ORGANIC LETTERS

2012
Vol. 14, No. 23
5864–5867

Intramolecular Dehydrogenative Coupling of sp^2 C−H and sp^3 C−H Bonds: An Expeditious Route to 2-Oxindoles

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Received October 8, 2012

ABSTRACT

An intramolecular-dehydrogenative-coupling (IDC) using "transition-metal-free" oxidation conditions has been achieved to synthesize a variety of 2-oxindoles bearing an all-carbon quaternary stereogenic center at the benzylic position. The methodology involves a one-pot C-alkylation of *β*-*N*-arylamido esters (3, 6) with alkyl halides using potassium *tert*-butoxide concomitant with a dehydrogenative coupling. A radical-mediated pathway has been tentatively proposed for the oxidative process.

Efficient strategies to convert C−H bonds directly to other functionalities remains an important goal of modern synthetic organic chemistry.[1] In this context, construction of carbon−carbon (C−C) bonds via the oxidative cross-coupling of two carbon−hydrogen (C−H) bonds has gained intense interest resulting in the development of numerous new synthetic methods.[2−4]

Recently, an intramolecular oxidative coupling (intramolecular dehydrogenative coupling, IDC) of Csp^2−H and Csp^3−H in the context of 2-oxindole synthesis was reported independently by Kundig[5] and Taylor[6] in the presence of Cu(II) complexes (Scheme 1). These pioneering efforts led to the synthesis of a wide range of 2-oxindoles[7] bearing all-carbon quaternary stereocenters at the benzylic position.[8]

(1) (a) Dyker, G., Ed. *Handbook of C−H Transformations: Applications in Organic Synthesis*; Wiley-VCH: Weinheim, 2005; Vol. 2. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540. (d) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (e) Rossi, R.; Bellina, F.; Lessi, M. *Synthesis* **2010**, 4131. (f) Scheuermann, C. J. *Chem. Asian J.* **2010**, *5*, 436. (g) You, S.-l.; Xia, J.-B. *Top. Curr. Chem.* **2010**, *292*, 165. For reviews on the ideal chemical synthesis, see: (h) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010. (i) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657. (j) Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784.

(2) For reviews describing oxidative C−C bond-forming reactions, see: (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447.

(3) For related reviews, see: (a) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632. For an account, see: (c) Li, C. -J. *Acc. Chem. Res.* **2009**, *42*, 335.

(4) For reviews on cross-dehydrogenative couplings (CDC), see: (a) Li, Z.; Bohle, D. S.; Li, C. -J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (b) Li, C. -J.; Li, Z. *Pure Appl. Chem.* **2006**, *78*, 935. (c) Yoo, W.-J.; Li, C. -J. *Top. Curr. Chem.* **2010**, *292*, 281. (d) For metal-free cross-dehydrogenative coupling, see: Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. (e) For oxidative C−N bond-forming reactions, see: Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960. (f) For in situ generated hypoiodite ions for oxidative coupling, see: Uyanik, M.; Ishihara, K. *ChemCatChem* **2012**, *4*, 177.

(5) For oxidative coupling using 2.2 equiv of $CuCl_2$, see: (a) Jia, Y. X.; Kundig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636. (b) Dey, C.; Kundig, E. P. *Chem. Commun.* **2012**, 3064.

(6) For oxidative coupling using 1.0 equiv of $Cu(OAc)_2 \cdot H_2O$, see: (a) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249. (b) Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010**, 934. (c) Franckevičius, V.; Cuthbertson, J. D.; Pickworth, M.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2011**, *13*, 4264. For coupling using catalytic amount of $Cu(OAc)_2 \cdot H_2O$, see: (d) Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446. (e) Moody, C. L.; Franckevicius, V.; Drouhin, P.; Klein, J. E. M. N.; Taylor, R. J. K. *Tetrahedron. Lett.* **2012**, *53*, 1897.

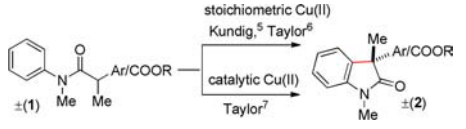
(7) For reviews on 2-oxindoles, see: (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. For asymmetric catalytic oxindole syntheses, see: (d) Zhou, F.; Liu, Y. L.; Zhou, J. A. *Adv. Synth. Catal.* **2010**, *352*, 1381. (e) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165.

(8) (a) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discov. Devel.* **2010**, *13*, 758. (b) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003. (c) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36.

10.1021/ol302767w
Published on Web 11/07/2012

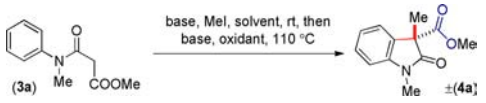
This subset of oxindoles constitutes a common structural motif in many biologically active alkaloids and is therefore an attractive synthetic target. We envisioned an IDC strategy to these oxindole motifs that involves a C-alkylation step concomitant with an oxidative construction of the C−C bond via tandem activation of two C−H bonds (Scheme 1) under transition-metal-free conditions.

Scheme 1. Previous Approaches



Because of well-established precedent in its use as an oxidant in organic chemistry,[9] we thought of using iodine as the oxidant for our 2-oxindole forming methodology. We selected *β*-*N*-arylamido ester (**3a**) and methyl iodide as the substrate and electrophile, respectively, for our initial studies (Table 1).

Table 1. Optimization of 2-Oxindole Synthesis



entry	solvent	base	alkylation (min)	oxidant	equiv	time	yield[a,b] (%)
1	DMF	K^{t}OBu	20	I_2	1.5	6 h	65
2	DMF	K^{t}OBu	20	I_2	1.2	3 h	62
3	THF	K^{t}OBu	30	I_2	1.2	3 h	85
4	xylene	K^{t}OBu	45	I_2	1.2	60 min	49[e]
5	dioxane	K^{t}OBu	20	I_2	1.2	2 h	88
6	benzene	K^{t}OBu	50	I_2	1.2	2 h	43[e]
7	toluene	K^{t}OBu	45	I_2	1.2	60 min	45[e]
8	DMSO	K^{t}OBu	20	I_2	1.5	30 min	90
9	DMSO	NaH	20	I_2	1.5	30 min	33[d]
10	DMSO	NaOMe	120	I_2	1.5	30 min	[d]
11	DMSO	K_2CO_3	60[e]				
12	DMSO	Cs_2CO_3	120	I_2	1.5	30 min	26[f]
13	DMSO	Na^{t}OBu	30	I_2	1.5	30 min[f]	
14	DMSO	K^{t}OBu	15	I_2	1.2	30 min	88
15	DMSO	K^{t}OBu	15	I_2	0.6	60 min	54
16	DMSO	K^{t}OBu	15	I_2	0.3	60 min	29
17	DMSO	K^{t}OBu	15	PIDA	1.2	30 min	82
18	DMSO	K^{t}OBu	15	DBDMH[g]	1.2	30 min	16[f]

[a] Reactions were carried out on a 0.25 mmol of **3a** with 0.275 mmol of methyl iodide in the presence of 0.30 mmol of base in 1 mL of solvent at 25 °C for alkylations and 0.30 mmol of oxidant in presence of 0.30 mmol of base under heating at 110 °C for oxidative couplings. [b] Isolated yields of **3a**. [c] Mixture of products for the rest of the mass balance. [d] C-Methylation as major product. [e] Starting material was recovered (92%). [f] Decomposition of starting materials. [g] DBDMH (1,3-dibromo-5,5-dimethylhydantoin) as oxidant.

Following extensive optimization, it was found that methylation can be carried out with K^{t}OBu (1.2 equiv) and methyl iodide followed by IDC using K^{t}OBu (1.2 equiv) and iodine (1.2−1.5 equiv) yielding 65% of the desired 2-oxindole (entries 1 and 2). Optimization focused on the solvent revealed that the desired product could be obtained in good yield i.e. 85%, 88%, and 90% in THF, dioxane, and DMSO, respectively (entries 3, 5, and 8). However, in aromatic nonpolar solvents like xylene, benzene, and toluene, poor yield of the desired products (∼43−49%; entries 4, 6, and 7) is obtained along with a multitude of byproducts.[4e] Among the different bases employed, K^{t}OBu was found to be superior over NaH, NaOMe, K_2CO_3, Cs_2CO_3, and Na^{t}OBu (entries 9−13). Oxidants including iodosobenzene diacetate (PIDA)[9e] were found to be more efficient as compared to DBDMH (entries 17 and 18) for this reaction. No products were detected in the absence of iodine, or PIDA. Our studies indicated that 1.2 equiv of iodine was sufficient in order to obtain high yields (entry 14).

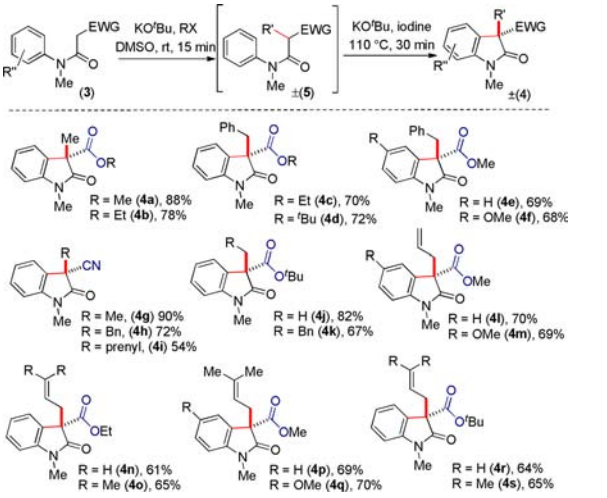
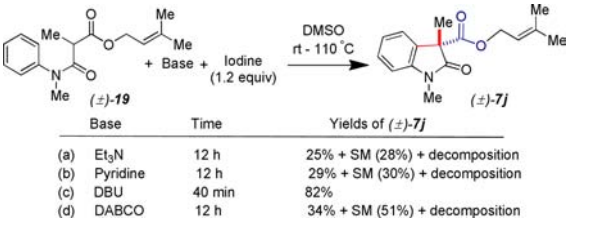


Figure 1. Substrates scope of transition-metal-free IDC.

As shown in Figure 1, our optimized conditions could be extended to various *β*-*N*-arylamido esters and nitriles (**3**) and alkyl halides.[10] A wide range of 2-oxindoles (**4a**−**s**; Figure 2) are obtained in good to excellent yields.

(9) (a) Corey, E. J.; Cheng, X. -M. In *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1995. (b) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. For an intramolecular oxidative C−N bond-forming reaction, see: (d) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187. (e) For a PIFA-mediated synthesis of spiroindoles, see: Wang, J.; Yuan, Y.; Xiong, R.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2012**, *14*, 2210.

(10) Interestingly, it was found that simple organic base can promote the IDC using 1.5 equiv of DBU and 1.2 equiv of iodine:



The prevalence of prenylated, *reverse*-prenylated, and geranylated hexahydropyrrolo[2,3-*b*]indole natural products, which exhibit a broad spectrum of biological activities drew our interest.[7,11] To construct these compounds, we envisioned a direct incorporation of the prenyl, reverse-prenyl, or geranyl group at the 3-position of 2-oxindole products via Pd-catalyzed decarboxylative allylation of related β-amidoesters such as **7**.[12] Thus, the methodology was extended to a variety of β-*N*-arylamido allyl, methallyl, dimethylallyl, and geranyl esters (**6**) (Figure 2). We were also able to directly install the geranyl group at the 3-position of the 2-oxindoles using geranyl bromide as an alkylating agent to afford products **8a**−**c** (Figure 2) in good yields.

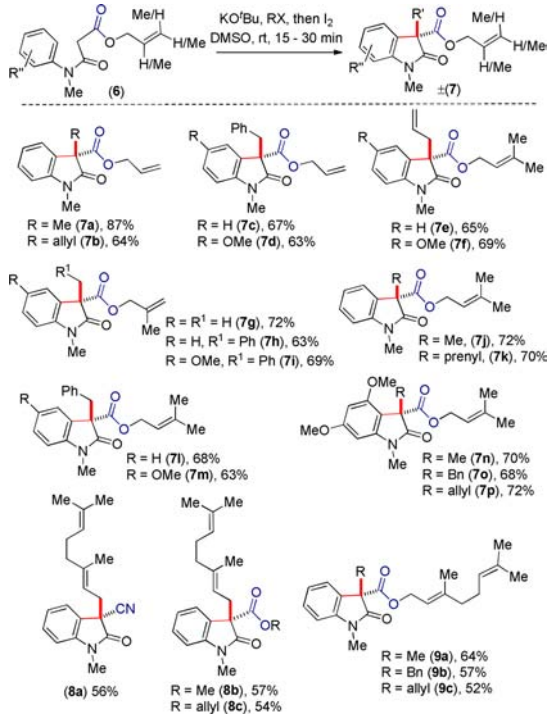
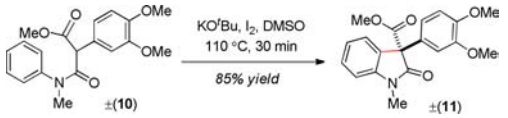


Figure 2. Substrates scope for transition-metal-free IDC.

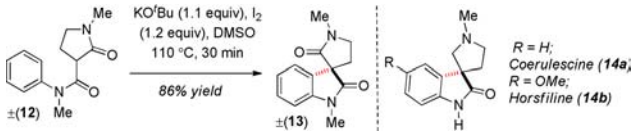
The IDC can be extended to a substrate having β-*N*-arylamido geranyl esters to afford compounds **9a**−**c** (Figure 2). These compounds may serve as the starting point of Tsuji−Trost decarboxylative geranylations/*reverse*-geranylations in order to access geranylated and *reverse*-geranylated hexahydropyrrolo[2,3-*b*]indoles.[12,13]

Scheme 2. Oxidative Coupling of Compound (±)-**10**



Abundant literature reports are there for indole natural products bearing a 3-arylated 2-oxindole moiety.[14] In a quest for such structures, compound **10** was subjected to standard reaction conditions to afford compound **11** smoothly in 85% yields (Scheme 2).

Scheme 3. Spirocyclic Products through IDC



The methodology also provides an access to spiro-fused oxindole compound **13**, resembling the core of coerulescine (**14a**) and horsfiline (**14b**) (Scheme 3).[15]

Next, we explored the possibility of carrying out direct IDC without alkylations of compounds **3a** and **15a**,**b** (Scheme 4). Initially, these attempts simply led to decomposition. However, changing the solvent to THF, we found that **3a**,**b** leads to dimerization[16] at room temperature in 5 min to provide **16a**,**b** as the sole product in 91−93% yield and in up to >20:1 dr (Scheme 4), indicating that the IDC process is probably facilitated by formation of a tertiary radical. To our delight, under the optimized conditions, β-*N*-arylamidoester **3a**,**b** undergoes one-pot dimerization (on treatment with 1.2 equiv of K^{t}OBu and I$_2$) followed by double IDC (on treatment with 1.2 equiv of K^{t}OBu and I$_2$) to afford moderate yields (up to 45% yield and 2:1 dr)

(11) (a) Jensen, B. S. *CNS Drug Rev.* **2002**, *8*, 353. (b) Oleynek, J. J.; Sedlock, D. M.; Barrow, C. J.; Appell, K. C.; Casiano, F.; Haycock, D.; Ward, S. J.; Kaplita, P.; Gillum, A. M. *J. Antibiot.* **1994**, *47*, 399. (c) Yu, Q. S.; Holloway, H. W.; Flippen-Anderson, J. L.; Hoffman, B.; Brossi, A.; Greig., N. H. *J. Med. Chem.* **2001**, *44*, 4062. (d) Yu, Q. S.; Zhu, X.; Holloway, H. W.; Whittaker, N. F.; Brossi, A.; Greig., N. H. *J. Med. Chem.* **2002**, *45*, 3684. (e) Luo, W.; Yu, Q. S.; Zhan, M.; Parrish, D.; Deschamps, J. R.; Kulkarni, S. S.; Holloway, H. W.; Alley, G. M.; Lahiri, D. K.; Brossi, A.; Greig., N. H. *J. Med. Chem.* **2005**, *48*, 986. (f) Kobayashi, J.; Ishibashi, M. *Alkaloids* **1992**, *41*, 41.

(12) For Pd-catalyzed asymmetric prenylations and geranylations, see: Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 7328.

(13) For geranylated hexahydropyrrolo[2,3-*b*]indole-based alkaloids, see: (a) Okada, M.; Sato, I.; Cho, S. J.; Dubnau, D.; Sakagami, Y. *Tetrahedron* **2006**, *62*, 8907. (b) Rochfort, S. J.; Moore, S.; Craft, C.; Martin, N. H.; Van Wagoner, R. M.; Wright, J. L. C. *J. Nat. Prod.* **2009**, *72*, 1773.

(14) (a) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961. (b) Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Bheema Rao, P.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Guiseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897. (c) Wu, Q.-X.; Crew, M. S.; Draskovic, M.; Sohn, J.; Johnson, T. A.; Tenney, K.; Valeriote, F. A.; Yao, X.-J.; Bjeldanes, L. F.; Crews, P. *Org. Lett.* **2010**, *12*, 4458. (d) Ghosh, S.; Kinthada, L. K.; Bhunia, S.; Bisai, A. *Chem. Commun.* **2012**, 10132.

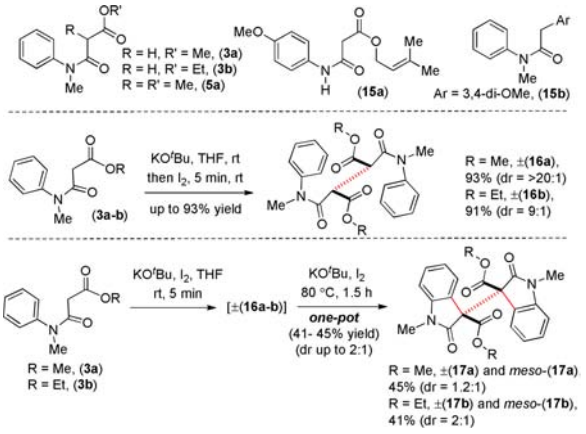
(15) (a) Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001**, *5*, 233. (b) Rosenberg, S.; Leino, R. *Synthesis* **2009**, 2651. (c) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147. (d) Deppermann, N.; Thomanek, H.; Prenzel, A. H. G. P.; Maison, W. *J. Org. Chem.* **2010**, *75*, 5994. (e) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027.

(16) For iodine in homodimerization reactions, see: (a) Hendrickson, J. B.; Göschke, R.; Rees, R. *Tetrahedron* **1964**, *20*, 565. (b) Alvarez-Ibarra, C.; Csáky, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478. (c) Kuo, W.-J.; Chen, Y.-H.; Jeng, R.-J.; Chan, L.-H.; Lin, W.-P.; Yang, Z.-M. *Tetrahedron* **2007**, *63*, 7086. (d) Li, Y.-X.; Wang, H.-X.; Ali, S.; Xia, X.-F.; Liang, Y.-M. *Chem. Commun* **2012**, 2343.

of compounds ±**17a**,**b** along with 15−18% of ±**16a**,**b** (Scheme 4). This transformation constructs three consecutive C−C bonds in one-pot operation. The X-ray crystal structure of (±)-**17b** provided unambiguous proof of this process (see, Supporting Information).

In all cases, the intramolecular dehydrogenative coupling is feasible when the reaction was carried out either after alkylation (Figures 1 and 2) or when the carbon atom α to the amides bears two substituents (Schemes 2−4). This observation led us to postulate a radical-mediated process (Scheme 5) involving a single electron transfer (SET).

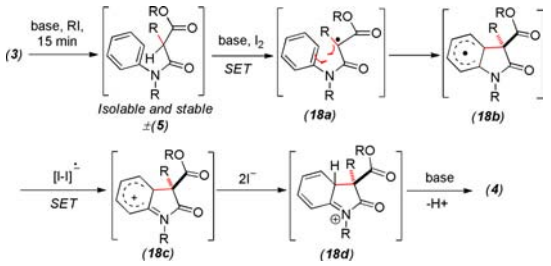
Scheme 4. Substrates Scope under IDC



An initial SET would lead to **18a**, which in turn can form an intermediate aryl radical **18b**. The aryl radical **18b** could transfer one electron to the oxidant to form intermediate aryl carbocation **18c**, which is probably stabilized by the amide nitrogen (see **18d**). Eventually, rearomatization of **18d**, in the presence of base, would afford the final oxidative coupling product. A radical mechanism has previously been proposed by Kundig et al. in their oxidative coupling process using 2.2 equiv of $CuCl_2$.[5]

Alternatively, the reaction may proceed through in situ formation of *tert*-butyl hypoiodite (*t*-BuOI), which could be responsible for the oxidative process.[17] To validate this possibility, we carried out the IDC with C-methylated *β*-amidoester **5a** (Scheme 4) in the presence of freshly prepared *t*-BuOI.[17,18] We found that **5a** underwent a smooth IDC in presence of 1.2 equiv of K^{t}OBu followed by treatment with 1.2 equiv of *t*-BuOI to afford product **4a** in 62% yield, which further supports our hypothesis of radical-mediated pathway (see the Supporting Information for details).[18] Noticeably, the IDC can be carried out in presence of stoichiometric $Mn(OAc)_3$ to afford 69% yield of **4a**.[19,20] It is interesting to observe that, the iodinating agents such as NIS and ICl also afforded IDC products in 72%, and 69% yields, respectively, without the formation of C-iodinated product.[21]

Scheme 5. Plausible Mechanism of Transition-Metal-Free IDC



Ultimately, a few substrates were tested under well-known decarboxylative allylation. Oxidative coupling products (**7j**) with dimethylallyl esters underwent smooth decarboxylative prenylation leading to the C-prenylated and C-reverse-prenylated structures in a moderate 2:1 dr (see the Supporting Information for details). These motifs are common in many hexahydropyrrolo[2,3-*b*]indole-based alkaloids.[12]

In conclusion, we report a transition-metal-free intramolecular dehydrogenative coupling (IDC) for the synthesis of a variety of 2-oxindoles bearing an all-carbon quaternary stereocenter at the pseudobenzylic position. The strategy involves a facile one-pot C-alkylation concomitant with oxidative coupling in the presence of stoichiometric I_2. Preliminary results suggest that a radical process (SET) might be involved in the oxidation process. Further exploration of this strategy as well as its application toward the synthesis of complex indole alkaloids is currently underway.

Acknowledgment. We are grateful to Prof. Richmond Sarpong, UC Berkeley, for pertinent discussions and valuable inputs. A.B. sincerely thanks Prof. Vinod K. Singh, Director, IISER Bhopal, for research facilities. Our sincere thanks to Dr. Sanjit Konar, Assistant Professor of Chemistry, IISER Bhopal, for assistance with X-ray crystallography. Financial support from the DAE (BRNS), CSIR, and DST, Government of India, is gratefully acknowledged. S.G., S.D., B.N.K., S.B., and A.A. thank the CSIR, New Delhi, for doctoral fellowships.

Supporting Information Available. General experimental procedures; characterization data including ^1H and ^{13}C NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For *tert*-butyl hypoiodite mediated radical reactions, see: (a) Akhtar, M.; Barton, D. H. R. *J. Am. Chem. Soc.* **1964**, *86*, 1528. (b) Montoro, R.; Wirth, T. *Org. Lett.* **2003**, *5*, 4729.

(18) We sincerely thank the reviewers for their valuable suggestions to validate the mechanistic details.

(19) Our observation of the formation of IDC product using $Mn(OAc)_3$ further supports our hypothesis of a radical-mediated pathway.

(20) For a review on Mn(III)-mediated radical processes, see: Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519 and references cited therein.

(21) A trial to synthesize C-iodinated product using NIS (*N*-iodosuccinimide) or ICl after one-pot methylation simply afforded IDC as the sole product. Similar results were also obtained from **5a** upon treatment with K^{t}OBu and NIS or ICl (see the Supporting Information for details).[18]

The authors declare no competing financial interest.