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.201801725

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801725

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Stereoselective Aminoiodination of Activated Alkynes with Organoiodine(III) Reagents and Amines *via* Multiple-Site Functionalization: Access to Iodinated Enamines and *N*-Aryl Indoles

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Abstract: A stereoselective aminoiodination of activated alkynes with $PhI(OAc)_2$ and amines *via* multiple-site functionalization to afford (*Z*)diethyl 2-(diphenylamino)-3-iodomaleate derivatives with superior yields has been described. The key feature of this reaction is the incorporation of iodide and aryl group concurrently in the same molecule in a stereoselective manner by employing $PhI(OAc)_2$ as electrophilic reagent as well as iodide and aryl group source. The high stereoselectivity of the reaction can be explained based on the structure of the possible intermediates, the conformations of which controlled by the hydrogen bonding, steric hindrance and electrostatic attractions. This reaction proceeds under mild conditions, providing various dialkyl 2-(diphenylamino)-3-iodomaleates by a single operation starting from activated alkynes. The robustness of our strategy is revealed by making of bis (dialkyl 2-(diphenylamino)-3-iodomaleate) derivatives involving formation of four new C-N bonds and two C-I bonds in a single step. The synthesized inactive 3° enamines (dialkyl 2-(diphenylamino)-3-iodomaleates) could be further transformed into highly substituted indoles via Pd catalyzed C-H and C-I activation under non-acidic conditions.

Introduction

Alkyne difunctionalizations have attracted intensive attention in recent years particularly in developing regio and stereoselective reactions to access multifunctional alkene products with broad synthetic and biological applications.[1] For example the azidativehalo,[2] sulfonative,[3] aminohalogenative,[4] silylzincative [5] iodoacyloxylations[6] and perfluoroalkylative[7] difunctionalizations of alkynes have been successfully

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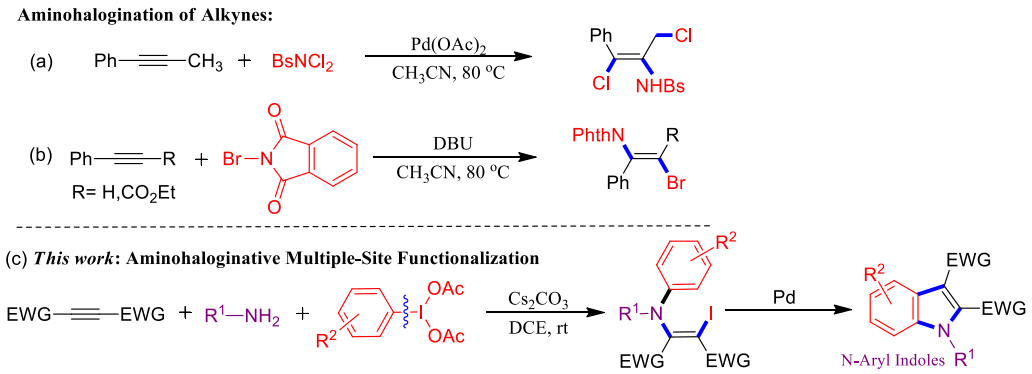
realized for the synthesis of various difunctionalization products. In this context, methods to produce halogenated enamines *via* aminohalogenation of alkynes are very attractive owing to the utility of these compounds in medicinal chemistry and organic synthesis.[8] Accordingly, considerable efforts have been made to their syntheses resulting in various synthetic strategies. For example cyclic enaminones,[9] 2-alkynyloxycarbonyl azides/amines/O-propargyl carbamates[10] have been typically employed as precursors for halogenated enamines and catalyzed by metal or non-metals with various halogen sources.

Scheme 1. Aminohalogenation of Alkynes and Our Strategy



Furthermore, dehydrogenative aminohalogenation of alkenes *via* Pd catalysis was developed by Jiang and co-workers[11] for the synthesis of brominated enamines. Later Li *et al.*[12] developed Nickel or Diacetoxyiodobenzene promoted halogenation of enamines and enamides. However, examples of alkyne aminohalogenation towards halogenated enamines are scarce (Scheme 1a &b).[13] For instance, Headley & Li and co-workers demonstrated the aminochlorination of arylalkynes with N,N dichlorobenzenesulfonamide (Scheme 1a).[13a] In 2014, Liang and Zhang *et al.* described the aminohalogenation of alkynes with N-haloimides activated by DBU (Scheme 1b).[13b] Despite this progress, developing the multiple-site functionalization of C-C multiple bonds with reagents as both halogen source as well as promoter in a stereoselective manner remains an intriguing challenge. As part of our ongoing study on multiple functionalization reactions of alkynes and amines using azides as nitrogen source and organoiodine compounds as promoter,[14] we fancied to synthesize iodinated enamines directly from alkynes and amines by using organoiodine reagents as both iodine and aryl group source.

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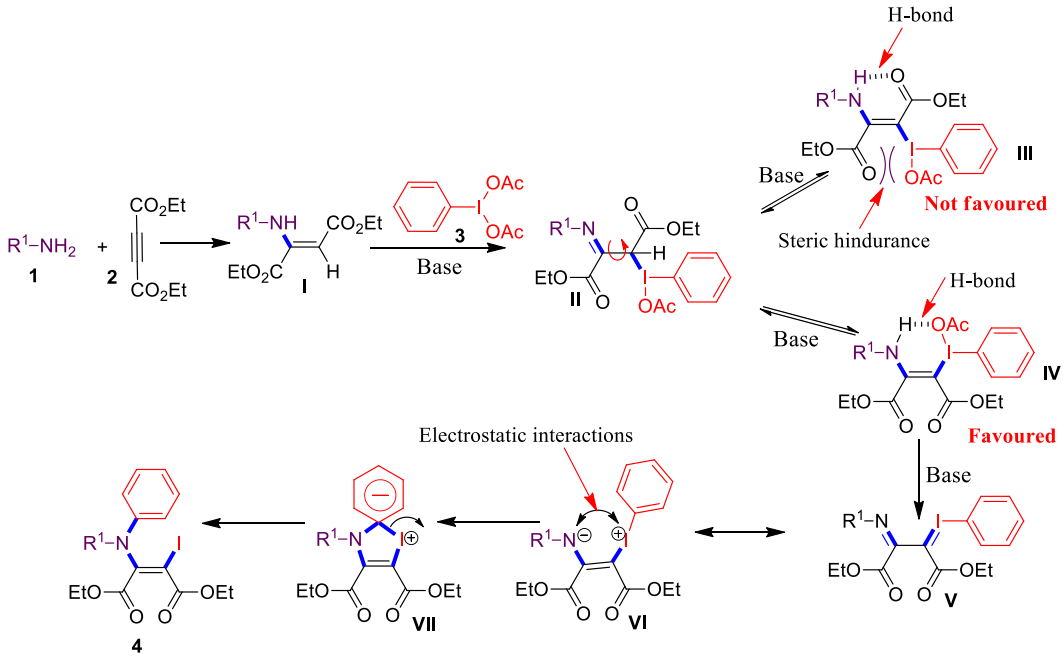
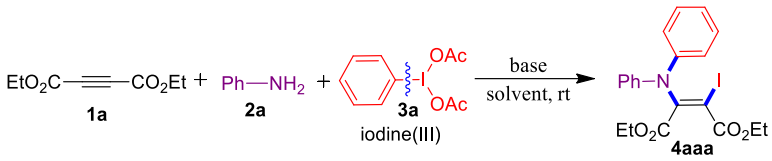
Scheme 2. Plausible Conformations of Intermediates for Stereoselectivity of the Reaction



Organoiodine(III) compounds are usually used as oxidants and electrophilic reagents where only one ligand of iodine(III) is removed by the substrate or replacement of both ligands with external nucleophile followed by its decomposition into radicals[12,15,16] However, sequential removal of two ligands from the iodine(III) reagent by active C-H bond of substrate and incorporation of iodobenzene into the same substrate would indubitably make the reactions atom economic, but such organic transformations are not much explored.[9] On the other hand, compared with known aminohalogenation of alkynes, this multiple-site functionalization would be of great importance to produce synthetically potential halogenated enamines in a stereoselective manner. The high stereoselectivity of the reaction can be explained based on the structure of the possible intermediates. The conformations of intermediates are controlled by the hydrogen bonding, steric hindrance and electrostatic attractions as shown in scheme 2. These type of interactions have never been explored for stereoselective alkyne aminohalogenation. Herein we report the first example of a highly stereoselective multiple-site functionalization of activated alkynes with amines and organoiodine(III) (Scheme 1c) as the halo and aryl group source for haloenamines. We have also successfully employed these

relatively inactive 3° enamines in intramolecular cyclizations *via* Pd catalyzed C-H and C-I activation resulting in highly functionalized indoles.

Table 1. Optimization reaction of Aminohalogenation of Alkynes[a]



entry	iodine(III) (equiv)	base (equiv)	solvent	yield (%)[b]
1	PIDA (1.5)	-----	DCE	30
2	PIDA (1.5)	-----	DCE	31[c]
3	PIDA (1.5)	-----	DCE	0[d]
4	PIDA (1.5)	-----	DCE	0[e]
5	PIDA (1.5)	Cs_2CO_3 (1.0)	DCE	60
6	PIDA (1.5)	Cs_2CO_3 (1.5)	DCE	67
7	PIDA (1.5)	K_2CO_3 (1.5)	DCE	50
8	PIDA (1.5)	K_3PO_4 (1.5)	DCE	36
9	PIDA (1.5)	$NaHCO_3$ (1.5)	DCE	52
10	PIDA (1.5)	Na_2CO_3 (1.5)	DCE	46
11	PIDA (1.5)	DABCO (1.5)	DCE	ND
12	PIDA (1.3)	Cs_2CO_3 (1.5)	DCE	55
13	PIDA (2.0)	Cs_2CO_3 (1.5)	DCE	73
14	**PIDA (2.5)**	**Cs_2CO_3 (1.5)**	**DCE**	**84**
16	PIDA (2.5)	Cs_2CO_3 (2.0)	DCE	84
17	PIDA (1.8)	Cs_2CO_3 (1.5)	DCE	71
18	PIDA (2.5)	Cs_2CO_3 (1.5)	DCM	54
19	PIDA (2.5)	Cs_2CO_3 (1.5)	MeCN	61
20	PIDA (2.5)	Cs_2CO_3 (1.5)	THF	ND
21	PIDA (2.5)	Cs_2CO_3 (1.5)	H_2O	21

22	PIDA (2.5)	Cs_2CO_3 (1.5)	EtOAc	30
23	PIDA (2.5)	Cs_2CO_3 (1.5)	DMF	17
24	PIFA (2.5)	Cs_2CO_3 (1.5)	DCE	ND
25	PhIO (2.5)	Cs_2CO_3 (1.5)	DCE	ND
26	PhI(OH)(OTs) (2.5)	Cs_2CO_3 (1.5)	DCE	ND

[a]Reaction conditions: Alkyne **1a** (1 mmol), Amine **2a** (1 mmol), PIDA **3a** (2.5 mmol), Cs_2CO_3 (1.5), dry solvent 3 mL, rt (27 ^oC) for 8 h; [b]Isolated yield after silica column chromatography; [c] Na_2SO_4 (4 equiv); [d] TBAI (2 equiv); [e] NBS (2 equiv); ND = Not detected.

Results and discussion

We choose diethyl acetylenedicarboxylate **1a**, aniline **2a** and phenyliodine(III) diacetate (PIDA) **3a** as the model substrates to initiates our studies. At the beginning, the reaction was performed at room temperature in dichloromethane (DCE). To our delight, we observed the formation of desired product **4aaa** in 31% yield with (*Z*)-configuration (Table 1, entry 1). The structure and stereochemistry of **4aaa** was determined by the X-ray crystallography analysis (Supporting information, SI). With this promising result in hand, we further optimized the reaction conditions. When reaction was carried out in the presence of 4 equiv of Na_2SO_4 as additive, the product **4aaa** was yielded in 31 % after 18 h reaction time (Table 1, entry 2). No product was obtained when the reaction was performed with TBAI and NBS as additives (entries 3&4). We then turned our attention to the screening of bases to improve the reaction performance. When reaction performed with Cs_2CO_3 pleasingly, the product **4aaa** was obtained in 67% yield in 12 h (entries 5&6). Other bases such as K_2CO_3, K_3PO_4, $NaHCO_3$, Na_2CO_3, and DABCO did not improve the yield of the product (entries 7-11). We then screened the equivalents of PIDA and Cs_2CO_3 (entries 12-17), 1.5 equiv of Cs_2CO_3 and 2.5 equiv of PIDA were found to be the best conditions to afford the product **4aaa** in 84 % yield after 8 h (entry 14). Among the solvents tested, DCE was found to be the best solvent choice (entries 18-23). In our attempts to further improve the yield, we have screened other organoiodine sources, unfortunately our attempts went in vain (entries 24-26).

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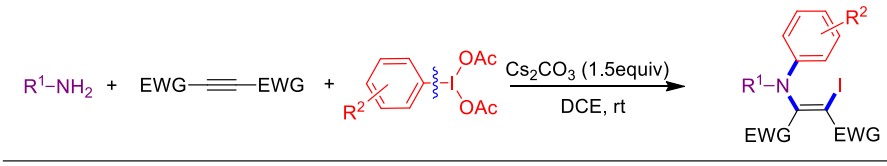
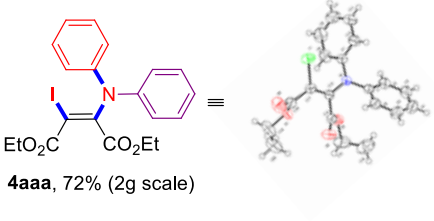
In order to realize the versatility of this newly developed method, we anticipated to apply it to a series of amines having neutral, electron donating and withdrawing substituents on phenyl ring. This results demonstrated that the substrates containing neutral and electron donating groups on phenyl ring afforded the products (Table 2(A)) in good to very good yield. The weak electron withdrawing substituents on phenyl ring resulted in relatively low yields (Table 2(B)). Presence of both weak electron withdrawing and donating groups on the same phenyl ring gave the products fairly in good yields (Table 2, **4fab** & **4maa**). Organoiodine with strong electron withdrawing groups (-CO_2Me, NO_2) gave the products in excellent yields (Table 2(C)), this may be due to stabilization of intermediate **VII** (Scheme 4). It is worth to mention here that, the robustness of our strategy is demonstrated by the synthesis of derivatives (Table 2 (D), **4a"aa** & **4a"ab**) involving formation of four new C-N bonds and two C-I bonds in single step. After developing successful syntheses of halogenated enamines, we envisaged that it would be appropriate to check the scalability of our protocol for the synthesis halogenated enamines owing to their synthetic utility. Accordingly, we performed the reaction on gram scale for the synthesis of halogenated enamine resulted in 72% yield (Table 2, **4aaa**).

Table 2. **Substrate Scope of Aminoiodination Reaction**[a]



(A) Scope of Arylamines with neutral and electron donating substituents and Alkynes

R^1	R^2	EWG	yield (%)[b]
C_6H_5-	H	CO_2Et	[c]**4aaa**, 84
C_6H_5-	H	CO_2Me	**4aab**, 82
3-Me-C_6H_5-	H	CO_2Et	**4caa**, 85
3,5-di Me-C_6H_4-	H	CO_2Et	**4daa**, 82
2-isopropyl-C_6H_5-	H	CO_2Me	**4eab**, 78
2-Br-3-Me-C_6H_4-	H	CO_2Me	**4fab**, 77
4-OMe-C_6H_5-	H	CO_2Et	**4gaa**, 78
4-OMe-C_6H_5-	H	CO_2Me	**4gab**, 80
3,4,5-OMe-C_6H_5-	H	CO_2Et	**4haa**, 75



4aaa, 72% (2g scale)

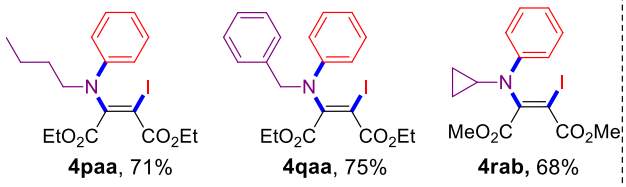
(B) Scope of Arylamines with weak electron withdrawing goups and Alkynes

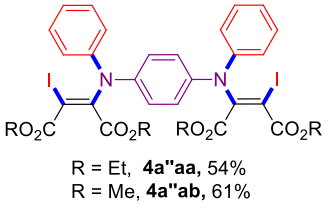
R^1	R^2	EWG	yield (%)[b]
2-F-C_6H_5-	H	CO_2Me	**4iab**, 88
4-Cl-C_6H_5-	H	CO_2Et	**4jaa**, 85
4-Br-C_6H_5-	H	CO_2Et	**4kaa**, 88
4-Br-C_6H_5-	H	CO_2Me	**4kab**, 83
2-Br-C_6H_5-	H	CO_2Et	**4laa**, 79
2-Me,3- NO_2-C_6H_5-	H	CO_2Et	**4maa**, 75

(C) Scope of Organoiodine(III) reagents and Alkynes

R^1	R^2	EWG	yield (%)[b]
C_6H_5-	4-CO_2Me	CO_2Et	**4aba,** 90
C_6H_5-	4-CO_2Me	CO_2Me	**4abb,** 87
4-OMe-C_6H_5-	4-CO_2Me	CO_2Me	**4gbb,** 77
4-Br-C_6H_5-	4-CO_2Me	CO_2Me	**4kbb,** 91
2-Br-4-Me-C_6H_4-	4-CO_2Me	CO_2Et	**4nba,** 86
C_6H_5-	3-NO_2	CO_2Et	**4aca,** 84
C_6H_5-	4-F	CO_2Me	**4adb**, 90
2,4-di Me-C_6H_4-	4-F	CO_2Et	**4oda**, 87

(D) Scope of aliphatic amines and Alkynes





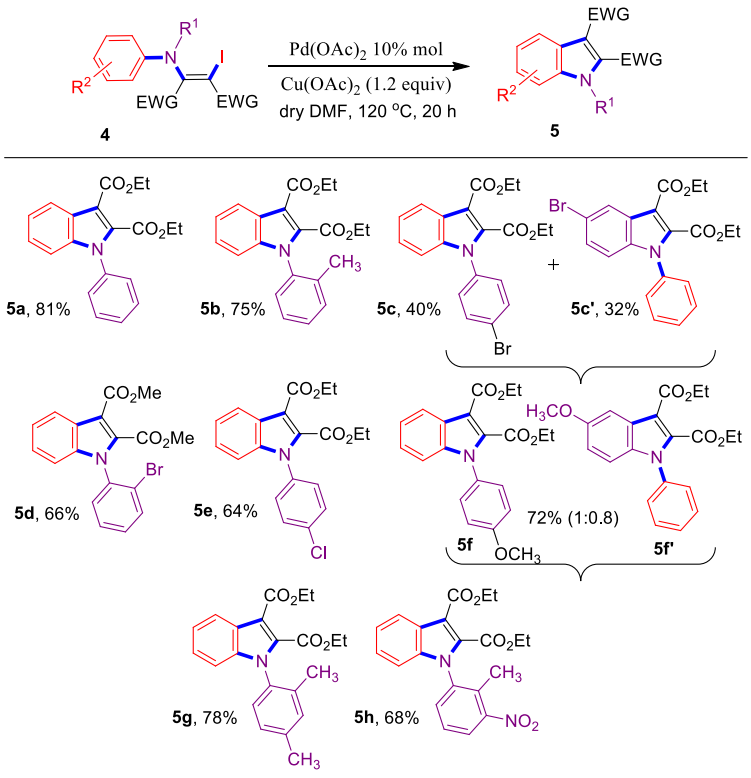
[a]Reaction conditions: Alkyne **1a** (1 mmol), Amine **2a** (1 mmol), PIDA **3a** (2.5 mmol), Cs_2CO_3 (1.5 mmol), dry DCE 3 mL, rt (27 ° C) for 8-14 h; [b]Isolated yield after silica column chromatography.[c]CCDC 1579282 for **4aaa**

Owing to the importance of halogenated enamines as flexible building blocks in organic synthesis, we envisioned to employ them in organic transformations. In this direction, we thought to perform transition-metal catalyzed intramolecular cyclizations by C-I and (sp^2)C-H activation. However, less reactive 3° enamines than 2° enamine homologues in transition-metal catalyzed C-H activation reactions

are scarce[17] and poses a daunting challenge. The conversion of such enamines to indoles was accomplished by improving the electrophilicity of Pd catalysts under acidic conditions.[18]

Herein we delighted to employ these iodinated enamines for smooth transformation to *N*-aryl indoles *via* palladium-catalyzed intramolecular cyclization under non-acidic conditions. It was noted that iodinated enamines containing weak electron withdrawing and electron donating groups on phenyl rings provided the indoles with good yields than those having electron-withdrawing groups (Table 3). On the basis of the results and previous reports[18], we have proposed a plausible mechanism for palladium-catalyzed intramolecular cyclization in Scheme S1 (see Supporting Information).

Table 3. *N*-aryl Indole Synthesis from Iodinated Enamines *via* Pd-Catalyzed Intramolecular Cyclizaiton[a]



[a]Reaction conditions: Iodoenamine **4** (1 mmol), $Pd(OAc)_2$ (10% mol), $Cu(OAc)_2$ (1.2 mmol), dry DMF 1.5 mL, at 120 °C for 20 h. [b]Isolated yield after silica column chromatography. [c]Ratio estimated by H^1 NMR.

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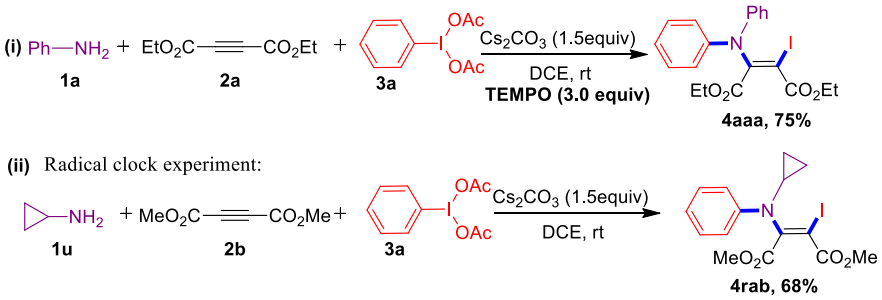
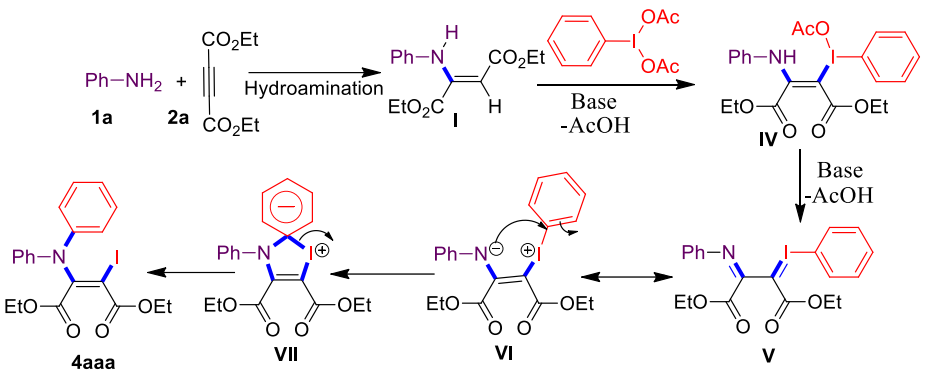
To investigate the reaction mechanism, we performed couple of control experiments (Scheme 3). The addition of TEMPO uninhibited the formation of **4aaa** (Scheme 3(i)), suggesting that reaction might proceed through ionic pathway. To further rule out the radical pathway, we performed a radical clock experiment under standard conditions, which afforded only the halogenated enamine product **4rab** and no other ring-opened coupling products (Scheme 3(ii)).

Scheme 3. Control Experiments



Based on the above experiments and literature reports[9] we have formulated the following plausible mechanism (**scheme 4**). The intermolecular reaction of **1a** and **2a** generates hydroamination product **I** which undergo ligand exchange with PIDA by the loss of acetic acid to give favored intermediate **IV**, which would further transformed to intermediate (**V**) by the loss of one more acetic acid, which followed by subsequent rearrangement leads to the formation of a possible zwitterion (**VII**) which then afford the final product **4aaa**. The involvement of *ipso*-substitution by negative nitrogen (**VI**) on the phenyl ring through a five membered cyclic intermediate (**VII**) would facilitates the transfer of the Aryl group.

Scheme 4. Plausible Mechanism for Aminohalogenation of Alkynes



Conclusion

In summary, we have developed a novel and facile approach for the stereoselective alkyne aminoiodination using amines, phenyliodine(III) diacetate (PIDA) as iodide and aryl moiety source as well as promoter. The key feature of this reaction is the incorporation of iodide and aryl group concurrently in the same molecule in a stereoselective manner. The advantages of this method are metal-free, mild reaction conditions and scalability. We have also successfully employed these inactive iodinated 3° enamines in intramolecular cyclizations *via* Pd catalyzed C-H and C-I activation resulting in highly functionalized indoles. Further exploration of iodinated 3° enamines are currently under way in our laboratory.

Experimental Section

Aniline **1a** (50 mg, 1 mmol) was taken in a dried round bottom flask, and dialkyl acetylenedicarboxylate **2a** (91.3 mg, 1 mmol) was then added slowly with thorough mixing to form a homogeneous paste, then add 0.5 mL DCE solvent (if required). After confirming the formation of enamine (monitored by TLC), then added 4 mL DCE solvent, followed by addition of Cs_2CO_3 (261.959 mg, 1.5 mmol), phenyliodine(III) diacetate (PIDA) (431.614 mg, 2.5 mmol) in portion wise for 20 min. The progress of the reaction was monitored by TLC. The reaction mixture was quenched by addition of saturated solution of $NaHCO_3$ and extracted with ethyl acetate (EtOAc), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified through a silica gel column chromatography using petroleum ether/ethyl acetate (0.2/9.8) as eluent to yield (209 mg, 84%). All compounds (**4aaa**-**4rab**) were unknown and confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and HR-MS spectral analyses.

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ACKNOWLEDGMENTS

We gratefully acknowledge the Department of Science and Technology-Science and Engineering Research Board (DST-SERB-EMR/2016/1000952) New Delhi, India and Indian Institute of Technology Hyderabad (IITH) for financial support. SA thanks CSIR, NRK thanks DST-SERB, New Delhi, India for the award of research fellowship.

Keywords: multiple-site functionalization; alkyne aminoiodination; stereoselective; indoles; iodinated 3° enamines; intramolecular cyclization.

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