doi:10.1246/cl.2012.1672
Published on the web December 8, 2012

Transition-metal-free Benzylic C–H Bond Intermolecular Amination Utilizing Chloramine-T and I_2

Youhei Takeda,[1,2] Junpei Hayakawa,[1] Kazuki Yano,[1] and Satoshi Minakata*[1]
[1]*Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871*
[2]*Frontier Research Base for Global Young Researchers, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871*

(Received September 13, 2012; CL-120942; E-mail: minakata@chem.eng.osaka-u.ac.jp)

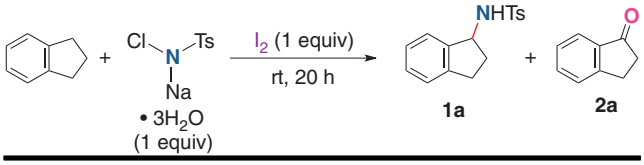
An intermolecular benzylic C–H bond amination utilizing the combination of chloramine-T and I_2 without the aid of transition-metal catalysts has been developed. The reaction was found applicable to a variety of benzene-substituted alkanes, as well as to an adamantane derivative to give *N*-alkylated *p*-tosylamides in good yields.

Direct functionalization of C–H bonds has been a hot topic in the field of modern synthetic organic chemistry.[1] Specifically, direct amination of C–H bonds allows for providing amine compounds, which are ubiquitous in biologically active agents such as natural products and pharmaceuticals. Therefore, the development of direct C–H amination reactions (the term "amination" used here includes amidation and imidation as a broad definition) is of significant importance. In this context, transition-metal-catalyzed insertion reactions of nitrenoid species into C–H bonds have been intensively developed[2] since the advent of seminal works by Breslow and Gellman in the early of 1980s.[3] On the other hand, transition-metal-free counterparts have been less explored to date, although such reactions would be beneficial with respect to economic and environmental points of view,[4–10] which have employed stoichiometric organic oxidants such as $PhI(OAc)_2$,[5] $PhI(OAc)_2$ and I_2,[6] DIH,[7] $TEMPO^+BF_4^-$,[8] or bromanes.[9] Recently, catalytic variants have also been emerging as alternative approaches to direct C–H amination.[10] Thus, the development of direct C–H bond amination reactions under transition-metal-free conditions is an attractive task of synthetic research.

Herein we present a transition-metal-free intermolecular benzylic C–H amination reaction that utilizes the combination of easy-handling and inexpensive oxidants, chloramine-T and I_2. The reaction can be operated under extremely mild reaction conditions of room temperature to give *N*-alkylated *p*-tosylamides in good to high yields.

In our continuous efforts to explore unique reactions utilizing haloamine salts,[11] we have recently developed an iodoamidation reaction of alkenes with stoichiometric amounts of chloramine-T and I_2 in aqueous media.[12] The concomitant use of chloramine-T and iodine generates *N*-iodo-*N*-chlorosulfonamide TsNCl(I), which serves as a good iodonium donor given that C=C double bonds are present in reactants. Concurrently, we have revealed that TsNCl(I) also serves as a radical source when a strong electron-acceptor such as fullerene derivatives exists.[13] In conjunction with the fact that hydrocarbons having benzylic C–H bonds are amenable to single-electron-oxidation to generate benzyl radicals, we envisaged that TsNCl(I) would serve as a single-electron-oxidant as well as an N_1 source, realizing less-costly C–H amination reaction.

Table 1. C–H amination of indane using chloramine-T and I_2[a]



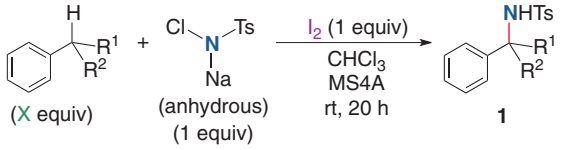
Entry	Solvent	Combined yield/%[b]	Ratio (**1a**:**2a**)[b]
1	Benzene	57	81:19
2	$Cl_2CHCHCl_2$	53	85:15
3	CH_2Cl_2	49	84:16
4	$CHCl_3$	81	91:9
5	CH_3CN	37	41:59
6	AcOEt	41	33:64
7	Acetone	38	29:71

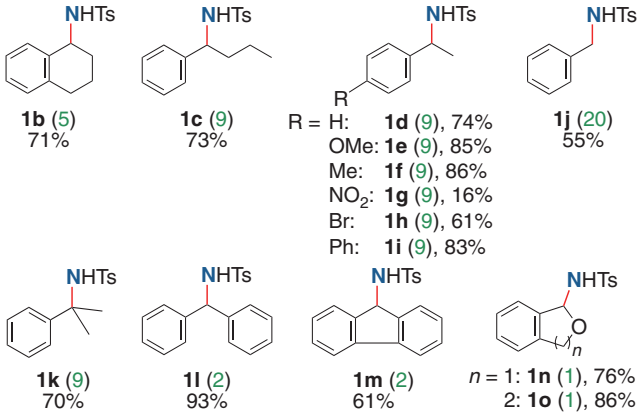
[a]Reaction conditions: indane (0.5 mmol), chloramine-T trihydrate (0.5 mmol), and iodine (0.5 mmol) were stirred in the solvent indicated under N_2 atmosphere at room temperature for 20 h. The reaction mixture was quenched with $Na_2S_2O_3$(aq) (1 M). [b]The values determined by ^1H NMR integration of the crude products.

To validate this hypothesis, we treated indane with an equimolar mixture of chloramine-T and I_2 at room temperature in several kinds of organic solvents (Table 1).[14] Gratifyingly, the benzylic C–H amination in benzene successfully proceeded to give aminated indane **1a** as a major product, together with indanone (**2a**) as a minor in 57% combined yield with the ratio of 81:19 (Entry 1). Among less-polar solvents tested (Entries 2–4), chloroform was the best in terms of chemical yield and the ratio of **1a** and **2a** (Entry 4). In contrast, when more-polar solvents such as acetonitrile, ethyl acetate, and acetone were used, the propensity of the product ratios was inverted, affording **2a** as a major product (Entries 5–7). The addition of I_2 was indispensable for the progression of the amination reaction, since no products were obtained without iodine. In respect to the amounts of iodine, an equimolar amount was required to obtain the products in satisfying yields, while the use of catalytic amounts of I_2 (20 mol %) gave **1a** and **2a** in only 34% and 4% yields, respectively.

It would be reasonable to consider that the oxygen atom of **2a** originates from the water of chloramine-T trihydrate. In fact, the exclusion of moisture from the reaction system by using anhydrous chloramine-T, which was easily prepared by drying

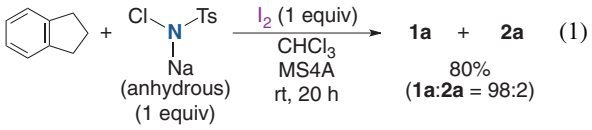
Table 2. Substrate scope of the benzylic C–H amination[a]





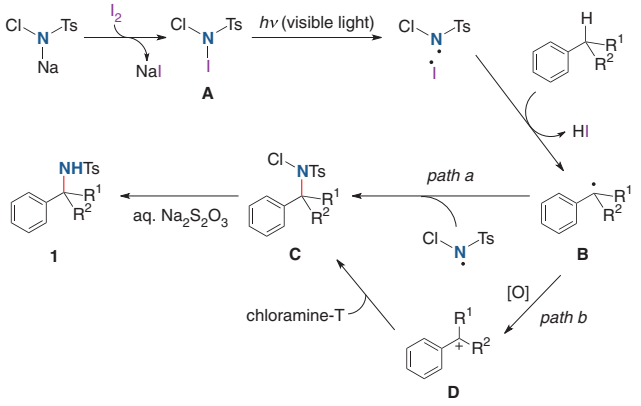
[a]Reaction conditions: hydrocarbon (0.5 mmol), anhydrous chloramine-T (0.5 mmol), iodine (0.5 mmol), and dried MS4A (100 mg) were stirred in $CHCl_3$ (1 mL) under N_2 atmosphere at room temperature for 20 h. The reaction mixture was quenched with $Na_2S_2O_3$(aq) (1 M). The values in parentheses are the equivalents of hydrocarbons employed.

the hydrate under vacuum,[15] with the concomitant use of molecular sieves as a drying agent resulted in exclusive formation of **1a** in comparable yield (eq 1).



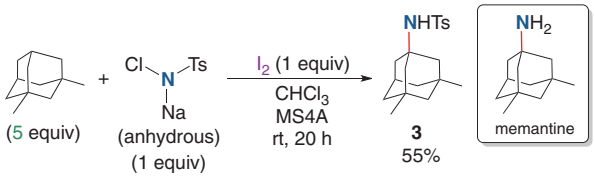
(1)

Having identified the reaction conditions that exclusively provide amino product **1a**, substrate scope of the amination reaction was investigated (Table 2). The reaction with tetralin gave the corresponding amino product **1b** in good yield (71%), albeit with the slight excessive use of tetralin. Acyclic *n*-alkyl-substituted benzenes and ethylbenzene derivatives having various functionalities at the *para*-position of the benzene ring were also applicable to the reaction system, affording **1c**–**1i** in good yields in a selective manner with the exception of quite low yield of *p*-NO_2-substituted amide **1g**. Notably, the simplest substrate, that is, toluene underwent the C–H amination to give **1j** in moderate yield, although a large excess of toluene was required to achieve the acceptable level of chemical yield. Furthermore, the reactions with sterically hindered substrates such as cumene, diphenylmethane, and fluorene even proceeded smoothly to give the corresponding products **1k**, **1l**, and **1m** in moderate to high yields, presumably due to their high abilities of stabilizing the resulting benzylic radicals. Intriguingly, the reactions with benzo-fused cyclic ethers such as 1,3-dihydroisobenzofuran and isochroman, efficiently giving rise to cyclic aminals **1n** and **1o**, respectively. In all cases, oxidized by-products (aromatic ketones) were detected as a minor product in at most 4% yield.



Scheme 1. Plausible mechanisms for the benzylic C–H amination.

Encouraged by the successful results of benzylic C–H bond amination, we applied the reaction conditions to an adamantane derivative to demonstrate the utility of the system (eq 2). The reaction was found to chemoselectively proceed at the tertiary C–H bond over the reactions at 1° and 2° C–H bonds to give an N-protected form of memantine **3**, which is a representative therapeutic agent for moderate to severe Alzheimer disease.[16]



(2)

For understanding of the mechanistic aspects of the reaction, a few experiments were conducted. The reactions of **1a** with chloramine-T and I_2 performed while protected from ambient light, or in the presence of a catalytic amount of a radical inhibitor (10 mol % of TEMPO) were significantly retarded, giving **1a** in 18% and 12%, respectively.[15] These results would suggest the involvement of radical species which are generated by light illumination. Based on the experimental results, plausible mechanisms are shown in Scheme 1. Upon the treatment of chloramine-T with I_2, *N*-iodo-*N*-chlorotosylamide (**A**) generates accompanied by the precipitation of NaI.[11] Visible-light should prompt the homolytic fission of the weak N–I bond (bond-dissociation energy (BDE): ca. 130 kJ mol^{-1}),[17] affording the pair of an amidyl and an iodine radicals. The abstraction of a hydrogen from benzylic C–H bonds by I•, and the subsequent attack of the amidyl radical by the resulting benzyl radical **B** at the *N*-center should provide *N*-chloro-*N*-alkyl compound as a primarily forming product **C** (path a). Alternatively, further oxidation of **B** could generate benzyl cation **D**, which would be attacked by chloramine-T to afford **C** (path b). The generation of the benzyl cation **D** could be rationalized by the formation of aromatic ketone by-products, which might be produced through hydration of the cation. The quench of the reaction mixture with aqueous $Na_2S_2O_3$ reduces the N–Cl bond of **C** to the N–H bond and then affords **1**.

In conclusion, we have developed a transition-metal-free, mild, and less-costly benzylic C–H amination protocol utilizing chloramine-T and I_2. The reaction conditions were found applicable to various benzylic compounds to give a series of the corresponding amino products in good to high yields.

This research was partly supported by a Grant-in-Aid for Scientific Research on Innovative Areas, "Molecular Activation Directed toward Straightforward Synthesis," from the MEXT (Japan). One of the authors (Y.T.) acknowledges supports from the Frontier Research Base for Global Young Researchers, Osaka University, from the Program of MEXT. Also, J.P. acknowledges financial supports from the "JSPS Research Fellowship for Young Scientists."

References and Notes

1 For a comprehensive review on direct C–H bond functionalization, see: J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.
2 For reviews on transition-metal-catalyzed nitrene insertion into C–H bonds, see: a) F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926. b) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061. c) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417. d) H. M. L. Davies, *Angew. Chem., Int. Ed.* **2006**, *45*, 6422. e) H. M. L. Davies, M. S. Long, *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. f) P. Müller, C. Fruit, *Chem. Rev.* **2003**, *103*, 2905. g) P. Dauban, R. H. Dodd, *Synlett* **2003**, 1571.
3 a) E. W. Svastits, J. H. Dawson, R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1985**, *107*, 6427. b) R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1983**, *105*, 6728. c) R. Breslow, S. H. Gellman, *J. Chem. Soc., Chem. Commun.* **1982**, 1400.
4 For a review on transition-metal-free C–H amination reactions, see: R. Samanta, A. P. Antonchick, *Synlett* **2012**, 809.
5 a) J. Joseph, J. Y. Kim, S. Chang, *Chem.—Eur. J.* **2011**, *17*, 8294. b) A. A. Kantak, S. Potavathri, R. A. Barham, K. M. Romano, B. DeBoef, *J. Am. Chem. Soc.* **2011**, *133*, 19960. c) H. J. Kim, J. Kim, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 16382.
6 a) M. Koag, S. Lee, *Org. Lett.* **2011**, *13*, 4766. b) R. Fan, W. Li, D. Pu, L. Zhang, *Org. Lett.* **2009**, *11*, 1425. c) R. Fan, D. Pu, F. Wen, J. Wu, *J. Org. Chem.* **2007**, *72*, 8994. The similar reactions under the irradiation of UV-light: d) H. Togo, Y. Harada, M. Yokoyama, *J. Org. Chem.* **2000**, *65*, 926. e) H. Togo, Y. Hoshina, T. Muraki, H. Nakayama, M. Yokoyama, *J. Org. Chem.* **1998**, *63*, 5193.
7 H. Baba, H. Togo, *Tetrahedron Lett.* **2010**, *51*, 2063.
8 S. Wertz, S. Kodama, A. Studer, *Angew. Chem., Int. Ed.* **2011**, *50*, 11511.
9 a) M. Ochiai, S. Yamane, M. M. Hoque, M. Saito, K. Miyamoto, *Chem. Commun.* **2012**, *48*, 5280. b) M. Ochiai, K. Miyamoto, T. Kaneaki, S. Hayashi, W. Nakanishi, *Science* **2011**, *332*, 448.
10 a) S. Wertz, S. Kodama, A. Studer, *Angew. Chem., Int. Ed.* **2011**, *50*, 11511. b) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem., Int. Ed.* **2011**, *50*, 8605. c) M. Lamani, K. R. Prabhu, *J. Org. Chem.* **2011**, *76*, 7938. d) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner, B. J. Nachtsheim, *Org. Lett.* **2011**, *13*, 3754. e) A. A. Lamar, K. M. Nicholas, *J. Org. Chem.* **2010**, *75*, 7644.
11 S. Minakata, *Acc. Chem. Res.* **2009**, *42*, 1172.
12 S. Minakata, J. Hayakawa, *Chem. Commun.* **2011**, *47*, 1905.
13 T. Nagamachi, Y. Takeda, K. Nakayama, S. Minakata, *Chem.—Eur. J.* **2012**, *18*, 12035.
14 Chloramine-T is commercially available as its trihydrate.
15 For the experimental details, see the SI.[18]
16 C. Mount, C. Downton, *Nat. Med.* **2006**, *12*, 780.
17 S. A. Glover, A. Goosen, R. D. Venter, *S. Afr. J. Chem.* **1978**, *31*, 33.
18 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

