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COMMUNICATION

# An Intramolecular C(sp$^3$)–H Imination using PhI-*m*CPBA

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**Herein, highly exothermic primary amine - polyvalent iodine reaction has been used successfully for selective functionalization of acidic C(sp$^3$)-H group for a dehydrogenative C-H imination reaction by 4H elimination. Overall, C(sp$^3$)–H imination at 1,5 distances was readily done *via* organocatalysis using PhI (10 mol %)-*m*CPBA under ambient condition.**

Enzyme mediated selective oxidation of unactivated aliphatic C-H bonds are well-known since time immemorial. However, it remains challenging for the synthetic chemists due to unviability of suitable reagents.[1] The C(sp$^3$)-H bonds are considered to be less reactive than C(sp$^2$)-H because of their higher thermodynamic stability. Development of synthetic methods for the conversion of undirected C(sp$^3$)-H bonds to suitable functionalities are of great importance in fundamental research.[2] Therefore, chemists have investigated on selective catalysts for functionalization of C-H bonds to C-N bonds *via* dehydrogenative pathway. The approaches on dehydrogenative C(sp$^3$)-H amination of non-prefunctionalized systems are mainly known either using metal catalyzed or by radical initiated pathway.[3] Compared to C(sp$^3$)-H aminations, imination reactions are more challenging since the formation of imines from -$CH_2$ and -$NH_2$ combination with 4H elimination is thermodynamically unfavorable.[4] In 2016, Alabugin and co-workers reported a Fe(II)-catalyzed oxidative C-H imination reaction[5] through single electron transfer (SET). Later, the same group established a transition metal-free approach for similar transformation using $^t$BuOK under aerobic condition.[6] Nevertheless, these methods hold certain limitations like use of transition metals as catalysts, strong bases in excess amount, etc.

Due to their abundance in pharmaceutically active compounds and natural products, it's hard to exaggerate the significance of nitrogen-based heterocycles. As a result, effort towards synthesis of C-N bonds have become a fundamental subject of study in organic chemistry.

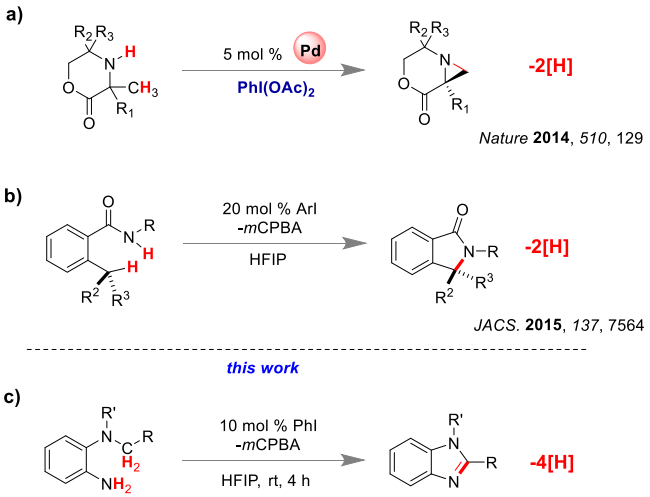


**Figure 1.** Iodine(III) in intramolecular aliphatic C-H amination reactions. a) Gaunt's Pd-catalyzed C-H amination method.[7] b) Shi's intramolecular C-H amination reaction.[8] c) Our 1,5 aliphatic-$CH_2$ - aryl-$NH_2$ imination approach using organocatalysis.

Dehydrogenative coupling between C-H and N-H bonds represent the state of art practice in C-N bond synthesis due to non-requirement of prefunctionalization of substrates. Gaunt and co-workers established the synthesis of three membered strained heterocycle aziridine *via* aliphatic C-H amination using Pd(II)-catalyst (Figure 1a).[7] Similarly, for synthesis of *γ*-lactams by 2H elimination, Shi and coworkers have shown intramolecular C-H amination reaction *via* iodoarene-catalysis (Figure 1b).[8] Moreover, the present work is based on 4H elimination for direct functionalization of two aliphatic-C(sp$^3$)H and two aryl-N(sp$^3$)H intramolecularly at 1,5 positions. This single step imination protocol works in absence of any metal or strong base *via* organocatalysis at room temperature (Figure 1c). Thus an additive free approach based on intramolecular C(sp$^3$)-H imination reaction *via* organocatalysis is developed using PhI (10 mol %)-*m*CPBA.[9] Use of the simplest organoiodine compound PhI as catalyst is the crucial advantage of this protocol.

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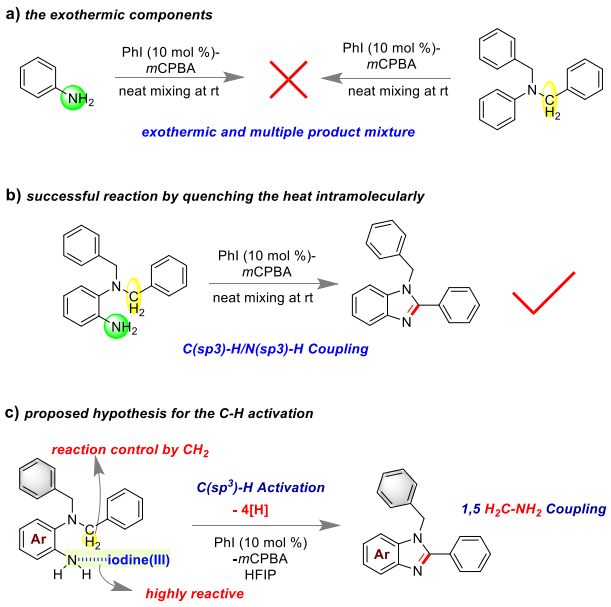


**Scheme 1.** a) Observed exothermic reactions. b) The oxidative C-N bond formation by two aliphatic-C($sp^3$)H and two aryl-N($sp^3$)H imination. c) The hypothesis of acidic C-H functionalization.

Iodine and ammonia mixture is known as *contact explosive* due to formation of $NI_3$.[10] The hypervalent iodines as oxidizer[11] are known to react violently with amines.[12] Therefore, performing any synthetic transformations using basic amines and polyvalent iodine reagents by simply mixing them at room temperature is difficult.[13] Generally, the hyper reactivity of such primary amines is controlled by converting them into secondary amine with introduction of carbonyl or sulfonyl groups at *N*-center. In this work, the synergic reactivity of unprotected primary amine and adjacent tertiary amine is controlled using *in situ* generated Iodine(III) from iodobenzene (PhI)-*m*CPBA (*meta*-chloroperbenzoic acid) combination.[14] When either aniline or *N,N*-dibenzylaniline was reacted with iodine(III) reagents, an uncontrolled reaction was observed and no selective product formation could be detected (Scheme 1a). The *N*$^1$,*N*$^1$-dibenzylbenzene-1,2-diamine (Scheme 1b) which is an integrated system of aniline and *N,N*-dibenzylaniline led to successful formation of 1-benzyl-2-phenyl-benzo[d]imidazole under iodine(III) reaction condition. Interestingly, the reaction went smoothly without any over oxidation. In order to maximize the contact of the reacting amines with iodine(III) reagents, the control experiments shown in Scheme 1 were done by simply mixing of the components at room temperature.[13b] Similar observation was made when the reaction was carried out in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[15] solvent. We anticipated that the violent reaction by the basic aniline could be controlled intramolecularly due to the presence of benzylic methylene ($CH_2$) group bearing acidic hydrogens. These benzylic $CH_2$-groups not only acted as amine-iodine(III) reaction controller but also helped for the oxidative C-N bond formation by 1,5 aliphatic-$CH_2$ - aryl-$NH_2$ imination.

**Table 1.** Condition Optimization.

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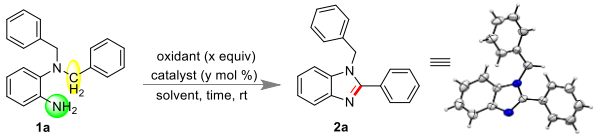


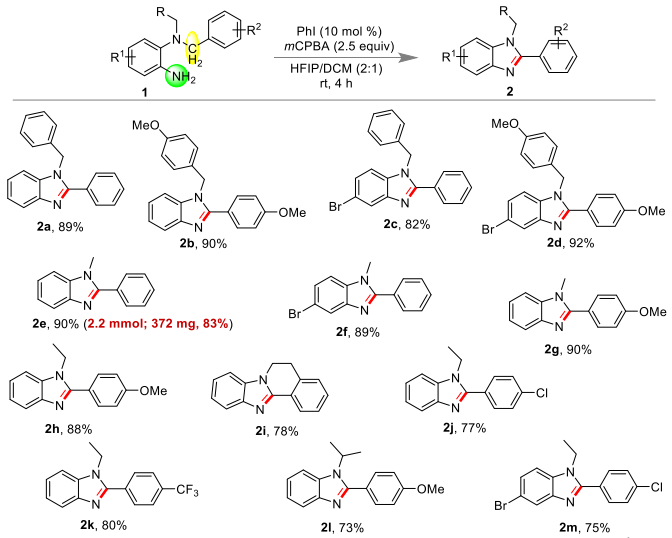

| entry | oxidant (equiv) | catalyst (mol %) | solvent | time (h) | yield %[a] |
|---|---|---|---|---|---|
| 1 | PIDA (2) | --- | HFIP | 1.5 | 82 |
| 2 | PIDA (2) | --- | TFE | 2 | 72 |
| 3 | PIDA (2) | --- | DCM | 16 | 18 |
| 4 | PIDA (2) | --- | ACN | 16 | NR |
| 5 | PIDA (2) | --- | DCE | 16 | NR |
| 6 | PIDA (2) | --- | 1,4-Dioxane | 16 | 50 |
| 7 | PIFA (2) | --- | HFIP | 1.5 | 55 |
| 8 | PhI(OPiv)$_2$ (2) | --- | HFIP | 1 | 61 |
| 9 | *m*CPBA (2.25) | PhI (20) | HFIP | 1.5 | 75 |
| 10 | *m*CPBA (2.5) | PhI (20) | HFIP | 1.5 | 84 |
| 11 | *m*CPBA (2.5) | PhI (20) | TFE | 2 | 68 |
| 12 | *m*CPBA (2.5) | PhI (20) | HFIP:DCM[b] | 3 | 89 |
| 13 | *m*CPBA (2.5) | PhI (10) | HFIP:DCM[b] | 4 | 89 |
| 14 | PIDA (2) | | HFIP:DCM[c] | 1.5 | 80 |
| 15 | *m*CPBA (2.5) | PhI (5) | HFIP:DCM[c] | 16 | 73[d] |
| 16 | *m*CPBA (2.5) | Ar$^1$I (10) | HFIP:DCM[c] | 4 | 53 |
| 17 | *m*CPBA (2.5) | Ar$^2$I (10) | HFIP:DCM[c] | 4 | 65 |
| 18 | *m*CPBA (2.5) | PhI (10) | HFIP:DCM[c] | 4 | 78[e] |

[a]Reaction condition: 0.208 mmol of **1a** (1.0 equiv) in 1.5 mL solvent at room temperature. [b]isolated yields after column chromatography. [c]HFIP:DCM ratio is 2:1 v/v. [d]After 16 h starting material remaining. Ar$^1$ = 4-Me-$C_6H_4$, Ar$^2$= 4-$NO_2$-$C_6H_4$; [e]Under argon atmosphere.

During optimization (Table 1), *N*$^1$,*N*$^1$-dibenzylbenzene-1,2-diamine (**1a**) was subjected to react under various conditions. Delightfully, when **1a** was treated with 2.0 equiv of PhI(OAc)$_2$ (PIDA) in HFIP,[15] the desired intramolecular C($sp^3$)-H imination reaction led to 82% yield of **2a** (1-benzyl-2-phenyl-benzo[d]imidazole) (entry 1) within 1.5 h at room temperature under open atmospheric condition. The structure of **2a** was unambiguously confirmed by single crystal X-ray analysis. However, the reaction in TFE (2,2,2-trifluoroethanol) led to 72% yield of product within 2 h (entry 2). Other solvents like dichloromethane (DCM), acetonitrile (ACN) and 1,2-dichloroethane (DCE), 1,4-dioxane gave inferior results (entry 3-6). Similarly, the reactions using PIFA (bis(trifluoroacetoxy)iodobenzene) or PhI(OPiv)$_2$ (bis(tert-butylcarbonyloxy)iodobenzene) were also not encouraging (entry 7-8). Interestingly, organocatalytic version of the reaction was more successful than the use of stoichiometric iodine(III) reagents. Among the conditions examined, the optimum condition was found to be with 10 mol % of PhI, 2.5 equiv of *m*CPBA and 4 h reaction time (entry 13). Lowering the catalyst loading to 5 mol % (entry 15) and varying the organoiodine catalyst to 4-iodotoluene or 4-nitroiodobenzene (entry 16, 17) led to inferior results. When the reaction was performed under argon atmosphere, no improvement of the result was observed (entry 18).

Under the optimized condition, the generality of the reaction was explored with a wide range of substrate scope (Table 2). Benzyl amines having electron donating methoxy (-OMe) group (**2b**, **2d**, **2g**, **2h**, **2l**) resulted in 1,2-disubstituted benzimidazoles up to 88-92% yield. Electron withdrawing halide functionalities in the aryl rings attached to active hydrogens (**2j**, **2k**, **2m**), also could not affect the yields of the reactions (75-80%). The exclusive chemoselectivity of the reaction for the substrates **2e-2h** and **2j-2m** was controlled by the electronic environment of the $CH_2$ group. The benzylic hydrogens are more acidic than aliphatic systems. Therefore, exclusive regioselective product dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (**2i**) was isolated in 78% yield from the corresponding 2-(3,4-dihydroisoquinolin-2-yl)aniline (**1i**).

**Table 2.** Scope of C-H imination reaction.

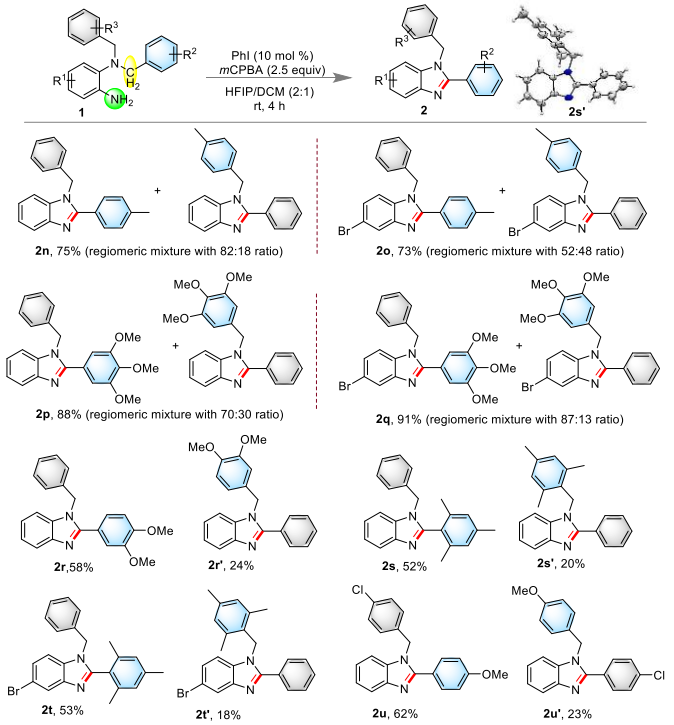



Reaction conditions: **1** (1.0 equiv), PhI (10 mol %), *m*CPBA (2.5 equiv), HFIP/DCM (2:1v/v, 1.5 mL), rt, 4 h.

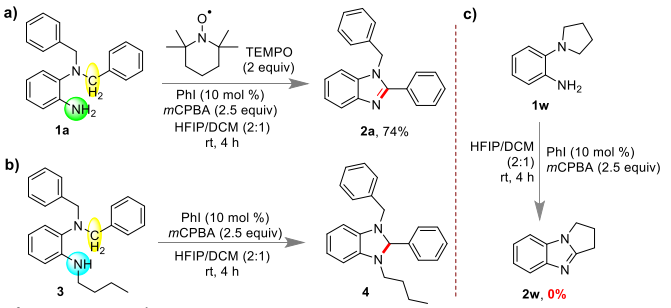
For symmetrical dibenzyl amines, single isomer of benzimidazoles (**2a-2d**) were obtained in good yields (Table 2). However, electronic control could be established while handling of unsymmetrical dibenzyl amines (Table 3). Mixture of isomers were obtained out of which major product was the imination involving benzylic carbon center attached with more electron rich arenes. The methoxy group containing substrates (**2p-2r**) resulted in formation of products with good to excellent overall yield (up to 91%). Electron withdrawing chloro substituent at *para* position (**2u**) also participated in reaction successfully to give 85% overall yield. Sterically hindered *ortho* methyl substituted derivatives (**2s, 2t**) underwent smooth reaction to give nearly 75% product formation. The X-ray analysis was helpful to elucidate the structure of minor isomer **2s'**. The major isomer **2s** was determined by $^{1}H$ and $^{13}C$ NMR characteristic peaks. Also, consistency of NMR characteristic peaks was helpful in determination of isomeric distributions for other compounds.

Control experiments shown in Scheme 2 helped to establish the mechanism of the reaction. When **1a** was treated with 2.0 equiv of radical scavenger TEMPO (2,2,6,6-Tetramethylpiperidin-1-yl-oxyl) under standard condition, **2a** was isolated in 74% yield (Scheme 2a) which ruled out the possibility of any radical intermediate formation during the reaction. The substrate **3** was treated under standard condition and the formation of dihydrobenzimidazole type intermediate **4** (Scheme 2b) was detected by ESI-MS (supporting information, Fig. S103). Therefore, detection of substrate **4** could suggest the involvement of iminium ion as the key intermediate during the reaction. When substrate **1w** was treated under standard condition no desired product formation was observed (Scheme 2c). Thus, presence of at least one aryl ring is necessary to stabilize the adjacent carbocation in the reaction pathway.

**Table 3.** Electronic effects of *N*-alkyl substituents.



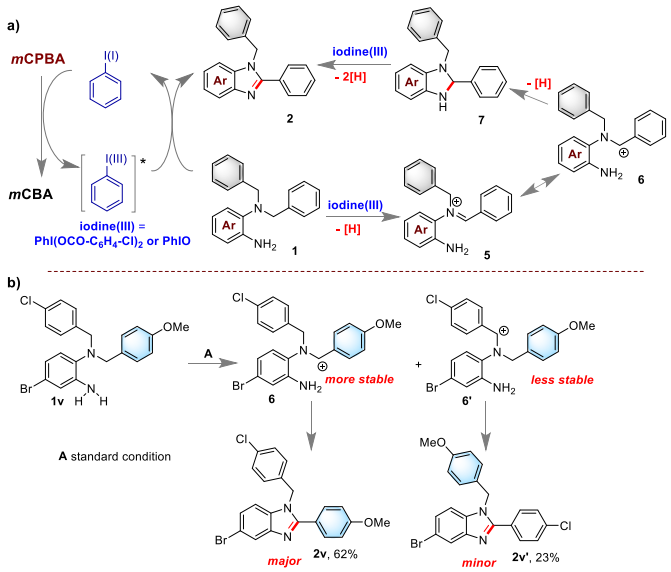

Reaction conditions: **1** (1.0 equiv), PhI (10 mol %), *m*CPBA (2.5 equiv), HFIP/DCM (2:1 v/v, 1.5 mL), rt, 4 h.




**Scheme 2.** Control experiments.

Based on the observations from control experiments, a plausible mechanism for the imination reaction is shown in Scheme 3a. The role of *m*CPBA as oxidant is to transform iodobenzene into iodine(III) species and itself gets reduced

into *meta*-chlorobenzoic acid (*m*CBA). Being substituted with two alkyl groups, the tertiary amine group is expected to have greater nucleophilicity than free amine towards iodine(III) reagent. Thus nucleophilic attack from nitrogen center of tertiary amine to iodine center of the *in situ* generated iodine(III) reagent (either PhI(OCO-$C_6H_4$-Cl)$_2$ or PhIO)[9a] produce iminium ion intermediate **5** with the reductive elimination of iodobenzene.[16] The iminium ion could exist in an alternate resonance benzylic carbocation form **6** which is stabilized by adjacent aryl group. The monovalent iodobenzene is further oxidized by additional amount of *m*CPBA to regenerate iodine(III). Intramolecular nucleophilic addition of primary amine to benzylic carbocation resulted in the formation of cyclic intermediate **7**. Further oxidation of intermediate **7** with the help of iodine(III) oxidant facilitated the aromatization to give 1,2-disubstituted benzimidazole **2** by another 2H elimination. The use of fluorinated solvents to perform hypervalent iodine mediated transformations are well established in literature.[15] So, being non-nucleophilic and highly polar in nature, the solvent HFIP is expected to stabilize the cationic intermediates.[17]




**Scheme 3.** a) Plausible mechanism of the reaction and b) Understanding the regioselectivity by stereo-electronic control.

The origin of regioselectivity could be explained in terms of relative stability of benzylic carbocations aided by adjacent aryl group. The more electron rich the arene, higher will be the stability of carbocation. Thus after cyclization, corresponding benzimidazole **2v** was generated as the major isomer (Scheme 3b).

In summary, an organocatalytic intramolecular benzylic C-H imination *via* 4H elimination is reported. The reactivity of unprotected primary amine with iodine(III) reagent has been controlled with the help of acidic hydrogens available within the vicinity. Overall, two C(sp$^3$)-H and two N(sp$^3$)-H bonds were functionalized in a single step for a C-N coupling reaction. The use of simplest iodoarene PhI with 10 mol % loading and *m*CPBA as inexpensive oxidant, room temperature and open atmospheric conditions are the key advantages for this method. We anticipate that this C-H imination method might have a worthy impact in synthesizing complex molecular architectures. Also, expected that the mechanistic understanding will enable certain methods for reactivity control of other non-directed C(sp$^3$)-H bonds for many heterocycle synthesis.

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## Conflicts of interest

"There are no conflicts to declare"

## Notes and references

1. J. C. Lewis, P. S. Coelho and F. H. Arnold, *Chem. Soc. Rev.*, 2011, **40**, 2003.
2. P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564.
3. (a) J. R. Clark, K. Feng, A. Sookezian and M. C. White, *Nat. Chem.*, 2018, **10**, 583; (b) C. Martínez and K. Muñiz, *Angew. Chem. Int. Ed.*, 2015, **54**, 8287; (c) G. Pandey and R. Laha, *Angew. Chem. Int. Ed.*, 2015, **54**, 14875; (d) G. He, Y. Zhao, S. Zhang, C. Lu and G. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 3; (e) Q. Nguyen, K. Sun and T. G. Driver, *J. Am. Chem. Soc.*, 2012, **134**, 7262.
4. (a) X. Hu, G. Zhang, F. Bu, L. Nie and A. Lei, *ACS Catal.*, 2018, **8**, 9370; (b) T. Duhamel, C. J. Stein, C. Martínez, M. Reiher and K. Muñiz, *ACS Catal.*, 2018, **8**, 3918.
5. C. J. Evoniuk, S. P. Hill, K. Hanson and I. V. Alabugin, *Chem. Commun.*, 2016, **52**, 7138.
6. C. J. Evoniuk, G. d. P. Gomes, S. P. Hill, S. Fujita, K. Hanson and I. V. Alabugin, *J. Am. Chem. Soc.*, 2017, **139**, 16210.
7. A. McNally, B. Haffemayer, B. S. L. Collins and M. J. Gaunt, *Nature*, 2014, **510**, 129.
8. C. Zhu, Y. Liang, X. Hong, H. Sun, W.-Y. Sun, K. N. Houk and Z. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 7564.
9. (a) A. Yoshimura and V. V. Zhdankin, *Chem. Rev.*, 2016, **116**, 3328; (b) K. Muñiz, *Top. Curr. Chem.*, 2016, **373**, 105; (c) R. Marcus, V. Piret and O. Berit, *Angew. Chem. Int. Ed.*, 2016, **55**, 8928.
10. I. Tornieporth-Oetting and T. Klapötke, *Angew. Chem. Int. Ed. Engl.*, 1990, **29**, 677.
11. K. C. Nicolaou, P. S. Baran, R. Kranich, Y.-L. Zhong, K. Sugita and N. Zou, *Angew. Chem. Int. Ed.*, 2001, **40**, 202.
12. O. Hassel, *Science*, 1970, **170**, 497.
13. (a) K. Monir, M. Ghosh, S. Mishra, A. Majee and A. Hajra, *Eur. J. Org. Chem.*, 2014, 1096; (b) T. K. Achar and P. Mal, *Adv. Synth. Catal.*, 2015, **357**, 3977.
14. S. Murarka and A. P. Antonchick, in *Hypervalent Iodine Chemistry*, ed. T. Wirth, Springer International: Cham, Switzerland, 2016, pp. 75.
15. I. Colomer, A. E. R. Chamberlain, M. B. Haughey and T. J. Donohoe, *Nat. Rev. Chem.*, 2017, **1**, 0088.
16. V. Jamsheena, C. K. Mahesha, M. N. Joy and R. S. Lankalapalli, *Org. Lett.*, 2017, **19**, 6614.
17. S. Izquierdo, S. Essafi, I. del Rosal, P. Vidossich, R. Pleixats, A. Vallribera, G. Ujaque, A. Lledós and A. Shafir, *J. Am. Chem. Soc.*, 2016, **138**, 12747.

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# An Intramolecular C(sp³)−H Imination using PhI-*m*CPBA

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Development of sustainable methods for the activation of less reactive undirected C(sp³)-H bonds is challenging but desired in organic synthesis. The present manuscript demonstrates selective activation of acidic C(sp³)-H group for a dehydrogenative C-H imination by 4H elimination using PhI (10 mol %)-*m*CPBA as organocatalysis.