EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900732

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900732

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COMMUNICATION

Intramolecular C(sp^3)−H Imination using TBAI-TBHP

Anima Bose,[a] Sudip Sau,[a] and Prasenjit Mal*[a]

Abstract: Development of sustainable and economically viable methods is challenging but desired in organic synthesis. Herein, intramolecular C(sp^3)−H imination between a free amine group and *N*-methylene group is established using TBAI (20 mol %)-TBHP (3.0 equiv) in DMSO which is found to be an inexpensive replacement of PhI-*m*CPBA in HFIP.

Introduction

Selective oxidation of undirected aliphatic C-H bonds are mostly known *via* enzyme mediated methods,[1] but, it remains challenging to the chemists because of unviability of appropriate reagents.[2] The C(sp^3)-H bonds are thermodynamically more stable and generally become less reactive than the C(sp^2)-H bonds.[3] The known methods available for the activation of non-prefunctionalized C-H bonds are mainly based on either as metal initiated or by radical mediated pathway.[4] Notably, iodine(III) mediated most of the C-H amination developments are based on 2H elimination and starting from secondary amines.[5] The C(sp^3)-H imination reactions are more challenging than the amination reactions, because combining the $-CH_2$ and $-NH_2$ for 4H elimination can be thermodynamically unfavorable process.[6] Alabugin and co-workers reported oxidative C-H imination reaction by iron(II)-catalyzed[7] and followed by transition metal-free approach using ^{t}BuOK.[8]

Nitrogen based heterocycles are widespread in myriad synthetic pharmaceuticals and natural products. Intramolecular C-N bond formation reaction is one of the most targeted approaches for the synthesis of *N*-heterocycles.[9] The methods developed based on dehydrogenative C(sp^3)−H amination on undirected C-H systems are well-known either as metal initiated or *via* radical mediated pathway.[4, 10] For oxidative C-N bond synthesis by C-H bond functionalization, hypervalent iodine reagents have received significant attention because of their low toxicity, environmentally benign nature and easy availability.[11] In recent times, we have also developed methods to use iodine based regents in organic synthesis.[12] Interestingly, the methods based on *in situ* generation of reactive iodine reagent from lower valent iodine[13] compound with the help of inexpensive co-oxidant like *m*CPBA (*meta*-chloroperbenzoic acid),[14] H_2O_2 (hydrogen peroxide),[15] TBHP (*tert*-butylhydroperoxide), etc.[13a, 16] have become popular for construction of various new bonds and important molecules. Simple organic molecule like iodobenzene, iodotoluene and inorganic iodide reagents have find practical application for this *in situ* generated methods.[11a] The advantages with the inorganic reagents are high water solubility, low-cost and can act as phase transfer catalyst. Various groups have demonstrated the use of tetrabutylammonium iodide (TBAI) in combination with mild oxidant like TBHP, H_2O_2 and other peroxide based oxidants.[17] We have also anticipated that the TBAI-TBHP protocol can also be applicable for an intramolecular C(sp^3)-H imination *via* 4H elimination. The work is developed based on our recent report of similar transformation using PhI-*m*CPBA in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP).[18]

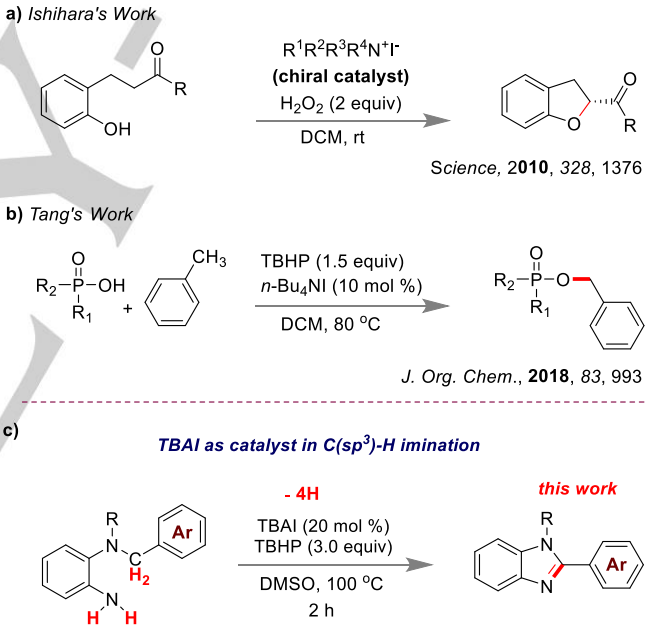

Figure 1. Selected approaches on tetraalkylammonium iodide catalyzed bond formation. a) Ishihara's chiral catalyst for cycloetherification method.[19] b) Tang's approach for phosphorylation.[20] c) Our TBAI catalyzed intramolecular C(sp^3)-H imination.

Results and Discussion

Ishihara's approach on enantioselective cycloetherification[19] of phenol derivative by using chiral tetraalkylammonium iodide in combination with TBHP or H_2O_2 as co-oxidant has opened a new page in this research area (Figure 1a).[19] These reagents have proved to be very efficient in cross dehydrogenative coupling for the construction of carbon – hetero bonds. Recently, Tang and his group developed a cross dehydrogenative coupling of C(sp3)-H bond of arenes with diarylphosphinic acid to construct carbon – phosphorus bond[20] by using catalytic amount of TBAI along with oxidant TBHP (Figure 1b).[20] Herein, we demonstrate an

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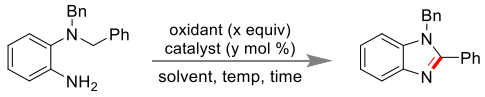
intramolecular C(sp^3)-H imination reaction using TBAI (20 mol %) – TBHP (3.0 equiv). This methodology has been used successfully for the synthesis of highly substituted benzimidazoles using N^1,N^1-dibenzylbenzene-1,2-diamine as precursors (Figure 1c).

Table 1. Condition Optimization.



entry	oxidant[a] (equiv)	catalyst (mol %)	solvent, temp (ºC)	time (h)	yield (%)
1	TBHP (2)	TBAI (10)	DMSO, 80	4	61
2	TBHP (3)	TBAI (10)	DMSO, 100	2	80
3	TBHP (3)	TBAI (20)	DMSO, 100	2	92
4	TBHP (3)	TBAI (20)	ACN, 80	10	58
5	TBHP (3)	TBAI (20)	1,4-Dioxane, 80	16	trace
6	TBHP (3)	TBAI (20)	TFE, 60	4	62
7	TBHP (3)	TBAI (20)	TFE, rt	10	42
8	TBHP (3)	TBAI (20)	DMF, 100	3	59
9	TBHP (3)	TBAI (20)	DCE, 80	10	38
10	TBHP (3)	TBAI (20)	EtOH, 80	16	trace
11	TBHP (3)	TBAI (20)	HFIP, 80	4	78
12	TBHP (3)	CuBr (20)	DMSO, 100	16	48
13	TBHP (3)	$Cu(OAc)_2$ (20)	DMSO, 100	16	51
14	TBHP (3)	TBAB (20)	DMSO, 100	4	30
15	TBHP (3)	NIS (50)	DMSO, 100	10	39
16	TBHP (3)	I_2 (50)	DMSO, 100	10	trace
17	TBHP in decane (3)	TBAI (20)	DMSO, 100	4	64
18	TBHP (3)	----	DMSO, 100	48	trace
19	CHP	TBAI (20)	DMSO, 100	6	45

[a]If not indicated, TBHP used as 70% aq solution

Towards condition optimization (Table 1) the model substrate N^1,N^1-dibenzylbenzene-1,2-diamine (**1a**) was treated with 2 equiv of oxidant TBHP (used as 70% aqueous solution, *Caution!!*) and 10 mol % of TBAI. In dimethylsulfoxide (DMSO) at 80 ºC the desired 1-benzyl-2-phenyl-benzo[d]imidazole (**2a**) was obtained with 61% yield (entry 1) within 4 h of reaction time. However, within 2 h of reaction time 80% of the product was obtained when 3 equiv TBHP was used at 100 ºC (entry 2). The best result *i.e.*, 92% yield was obtained using 20 mol % of TBAI, 3 equiv TBHP and at 100 ºC (entry 3). Changing the solvents (entries 4-11) to acetonitrile (ACN), 1,4-dioxane, trifluoroethanol (TFE), dimethylformamide (DMF), 1,2-dichloroethane (DCE), 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) did not furnish better results. Similarly, varying the catalysts (entries 12-16) and oxidants (entries 17-18) were also not giving any encouraging results.

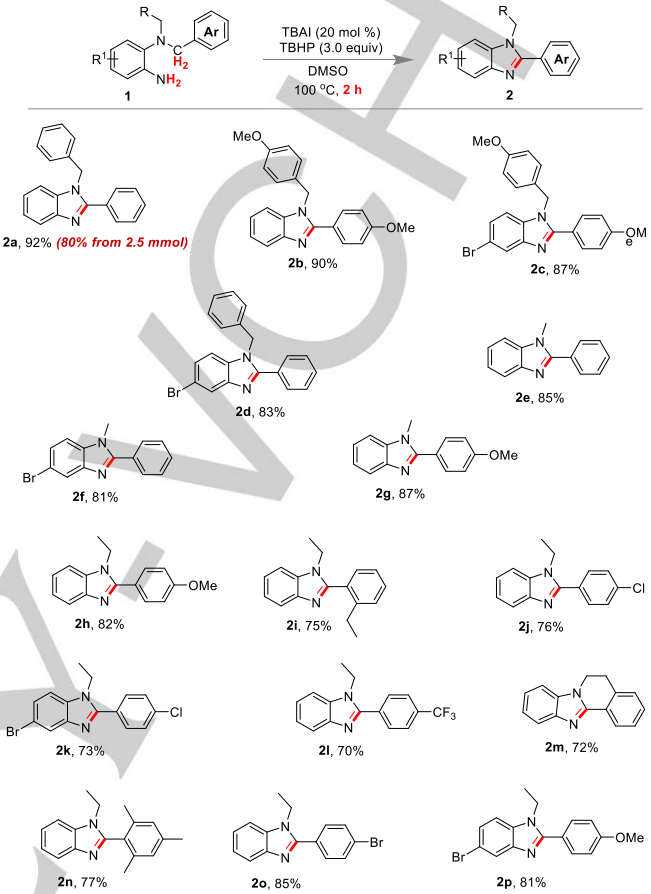


Figure 2. Substrate scope for C(sp^3)-H imination reaction.

Under optimized condition, substrate scope was explored for the imination reaction using various N^1,N^1-disubstituted benzene-1,2-diamines (Figure 2). Symmetrical dibenzyl substituted benzene-1,2- diamines resulted in 76 – 92% of the benzimidazoles. Electron donating methoxy (-OMe) group (**2b**: 90%, **2c**: 87%) worked well for this conversion. Bromo substitution at benzene-1,2-diamine part also yielded fairly the corresponding benzimidazoles (**2c**: 87%, **2d**: 83%). Single regio-isomeric products were observed (**2e-2m**) in case of N^1,N^1-benzylalkyl substituted benzene-1,2-diamines with 100% selectivity towards benzylic –CH_2 group. The *N*-methyl and *N*-ethyl substituted benzimidazoles were obtained up to 87%. Similarly, *p*-trifluoromethyl phenyl substituted benzimidazole **2l** was isolated in 70% yield. The 5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (**2m**) was isolated exclusively with 72% of yield. Fairly good yield of benzimidazoles were obtained when ortho position of phenyl rings hindered with methyl or ethyl groups (**2l**, **2n**). Electron withdrawing -Cl or -Br worked well for the conversion to give 73 – 85% yields of the corresponding benzimidazoles (**2j**, **2k**, **2o** and **2p**).

The symmetrical dibenzyl amines led to single isomeric benzimidazoles. Conversely, unsymmetrical dibenzyl amines exhibited certain regioselectivity *via* electronic control (Figure 3).

Interestingly, the major product among the mixture of isomers was the imination at the benzylic center substituted with relatively electron rich arenes. Substrate having both benzyl and tolyl group like *N*^{1}-benzyl-*N*^{1}-(4-methylbenzyl)benzene-1,2-diamine gave mixture of two regio-isomeric product with 80% yield as an inseparable mixture (**2q** and **2r**). Similarly, benzylic –CH_2 having electron donating –OMe group as well as electron withdrawing halogen group at para position both participated in C(sp3)-H functionalization to produce corresponding benzimidazoles with ~ 80% yield for **2s** (CCDC 1879241) and **2u**. Ortho substituted hindered mesitylene ring also participated in reaction giving 54% (**2t**) of corresponding benzimidazole along with its regio-isomer (**2t'**: 17%).

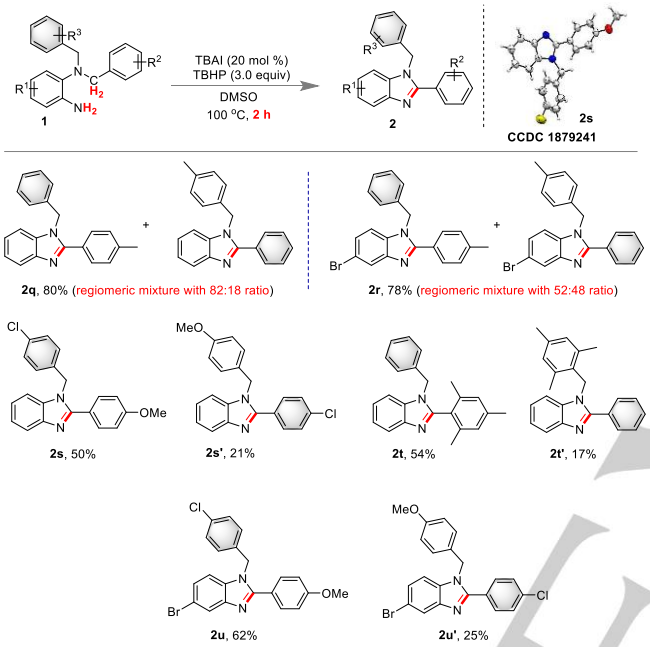


Figure 3. Investigation of electronic effects of *N*-alkyl substituents.

To understand the reaction pathway radical scavenger experiment was done using 2 equiv of 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) under standard condition for the conversion of *N*^{1},*N*^{1}-dibenzylbenzene-1,2-diamine (**1a**) to 1-benzyl-2-phenyl-benzo[d]imidazole (**2a**) where 87% of the desired product formation was observed within 2 h of time (Figure 4a). This experiment confirms that radical intermediates are not involved in the conversion. Based on the experimental observations and literature reports a plausible mechanism has been proposed in Figure 4b. In the first step tetrabutylammonium iodide (TBAI) in presence of *tert*-butylhydroperoxide (TBHP) was oxidized to tetrabutylammonium hypoiodite ($[Bu_4N]^+[IO]^-$) which was further oxidized *in situ* to tetrabutylammonium iodite $[Bu_4N]^+[IO_2]^-$. It was anticipate that the iodite salt was the active catalyst for the transformation (Figure 4b). The substrate **1** was converted to iminium intermediate **3** in presence of the active catalyst and produced ammonium hydroxide and regenerated the hypoiodite. The imminium intermediate **3** might have undergone intramolecular nucleophilic substitution to form an unstable intermediate **4**. The intermediate **4** was possibly oxidized to the final compound **2** in presence of another 1 equiv of TBHP (Figure 4c).

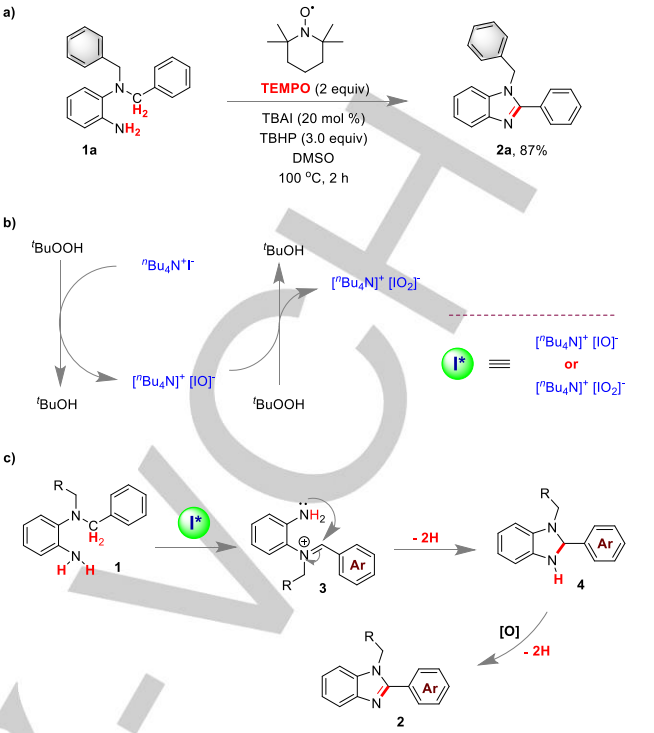


Figure 4. a) Radical scavenger experiment in presence of TEMPO. b) Generation of active iodine catalyst from TBAI-TBHP combination. c) Plausible mechanism of the transformation.

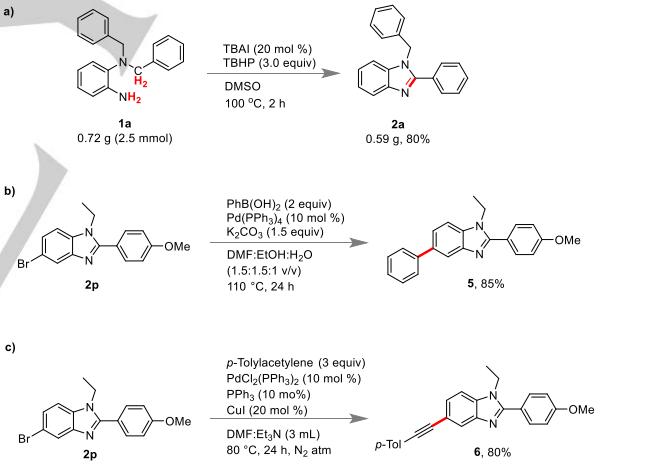


Figure 5. Synthetic application of the method. a) Gram scale synthesis from 2.5 mmol of **1a**. b) Suzuki coupling from the substrate **2p**. c) Sonogashira coupling from the substrate **2p.**

To verify the efficacy of the method, the reaction was scaled up to approximately 2.5 mmol of substrate **1a**. Under the standard reaction condition 80% of **2a** was isolated after 2 h reaction time (Figure 5a). Synthetic application has also been performed with substrate **2p** to make electron rich aromatic moieties. 1-Ethyl-2-(4-methoxyphenyl)-5-phenyl-benzo[d]imidazole (**5**) was obtained in 85% yield by following standard Suzuki reaction[21] using $PhB(OH)_2$ (Figure 5b). Similarly, Sonogashira reaction[22] was performed so synthesize 1-ethyl-2-(4-methoxyphenyl)-5-(p-tolylethynyl)-benzo[d]imidazole **6** in 80% yield. In this reaction one alkynyl group was introduce in the benzimidazole moiety (Figure 5c).

Following this protocol 2-phenyl-1H-benzo[d]imidazole **2v** was also synthesized in 60% yield from N^1-benzylbenzene-1,2-diamine. Previously this was reported by Bobade and co-workers using I_2-TBHP in acetonitrile.[23]

Conclusions

In summary, an efficient metal free approach for C(sp^3)-H imination reaction has been developed using the TBAI-TBHP combination and subsequently synthesis of 1,2-disubstituted benzimidazoles has been achieved with 4H elimination. This methodology avoids the use of expensive metal based catalyst and harsh reaction condition. Additionally, ambient condition, inexpensive oxidant, water soluble iodide reagent, functional group tolerance and shorter reaction time make the methodology more synthetically appealing towards construction of highly substituted benzimidazoles. We anticipate that this organocatalyzed C-H imination approach can provide direct access to various heteroaromatic compounds and might have a major impact on the synthesis of complex structural motifs.

Experimental Section

Representative procedure for the synthesis of 1-benzyl-2-phenyl-benzo[d]imidazole (2a). To an oven dried seal tube charged with a magnetic stirring bar and N^1,N^1-dibenzylbenzene-1,2-diamine (**1a**) (80 mg, 0.28 mmol, 1.0 equiv), TBAI (21 mg, 0.055 mmol, 20 mol %) was added and TBHP as 70% aq. solution (115 µL, 0.83 mmol, 3.0 equiv) dissolved in 2 mL of DMSO. The mixture was stirred in a preheated oil bath of 100 ºC temperature for 2 h. The completion of reaction was confirmed by TLC and afterwards it was cooled to room temperature. The reaction mixture was then washed with brine solution and organic layer extracted with ethyl acetate. The organic layers were collected and evaporated to dryness under reduced pressure. The crude reaction mixture was purified by 230 – 400 mesh silica gel column chromatography using 18% ethyl acetate/hexane as eluent to obtain 1-benzyl-2-phenyl-benzo[d]imidazole (**2a**) as white solid with 92% yield.

Procedure for the radical scavenger experiment with 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl radical (TEMPO). To an oven dried seal tube charged with a magnetic stirring bar and N^1,N^1-dibenzylbenzene-1,2-diamine (**1a**) (40 mg, 0.14 mmol, 1.0 equiv), TBAI (10 mg, 0.0275 mmol, 20 mol %) was added and TBHP as 70% aq solution (58 µL, 0.42 mmol, 3.0 equiv) dissolved in 2 mL of DMSO. To it TEMPO (43 mg, 0.28 mmol, 2.0 equiv) was added. The mixture was stirred in a preheated oil bath of 100 ºC temperature for 2 h. The completion of reaction was confirmed by TLC and afterwards it was cooled to room temperature. The reaction mixture was then washed with brine solution and organic layer extracted with ethyl acetate. The organic layers were collected and evaporated to dryness under reduced pressure. The crude reaction mixture was purified by 230 – 400 mesh silica gel column chromatography using 18% ethyl acetate/hexane as eluent to get 1-Benzyl-2-phenyl-benzo[d]imidazole (**2a**) as white solid with 87% yield.

Acknowledgments

We thank Dr. Milan Kumar Barman (NISER) for crystallography. AB thank CSIR (India) and SS thank NISER for fellowship.

Keywords: C(sp^3)−H activation • Hypervalent Iodine • C-H Imination • Dehydrogenative C-N Coupling • TBAI-TBHP

[1] J. C. Lewis, P. S. Coelho, F. H. Arnold, *Chem. Soc. Rev.* **2011**, *40*, 2003.
[2] a) X. Huang, T. M. Bergsten, J. T. Groves, *J. Am. Chem. Soc.* **2015**, *137*, 5300; b) E. T. Hennessy, T. A. Betley, *Science* **2013**, *340*, 591.
[3] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564.
[4] a) C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287; b) J. R. Clark, K. Feng, A. Sookezian, M. C. White, *Nat. Chem.* **2018**, *10*, 583; c) G. Pandey, R. Laha, *Angew. Chem. Int. Ed.* **2015**, *54*, 14875; d) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7.
[5] a) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129; b) C. Zhu, Y. Liang, X. Hong, H. Sun, W.-Y. Sun, K. N. Houk, Z. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 7564; c) S. Reddy Kandimalla, S. Prathima Parvathaneni, G. Sabitha, B. V. Subba Reddy, *Eur. J. Org. Chem.* **2019**, 1687.
[6] a) W. B. Ma, S. N. Li, Z. H. Zhou, H. S. Shen, X. Li, Q. Sun, L. He, Y. Xue, *Eur. J. Org. Chem.* **2012**, 1554; b) X.-F. Wu, J.-L. Gong, X. Qi, *Org. Biomol. Chem.* **2014**, *12*, 5807.
[7] C. J. Evoniuk, S. P. Hill, K. Hanson, I. V. Alabugin, *Chem. Commun.* **2016**, *52*, 7138.
[8] C. J. Evoniuk, G. d. P. Gomes, S. P. Hill, S. Fujita, K. Hanson, I. V. Alabugin, *J. Am. Chem. Soc.* **2017**, *139*, 16210.
[9] J. Roy, A. K. Jana, D. Mal, *Tetrahedron* **2012**, *68*, 6099.
[10] a) Q. Nguyen, K. Sun, T. G. Driver, *J. Am. Chem. Soc.* **2012**, *134*, 7262; b) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; c) S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, M. Christina White, *Nat. Chem.* **2015**, *7*, 987; d) N. R. Paz, D. Rodríguez-Sosa, H. Valdés, R. Marticorena, D. Melián, M. B. Copano, C. C. González, A. J. Herrera, *Org. Lett.* **2015**, *17*, 2370.
[11] a) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328; b) F. V. Singh, T. Wirth, *Chem. Asian J.* **2014**, *9*, 950; c) R. M. Romero, K. Muñiz, Carbon–Heteroatom Bond Formation Mediated by Hypervalent Iodine. In *PATAI'S Chemistry of Functional Groups*, B. Olofsson, I. Marek, Z. Rappoport, Eds. John Wiley & Sons, Ltd.: 2019; pp 1; d) K. Liu, C. Song, A. Lei, *Org. Biomol. Chem.* **2018**, *16*, 2375.
[12] a) A. Bal, S. Maiti, P. Mal, *J. Org. Chem.* **2018**, *83*, 11278; b) S. Maiti, A. Bose, P. Mal, *J. Org. Chem.* **2018**, *83*, 8127; c) S. Maiti, P. Mal, *J. Org. Chem.* **2018**, *83*, 1340; d) S. Maiti, P. Mal, *Org. Lett.* **2017**, *19*, 2454; e) S. Maiti, T. K. Achar, P. Mal, *Org. Lett.* **2017**, *19*, 2006.
[13] a) T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073; b) P. Finkbeiner, B. J. Nachtsheim, *Synthesis* **2013**, *45*, 979.
[14] H. Hussain, A. Al-Harrasi, I. R. Green, I. Ahmed, G. Abbas, N. U. Rehman, *RSC Adv.* **2014**, *4*, 12882.
[15] L. Liu, Q. Sun, Z. Yan, X. Liang, Z. Zha, Y. Yang, Z. Wang, *Green Chem.* **2018**, *20*, 3927.
[16] R. D. Richardson, T. Wirth, *Angew. Chem. Int. Ed.* **2006**, *45*, 4402.
[17] a) S. Rajamanickam, G. Majji, S. K. Santra, B. K. Patel, *Org. Lett.* **2015**, *17*, 5586; b) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner, B. J. Nachtsheim, *Org. Lett.* **2011**, *13*, 3754; c) F. Chen, Q. Meng, S.-Q. Han, B. Han, *Org. Lett.* **2016**, *18*, 3330; d) Y.-P. Lam, Y.-Y. Yeung, *Chem. Asian J.* **2018**, *13*, 2369.
[18] A. Bose, S. Maiti, S. Sau, P. Mal, *Chem. Commun.* **2019**, *55*, 2066.
[19] M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, *Science* **2010**, *328*, 1376.
[20] B. Xiong, G. Wang, C. Zhou, Y. Liu, P. Zhang, K. Tang, *J. Org. Chem.* **2018**, *83*, 993.
[21] K. Nemoto, S. Tanaka, M. Konno, S. Onozawa, M. Chiba, Y. Tanaka, Y. Sasaki, R. Okubo, T. Hattori, *Tetrahedron* **2016**, *72*, 734.
[22] T. Weilandt, N. L. Loew, G. Schnakenburg, J. Daniels, M. Nieger, C. A. Schalley, A. Luetzen, *Chem. Eur. J.* **2012**, *18*, 16665.
[23] S. V. Patil, S. S. Patil, V. D. Bobade, *Arab. J. Chem.* **2016**, *9*, S515.

10.1002/ejoc.201900732

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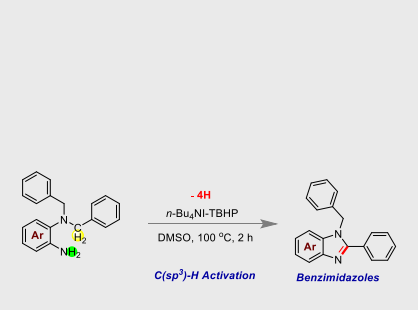
COMMUNICATION

For the synthesis of benzimidazoles, an intramolecular C(sp^3)−H imination is described by *in situ* formation of catalytic hypoiodite(I) or iodite(III) from water soluble inorganic iodide(I) reagent and mild oxidant TBHP.



Intramolecular Imination*

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