylarenes into Primary Aromatic Amides



[a]First step was carried out at 80 °C. [b]Solvent was removed under reduced pressure before the second step. [c]Reaction was carried out on a 10 mmol scale. [d]Second step was carried out at [1]rt or [2]60 °C. [e]NBS ([1]3.5, [2]5.0, or [3]6.0 equiv) was used. [f]I_2 ([1]2.5, [2]3.0, or [3]5.0 equiv) was used. [g]Reaction was carried out under conditions [1]**A**, [2]**B**, or [3]**C** (time 1:10 h). [h]First step was carried out without H_2O, and second step was carried out at 80 °C for 24 h. [i]Volume of $CHCl_3/H_2O$ in the first step was 6.0 mL instead of the usual 3.0 mL.

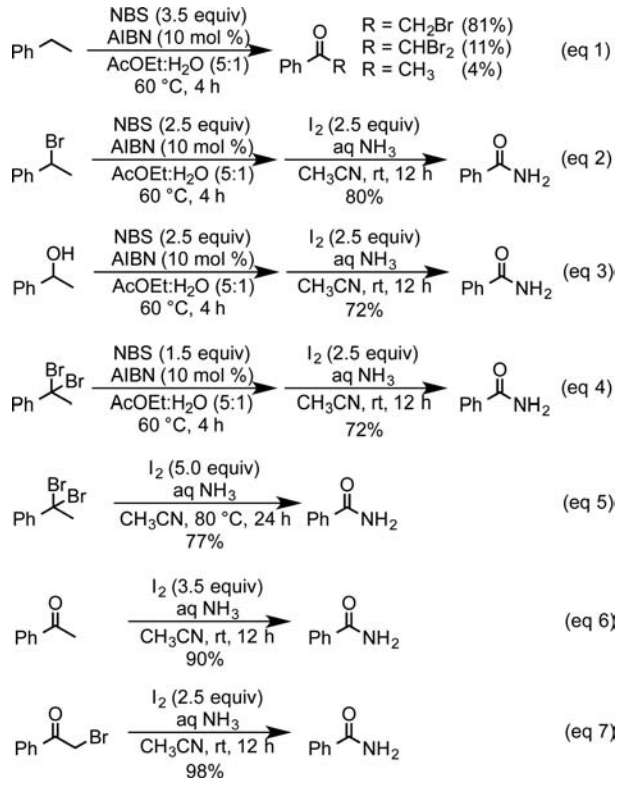
NBS under the same procedure and conditions, *p*-bromobenzamide **2e** was obtained in 76% yield.

DOI: 10.1021/acs.orglett.6b00048
Org. Lett. 2016, 18, 784−787

When conditions **A** were adopted for 4-cyano-1-ethylbenzene **1j**, 4-cyanobenzamide was obtained in only 21% yield. However, when ethylarenes **1** bearing an electron-withdrawing group, such as 4-cyano-1-ethylbenzene **1j**, 4-methoxycarbonyl-1-ethylbenzene **1k**, 4-nitro-1-ethylbenzene **1l**, 4-methanesulfonyl-1-ethylbenzene **1m**, 2-methanesulfonyloxy-1-ethylbenzene **1n**, 2-bromo-1-ethylbenzene **1o**, 2-iodo-1-ethylbenzene **1p**, 3,5-dibromo-1-ethylbenzene **1q**, and 2-ethyl-9,10-anthraquinone **1r**, were treated with NBS (3.5 equiv) in the presence of AIBN (10 mol %) in a mixture of acetonitrile and water (5:1) at 60 °C for the indicated time, followed by the reaction with molecular iodine (3.0 equiv or 2.5 equiv) and aq NH_3 (28−30%) at 60 °C for 12 h, primary aromatic amides **2j**, **2k**, **2l**, **2m**, **2n**, **2o**, **2p**, **2q**, and **2r** were produced in good yields, as shown in Table 2 (conditions **B**). Here, aryl α-bromomethyl ketone and aryl methyl ketone were the main products of the first reaction step. When 4-ethylpyridine **1s** was used, the first reaction step was carried out in acetonitrile alone with NBS (5.0 equiv) and AIBN at 60 °C for 12 h, and the second reaction step was carried out with molecular iodine (5.0 equiv) and aq NH_3 at 80 °C for 24 h due to low reactivity, giving isonicotinamide **2s** in good yield. Here, the product of the first reaction step was 4-(α,α-dibromoethyl)pyridine. On the other hand, when 4-methoxy-1-ethylbenzene **1t** was treated with conditions **A** and **B**, 3-bromo-4-methoxybenzamide **2t** was obtained in 29% and 0% yield, respectively. Thus, to improve the yield of aromatic amides **2**, ethylarenes **1** bearing an electron-donating group, such as 4-methoxy-1-ethylbenzene **1t**, 4-isopropoxy-1-ethylbenzene **1u**, 2-methoxy-1-ethylbenzene **1v**, 2-ethoxy-1-ethybenzene **1w**, and 2-ethylthiophene **1x**, were treated with NBS (5.0 equiv) in the presence of AIBN (10 mol %) in a mixture of chloroform and water (5:1) at 60 °C for the indicated time, followed by the reaction with molecular iodine (3.5 equiv) and aq NH_3 (28% ∼ 30%) at 60 °C for 12 h to give brominated primary aromatic amides **2t**, **2u**, **2v**, **2w**, and **2x** in good yields, as shown in Table 2 (conditions **C**), although a slightly diluted condition was used at the first reaction step for compound **1x**. Here, aryl methyl ketones were the main products of the first reaction step. The same treatment of 1-ethylnaphthalene **1y** and 2-ethylnaphthalene **1z** using conditions **C** with NBS (3.5 equiv) gave 1-naphthamide **2y** and 2-naphthamide **2z** in good yields, although a slightly diluted condition was used at the first reaction step for compound **1y**.

Then, to clarify the reaction mechanism underlying the present one-pot reaction, blank experiments were carried out, as shown in Scheme 1. When ethylbenzene **1a** was treated with NBS (3.5 equiv) in the presence of AIBN (10 mmol %) in a mixture of ethyl acetate and water (5:1) at 60 °C for 4 h, α-bromoacetophenone was obtained in 81% yield, together with α,α-dibromoacetophenone and acetophenone in 11% and 4% yields, respectively (eq 1). Therefore, α-bromo ketone was the major product of the first reaction step under conditions **A**. α-Bromoethylbenzene, which is the first reaction product of the Wohl−Ziegler reaction, and α-hydroxyethylbenzene, which may be formed by hydrolysis of α-bromoethylbenzene, were treated with NBS (2.5 equiv) in the presence of AIBN (10 mol %) in a mixture of ethyl acetate and water (5:1) at 60 °C for 4 h, followed by the reaction with molecular iodine (2.5 equiv) and aq NH_3 (28−30%) at room temperature for 12 h to give benzamide **2a** in 80% and 72% yields, respectively (eqs 2 and 3). In addition, when α,α-dibromoethylbenzene, which may be formed by the second Wohl−Ziegler reaction of α-bromoethylbenzene, was treated with NBS (1.5 equiv) in the

Scheme 1. Control Experiments

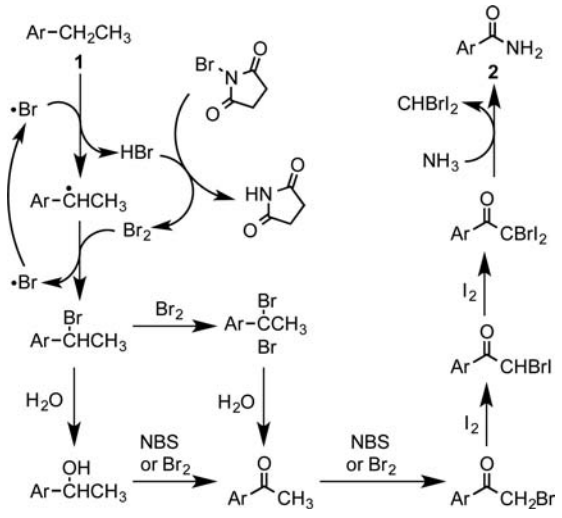


presence of AIBN (10 mol %) in a mixture of ethyl acetate and water (5:1) at 60 °C for 4 h, followed by the reaction with molecular iodine (2.5 equiv) and aq NH_3 (28−30%) at room temperature for 12 h, benzamide **2a** was obtained in 72% yield (eq 4). Thus, α-bromoethylbenzene, α-hydroxyethylbenzene, and α,α-dibromoethylbenzene could be also converted into benzamide **2a** using the present reaction procedure and conditions. When α,α-dibromoethylbenzene was directly treated with molecular iodine (5.0 equiv) and aq NH_3 (28% ∼ 30%) at 80 °C for 24 h, benzamide **2a** was obtained in 77% yield (eq 5). This reaction proceeded for the case of 4-ethylpyridine **1s**, and 4-(α,α-dibromoethyl)pyridine was the product of the first reaction step. Finally, when acetophenone and α-bromoacetophenone were treated with aq NH_3 and 3.5 equiv and 2.5 equiv of molecular iodine at room temperature for 12 h, benzamide **2a** was obtained in 90% and 98% yields, respectively (eqs 6 and 7). Based on those blank experiments, we propose the following reaction mechanism, as shown in Scheme 2. α-Bromoethylarene is formed in the reaction of ethylarene **1** with bromine atom formed from NBS (Wohl−Ziegler reaction). The second Wohl−Ziegler reaction of α-bromoethylarene occurs to give α,α-dibromoethylarene mainly. The hydrolysis of α,α-dibromoethylarene in a mixture of ethyl acetate (or acetonitrile or chloroform) and water under warming conditions proceeds to give aryl methyl ketone.

Simultaneously, the hydrolysis of α-bromoethylarene may occur to form α-hydroxyethylarene as a minor product. α-Hydroxyethylarene can be easily oxidized by NBS or Br_2 to aryl methyl ketone. Once aryl methyl ketone is formed, it smoothly reacts with NBS or Br_2 to form aryl α-bromomethyl ketone. Then, treatment of aryl α-bromomethyl ketone (conditions **A** and **B**) or aryl methyl ketones (condition **B** and **C**) with molecular iodine and aq NH_3 induces iodination to form aryl α,α,α-bromodiiodomethyl ketone and aryl α,α,α-triiodomethyl

DOI: 10.1021/acs.orglett.6b00048
Org. Lett. 2016, 18, 784−787

Scheme 2. Plausible Reaction Mechanism



ketones, respectively, at the second reaction step. Aryl α,α,α-bromodiiodomethyl ketone and aryl α,α,α-triiodomethyl ketones smoothly react with aq NH_3 to form primary aromatic amide **2** and $CHBrI_2$ and CHI_3, respectively. $CHBrI_2$ and CHI_3 were observed by mass spectral measurements of the reaction mixtures.

In conclusion, various ethylarenes were successfully transformed into the corresponding primary aromatic amides or brominated primary aromatic amides in good yields in one pot under mild and transition-metal-free conditions via treatment with NBS and a catalytic amount of AIBN in a mixture of ethyl acetate and water, acetonitrile and water, or chloroform and water, followed by the reaction with molecular iodine and aq NH_3. We believe the present method would be useful for the conversion of ethylarenes into primary aromatic amides due to the simple synthetic procedure, use of low-toxicity reagents, and the generality of the reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00048.

Experimental details; characterization data by mp, IR, ^{1}H NMR, and ^{13}C NMR (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: togo@faculty.chiba-u.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support in the form of a Grant-in-Aid for Scientific Research (No. 25105710) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, is acknowledged.

■ REFERENCES

(1) (a) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243. (b) Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1248. (c) Bray, B. L. *Nat. Rev. Drug Discovery* **2003**, *2*, 587. (d) Beckwith, A. L. J. Synthesis of Amides. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley-Interscience: New York, 1970; p 73.

(2) Larock, R. C. *Comprehensive Organic Transformation*, 2nd ed.; Wiley, 1999; p 1623.

(3) (a) Chakraborty, D. P.; Mandal, A. K.; Roy, S. K. *Synthesis* **1981**, *1981*, 977.

(4) (a) Lieben, A. *Ann.* **1870**, *7*, 218. (b) Newman, M. S.; Holmes, H. L. *Organic Syntheses*; John Wiley & Sons, 1966; Collect. Vol. *2*, p 428.

(5) (a) Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776. (b) Druzian, J.; Zucco, C.; Rezende, M. C.; Nome, K. *J. Org. Chem.* **1989**, *54*, 4767.

(6) (a) Sharif, M.; Chen, J.; Langer, P.; Beller, M.; Wu, X. *Org. Biomol. Chem.* **2014**, *12*, 6359. (b) Zhu, C.; Wei, W.; Du, P.; Wan, X. *Tetrahedron* **2014**, *70*, 9615.

(7) Cao, L.; Ding, J.; Gao, M.; Wang, Z.; Li, J.; Wu, A. *Org. Lett.* **2009**, *11*, 3810.

(8) (a) Tsuchiya, D.; Kawagoe, Y.; Moriyama, K.; Togo, H. *Org. Lett.* **2013**, *15*, 4194. (b) Kawagoe, Y.; Moriyama, K.; Togo, H. *Eur. J. Org. Chem.* **2014**, 4115.

(9) Reviews: (a) Togo, H.; Iida, S. *Synlett* **2006**, *2006*, 2159. (b) Togo, H. *Yuki Gosei Kagaku Kyokaishi* **2008**, *66*, 652. Recent papers: (c) Ishii, G.; Harigae, R.; Moriyama, K.; Togo, H. *Tetrahedron* **2013**, *69*, 1462. (d) Miyagi, K.; Moriyama, K.; Togo, H. *Eur. J. Org. Chem.* **2013**, 5886. (e) Dohi, S.; Moriyama, K.; Togo, H. *Eur. J. Org. Chem.* **2013**, 7815. (f) Harigae, R.; Moriyama, K.; Togo, H. *J. Org. Chem.* **2014**, *79*, 2049. (g) Nakai, Y.; Moriyama, K.; Togo, H. *Eur. J. Org. Chem.* **2014**, 6077. (h) Tamura, T.; Moriyama, K.; Togo, H. *Eur. J. Org. Chem.* **2015**, 2023.

(10) Vadagaonkar, K. S.; Kalmode, H. P.; Prakash, S.; Chaskar, A. C. *Synlett* **2015**, *26*, 1677.

DOI: 10.1021/acs.orglett.6b00048
Org. Lett. 2016, 18, 784−787