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An unprecedented oxidative intermolecular homo coupling reaction between two sp^3C–sp^3C centers under metal-free condition

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ABSTRACT

An unprecedented formation of benzylic sp^3C–sp^3C coupled dibenzylic products has been illustrated. The reactions have been carried out in the presence of three oxidizing reagents, i.e., diacetoxy-iodobenzene (IBDA), *N*-fluorobenzenesulfonimide (NFSI), and pyridine (Py) using toluene derivatives.

Applications of radical chemistry in the development of modern organic synthesis are well documented in the literature.[1] At present times, most of the radical reactions are carried out utilizing robust toxic metal complex such as tin hydride reagents and toxic radical initiators like peroxides.[1a] Major setback of such reactions is the formation of large amounts of unexpected residual metal catalysts and the inherent difficulty in purification of the desired products. These disadvantages greatly restrict the application of radical chemistry in the areas of pharmaceutical industry.[1b–d] Thus; it poses a challenge to update these traditional methods to greener and sustainable organic synthesis. As a result of its easy availability, environmental benignity, and high reactivity, hypervalent iodine(III) reagent initiated radical processes under metal-free conditions are undoubtedly the ideal and promising route to address the aforementioned challenges. Under metal-free conditions, the utilization of hypervalent iodine(III) reagents for C—N, C—O bond formations have been thoroughly investigated.[1b] Of late, hypervalent iodine(III) reagents have been found to show remarkable relativities for C—C bond formation[1e,f] following which, bi-aryl compounds and heterocycles could be obtained successfully.

Compounds containing the di-benzyl moiety as the core structure constitute an interesting group of molecules which have been used as key intermediates both for the synthesis of dyes, paints, resins, polymers, agrochemicals, and pharmaceuticals, and for the preparation of a number of natural products as stilbenzyl or dibenzyl derivatives.[2,3] However, the wide use of toxic transition metal catalysts/reagents in low oxidation state for such homo coupling reactions imposes considerable environmental problem.[4,5a,4m] Though metal free sp^3C–sp^3C homo coupling reactions using toluene as substrate is reported in literature,[5b] there are no reports of a generalized reaction for the same. Thus, a new, metal free, sp^3C–sp^3C homo coupling methodology for the synthesis of di-benzyl compounds using toluene derivatives has been developed herein.

The regioselective functionalization of pyridines, such as the C2-selective addition of highly reactive nucleophiles and C2-selective deprotonation with strong base followed by reactions with electrophiles, has long been investigated by many researchers.[6] In literature, lewis basic sp^2 nitrogen atom in the pyridine ring was utilized as the directing group, and C—H bond activation by transition-metal catalysts occurred selectively at the C2 position.[6] However, reports of C3- or C4-selective catalytic C—H bond functionalization of pyridines without an additional directing group are limited.[6,7] In 2011 Yu et al. reported the first Pd-catalyzed C-3 selective C—H olefination enabled by a bidentate ligand that weakens the coordination of the Pd catalyst with the pyridyl *N* atom through the *trans*-effect. Two major challenging factors addressed in this report were that, low reactivity of pyridyl C—H due to the poor electron density of the pyridyl ring and the strong coordination of the pyridine *N* atom with the Pd(II) center which

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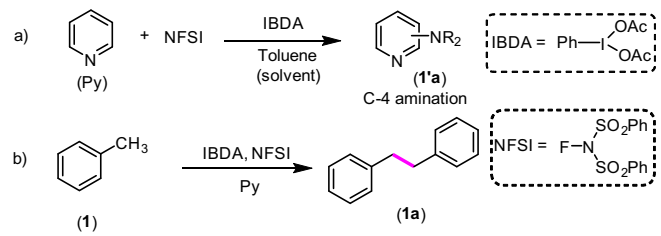
prevents the catalyst from interacting with pyridine C(3)—H and C(4)—H bonds. In 2013, Kanai and co-workers reported a challenging C4- selective direct alkylation protocol of pyridine substrates through hydrometalation/nucleophilic addition/rearomatization sequence catalyzed by Co(II) and hydride sources.[6a] In addition, hypervalent iodine mediated oxidative amination to arene,[8] alkene,[9] and alkyne[10] based substrates have been reported. In line with these observations, a hypothesis to apply pyridine based molecules for C-4 based amination reaction by using metal free hypervalent oxidizing reagent has been envisaged (Scheme 1a).

To test the hypothesis on the regioselective C-4 amination of pyridine scaffolds, *N*-fluorobenzenesulfonimide (NFSI) and iodo benzene diacetate (IBDA) were initially employed to react with Pyridine (Py) at 100 °C using various solvents like DCE, Dioxane, DMSO, DMF, THF, EtOH, and toluene. Unfortunately, under these conditions, the desired product was not observed. However gratifyingly, in the presence of toluene solvent, an unexpected dibenzylic product **1a** was observed instead of the expected C-4 aminated product **1′a** (Scheme 1). Following this observation, a thorough search for the importance of dibenzylic product resulted in many more of its applications and synthetic utility under robust and toxic metal catalyzed conditions[11] including a side dibenzylic product reported in metal catalyzed and unfriendly peroxide condition.[12] Delightfully, this is an interesting methodology to observe homo coupling $sp^3C–sp^3C$ bond formation using different oxidizing reagents (Scheme 1b).

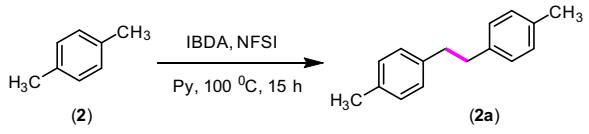
The reaction conditions were then implemented to *p*-xylene (**2**) substrate to generalize whether the reaction promotes the benzylic homo coupling dimerized product. Gratifyingly, almost major amount of bibenzylic product **2a** was observed along with uncharacterized trace amount of side product (Table 1, entry 1). For cross verification, the formation of bibenzylic product was further confirmed by the reduction of (*E*)-1,2 di*p*-tolylethene **2′a** substrate (Scheme 2).[13].

A controlled experiment was performed to ascertain the exact role of all NFSI, IBDA, and Py reagents on this reaction condition which confirmed that all the three abovementioned reagents are playing vital role in this reaction (Table 1). The reaction was further standardized by varying the stoichiometry of the three reagents. It is found that combination of 1 mmol NFSI, 2 mmol IBDA, and 1 mmol Py treated with *p*-xylene (**2**) gave better yield (NMR yield 72%, isolated yield 70%) compared to other conditions (see Supporting information (SI, Table S2.1)). It is worth mentioning that the yield of benzylic dimerized product (**2a**) is calculated compared to the amount of NFSI as oxidizing reagent used in the corresponding reaction condition. In this reaction condition, excess amount of *p*-xylene (**2**) was used (for the role of both solvent and substrate); hence NFSI was used as a limiting reagent. The reaction condition was tested with various solvents (see SI Table S2.2) to decrease the amount of *p*-xylene (**2**). Unfortunately, there was no improvement in the yield of the product. To find out the role of IBDA, the reaction was tested with different hypervalent reagents and oxidants (see SI Table S2.3), and it was concluded that IBDA



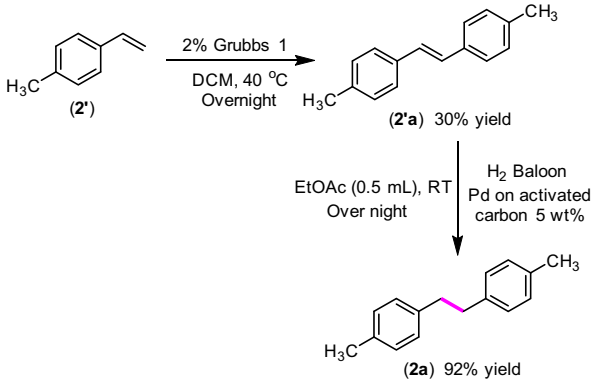
Scheme 1. (a) Working hypothesis (sp^2C—N bond formation). (b) Reaction observation (metal free $sp^3C–sp^3C$ bond formation).

Table 1
Control experiment for the exact role of reagents[a,b,c]



Entry	NFSI (mmol)	IBDA (mmol)	Py (mmol)	NMR yield (%)
1	**1**	**2**	**1**	**72**
2	1	2	X	02
3	1	X	1	01
4	X	1	1	01
5	1	X	X	01
6	X	1	X	01
7	X	X	1	01

X = Not used.
Bold refer to better yield compare to other method.
[a] *p*-Xylene (2) 30 mmol, 100 °C, 15 h.
[b] Yield was calculated comparing the amount of NFSI used.
[c] Tetra chloro ethane (TCE) internal standard for NMR yield.



Scheme 2. Indirect synthesis of dibenzylic product **2a**.

is a better oxidant under the present reaction condition. Further, the reaction was treated with various fluorinating, halogenated, and aminating reagents (see SI Table S2.4) and it was observed that NFSI is a more efficient reagent for the formation of the corresponding dimerized product **2a**. Further, Py proved to be a better supporting reagent for the formation of dimerized product **2a** compared to other pyridine derivative reagents (see SI Table S2.5).

Subsequently, it was found that 100 °C is the optimum temperature for this reaction (see SI Table S2.6). Likewise, the reaction was optimized with different time interval and found that 15 h is required (see SI Table S2.7) to furnish better yield of the product **2a**. Another noteworthy observation was that only 30 equiv (15 equiv of dimer product compare to NFSI) of the substrate **2a** was required to produce the expected dimerized product **2a** in quantitative yield (see SI Table S2.8).

Having acquired this decent optimization condition, the substrate scope was tested with a variety of toluene derivatives (Table 2). The substrates *m*-xylene (**3**) and *o*-xylene (**4**) also gave their corresponding homo coupled $sp^3C–sp^3C$ dimerized products **3a** and **4a** in good yields. An interesting observation in case of substrate mesitylene (**5**) was the coupling occurred at only one methyl position to furnish the dimerized product **5a** while the other two methyl substituents remained intact. The substrate 4-*tert*-butyl toluene (**6**) showed well tolerance under this condition giving moderate yield of the corresponding homo coupled dimerized product **6a**. Most importantly, the compound 4-methylanisole (**7**) having two possible positions for radical formation, one at

OMe-substituted side and another at Me-substituted side, gave dimerized product **7a** corresponding to dimerization at only Me-position. The chlorine containing toluene derivative substrates (**8**, **9**, **10**, and **11**) provided their respective homo coupled dimerized products (**8a**, **9a**, **10a**, and **11a**) in moderate to good yields. In addition, the fluorine containing toluene substituents (**12**, **13** and **14**) furnished their $sp^3C–sp^3C$ homo coupling products in decent yields. It is worth noting that; methyl group containing naphthalene substituent (**15**) provided the respective dimerized product (**15a**) in moderate yield. The diarene group possessing methane substrates (**16** and **17**) gave their desired products (**16a** and **17a**) in moderate yields. Unfortunately, substrates like ethyl benzene, cumene, cyclohexane, linear, and branched alkanes did not yield their expected $sp^3C–sp^3C$ homo coupling products under the similar conditions. Notably, the solid substrates like fluorene (**18**), xanthene (**19**), and dibenzosuberane (**20**) yielded the

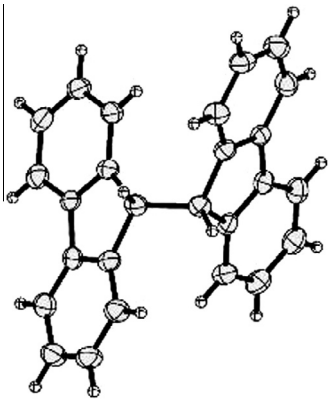
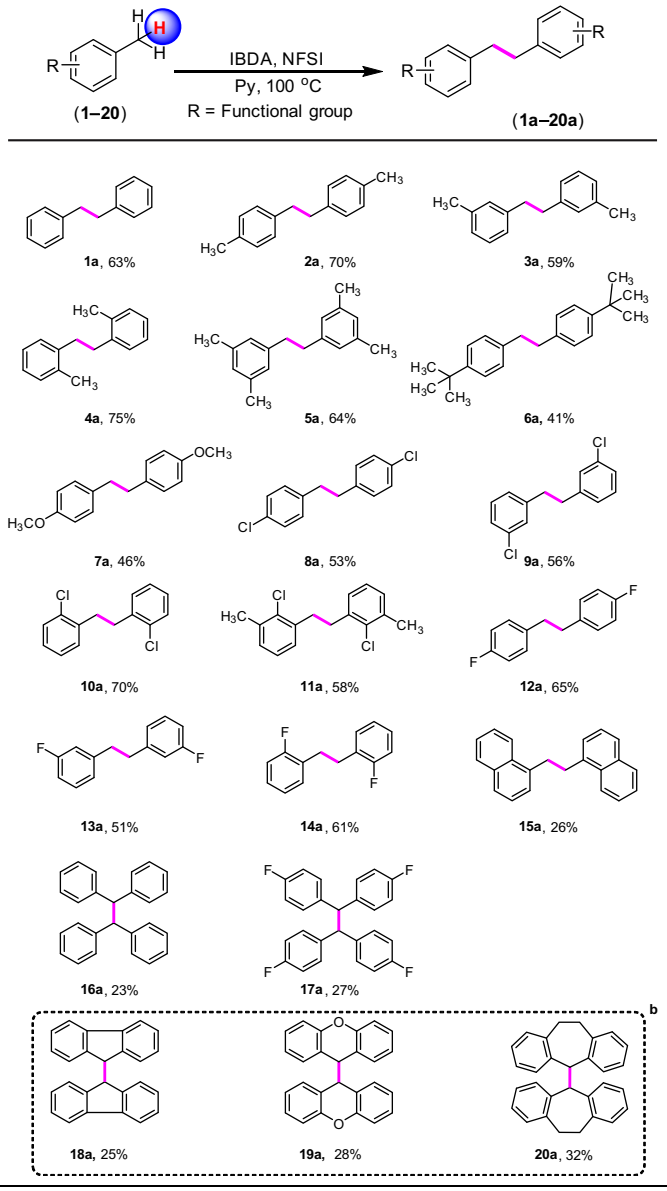
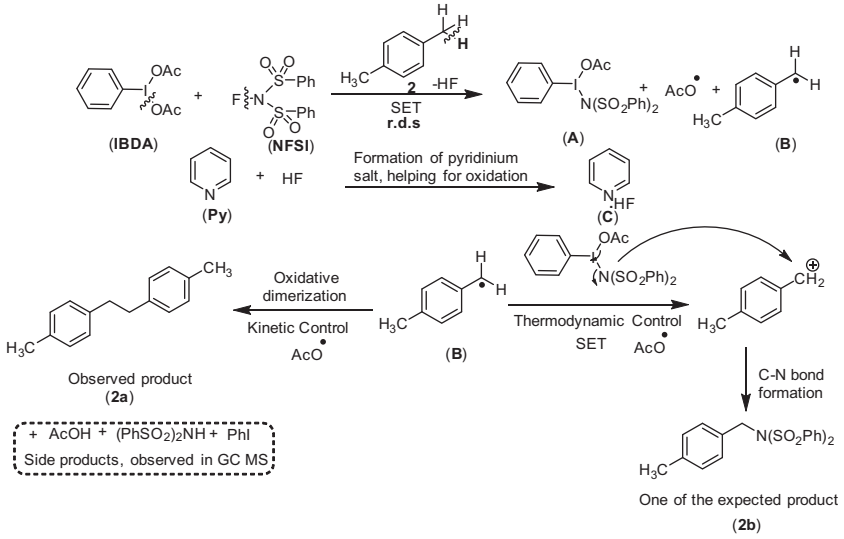


Figure 1. ORTEP diagram of 9-(9*H*-fluorene-9-yl)-9*H*-fluorene (**18a**) (50% ellipsoid).

Table 2
Substrate scope for the formation dimerized product[a,b,c]



[a] Reaction condition: substrate 30 mmol, IBDA 2 mmol, Py 1 mmol, NFSI 1 mmol, 100 °C, 15 h.
[b] Substrate 1 mmol, IBDA 2 mmol, Py 10 mmol, NFSI 1 mmol, 100 °C, 15 h.
[c] Isolated yield calculated based on the amount of NFSI used.



Scheme 3. Proposed mechanism for bibenzylic product.

dimerized products **18a**, **19a**, and **20a** respectively. Slight variation in the reaction condition was applied to solid substrates **18**–**20** wherein an excess amount of pyridine used as supportive reagent as well solvent to promote the reactions efficiently. The formation of dimerized product **18a** was further confirmed by single X-ray crystallography which is depicted in the Figure 1 (See Table 2).

Based on these observations, it is predicted that benzylic sp^3 hydrogen abstraction might be involved in the rate-limiting step (Scheme 3).[14] A radical scavenger study (see SI Table S2.9) and control experiment study (Table 1) revealed that the reagents IBDA and NFSI react together forming very active oxidative intermediate **A** in the presence of substrate **2**. The benzyl radical **B** is formed by a SET process.[14] The intermediate **B** is over oxidized to form the kinetically favored sp^3C–sp^3C homo coupling dimerize product **2a** instead of the thermodynamic controlled sp^3C–N coupling product **2b**. Perhaps, the role of pyridine in forming pyridium salt **C**, probably helps promote the oxidative homo coupling product formation and restrict acidification of the reaction medium. However, study of the mechanism of this transformation is currently underway.

In summary, a well-defined protocol has been demonstrated for the effective synthesis of the homo coupling reactions of toluene derivatives, in the presence of IBDA, NFSI, and Py reagents. The oxidation of toluene derivatives resulted in moderate to good yields of the corresponding dibenzylic products. Functional groups on the aromatic ring such as *t*-butyl, methoxy, and diphenyl methane groups tolerated well under the reaction conditions. Attributes of this new methodology are in overcoming the use of toxic metal catalyst and lachrymatory benzylic halide substrates which usually used to furnish sp^3C–sp^3C homo coupled dibenzylic products. The present protocol is metal free, atom economic, and environmentally friendly compared to metal catalyzed reactions. Potential applications of these highly efficient homo coupling reactions in material synthesis are being explored in industries.

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Supplementary data

Supplementary data (optimization details, reaction procedure, characterization data and ^1H, ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.092.

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