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DDQ-mediated Direct Intramolecular-Dehydrogenative-Coupling (IDC): Expeditious Approach to the Tetracyclic Core of Ergot Alkaloids‡

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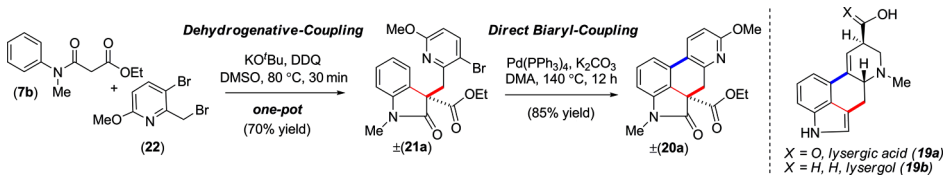
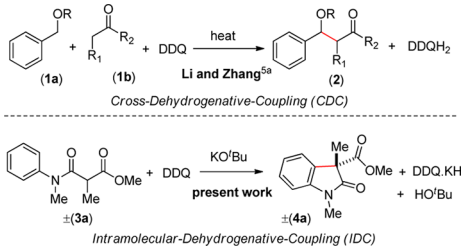
ABSTRACT



An efficient route to 2-oxindoles bearing an all-carbon quaternary center at the pseudobenzylic position has been developed via a DDQ-mediated Intramolecular-Dehydrogenative-Coupling (IDC). The methodology involves a one-pot C-alkylation of β-*N*-arylamido esters (7) concomitant with dehydrogenative-coupling in the presence of stoichiometric amount of DDQ. A tentative mechanistic route has been proposed for the oxidative coupling. The methodology provides a two-step entry to the ergoline structure of ergot alkaloids.

Direct C–H functionalization through oxidative coupling between two C–H bonds[1] offers a unique opportunity to access molecules of great synthetic interest from readily available starting materials.[2] Classically, this method involves one or two metal catalysts together with an oxidizing agent which can serve as a hydrogen acceptor.[3] Despite several advantages associated with these strategies, few challenges such as highly efficient and selective dehydrogenative-coupling utilizing two different hydrocarbons as reagents under metal-free conditions still remains to be addressed. Toward this end, on the basis of the well-established studies on various oxidations using DDQ,[4] Li and co-workers demonstrated a Cross-Dehydrogenative-Coupling (CDC)[5a] of benzyl ethers (**1a**) with unmodified ketones (**1b**) (Scheme 1) utilizing two C(sp^3)-H bonds.[5]

Scheme 1. DDQ-mediated Oxidative C–C Bond Formation



2-Oxindoles containing an all carbon quaternary center at the pseudobenzylic position constitute a common structural motif in many biologically active natural products and have become an attractive and challenging synthetic target.[6] Recently, Kündig,[7] Taylor,[8] and we[9a] have developed

‡ Dedicated to Professor Dr. Dr. h. c. Lutz F. Tietze.

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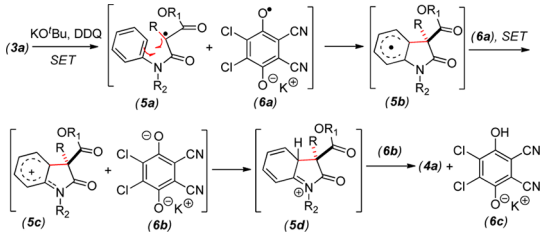
Intramolecular-Dehydrogenative-Coupling (IDC) reactions by utilizing the C(sp^2)-H bond with a C(sp^3)-H bond. Herein, we envisioned a DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) mediated direct C−H functionalization of *β*-*N*-arylamido ester (**3a**) to carry out an IDC of a C(sp^2)-H bond ortho to the *N*-alkylanilides with an internal C(sp^3)-H bond of active methine (**3a**) without using any metal based oxidant.

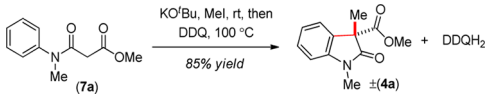
Employing DDQ-mediated strategy of oxidative coupling,[10] we set forth to investigate the possibility of an IDC to transform *β*-*N*-arylamido ester of the type **3a** into **4a** (Scheme 1). Mechanistically, a single electron transfer (SET) from the anion (prepared *in situ* from **3a** by the treatment of KO^{t}Bu) to DDQ may generate a K^+.DDQ radical (**6a**) and a radical **5a** (Scheme 2), which could in turn form an intermediate aryl radical **5b**. The latter, following another SET to **6a** could form K^+.DDQ anion (**6b**) and an intermediate aryl carbocation **5c**, which can be stabilized by amide nitrogen (see **5d**). Eventually, abstraction of a α-hydrogen from the iminium intermediate **5d** in the presence of **6b** with resultant rearomatization leads to the desired oxidative coupling product (**4a**) and K^+ of *p*-quinol derivative **6c**.

Scheme 2. Proposed Mechanism for DDQ-mediated IDC



Initially, we embarked on our studies taking C-methyl *β*-*N*-phenylamido methylester **3a** as substrate and charged it with 1.2 equiv of KO^{t}Bu at rt followed by treatment with 1.1 equiv DDQ in DMSO to afford product **4a** in 89% yield in 30 min. Similarly, in case of other oxidants such as iodosobenzene diacetate (PIDA) and [bis(trifluoroacetoxy) iodo]benzene (PIFA) which could also follow a SET mechanism, we found that the reaction worked equally efficient to afford **4a** in 80% and 86% yields, respectively [see, Supporting Information (SI) for details].[9b] No product was formed in the absence of DDQ, or PIDA, or PIFA. Since, KO^{t}Bu is also known to promote alkylation of **7a** (Scheme 3),[9a] we thought to carry out a simultaneous C-alkylation of *β*-*N*-arylamido ester (**7a**) using KO^{t}Bu and methyl iodide accompanied with a DDQ-mediated dehydrogenative-coupling in a one-pot protocol (Scheme 3).

Scheme 3. One-pot C-alkylation and IDC Mediated by DDQ



To establish a standard reaction protocol, we selected *β*-*N*-arylamido ester (**7a**) and methyl iodide as model substrates. Exhaustive optimization studies [see, SI for details] revealed that methylation of **7a** could be done in presence of 1.2 equiv of KO^{t}Bu and 1.1 equiv of methyl iodide, concomitant with oxidative coupling using 1.2 equiv of KO^{t}Bu and 1.1 equiv of DDQ to afford the desired product in 85% yield (Scheme 3).

In order to explore the synthetic viability of this oxidative coupling, we then extended it to various *β*-*N*-arylamido esters **7** [see, SI for details] and alkyl halides. As shown in Figure 1, a wide range of 2-oxindoles (**4a**−**n**) could be obtained in good yields. Gratifyingly, *β*-*N*-arylamido esters (**7**) with different substituents including allyl, methallyl, dimethylallyl, and geranyl, tolerate the standard reaction conditions well to afford a variety of 2-oxindoles **4q**−**z** (Figure 1) in good yields. This prompted us to examine the versatility of our approach by extending it to substrates like **8a**, which in turn provides an entry to spiro-fused 2-oxindoles **9** in 72% yield. The essence of spiro-fused 2-oxindole is evident from a range of natural products including coerulescine (**10a**) and horsfiline (**10b**) (Scheme 4).[11]

Under optimized conditions, a few more substrates have also been examined as shown in Figure 2. We observed that compounds **7a** and **11a** were not suitable for IDC and simply led to the decomposition, probably indicating the involvement of tertiary radical in the oxidative coupling process. Unprotected amides such as **8b** and **11b** were also leading to multiple spots on TLC. We speculate that this might be due to the involvement of competitive reactions of nitrogen and carbon centered radical species.[12]

The subset of 2-oxindoles constitutes a common structural motif in many biologically active alkaloids and therefore has gained significant attention from synthetic community. A wide range of hexahydropyrroloindolines

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(11) (a) Deppermann, N.; Thomanek, H.; Prenzel, A. H. G. P.; Maison, W. *J. Org. Chem.* **2010**, *75*, 5994. (b) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027.

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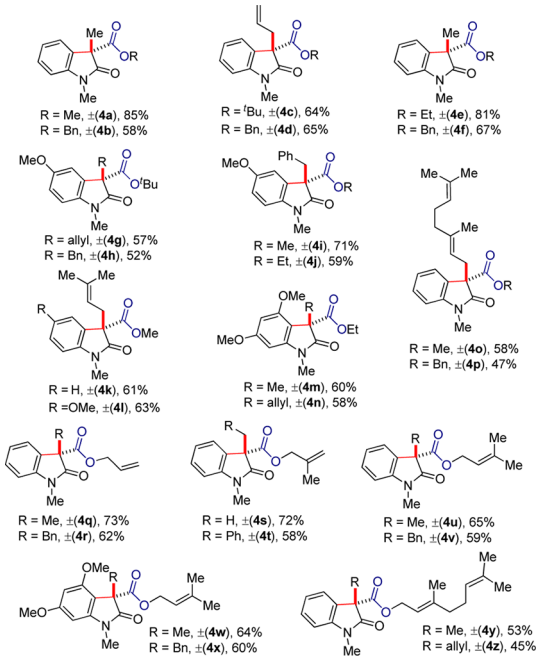
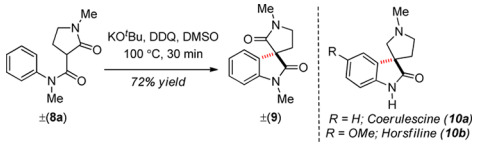


Figure 1. Substrate scope of DDQ-mediated IDC. The standard condition: reactions were carried out on a 1.0 mmol of **7** with 1.1 mmol of alkyl halide in the presence of 1.2 mmol of KO^{t}Bu in 3 mL of DMSO at 25 °C for alkylations and 1.1 mmol of DDQ in presence of 1.2 mmol of KO^{t}Bu under heating at 100 °C for oxidative couplings.

Scheme 4. Synthesis of Spiro 2-Oxindole by IDC



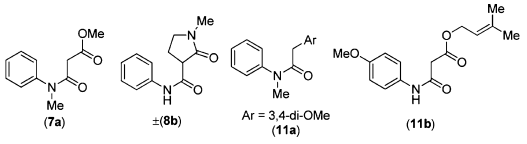


Figure 2. Substrate scope using different β-arylamidoesters.

(Figure 3) sharing a substituted prenyl functionality at C(3a), such as selaginellic acid (**12a**), *N*-selaginelloyl-L-phenylalanine (**12b**), neoselaginellic acid (**13a**), and *N*-neoselaginelloyl-L-phenylalanine (**13b**),[13] and reverse-prenyl functionality at C(3a),[14,15] as well as geranyl functionality at C(3a)[15] which exhibit a broad spectrum of biological activities, drew our interest to exploit the potential utility of 2-oxindole derivatives as precursors.

In order to achieve our target aiming synthetic approaches to these alkaloids, we further expanded the substrate scope. However, we found difficulties in one-pot alkylation followed by IDC when the reaction was conducted with iodide **15** as alkylating agent (Figure 3). Thus, it was decided to carry out the IDC with C-alkylated starting materials ±**16a**–**c**. Notably, we could synthesize IDC products ±**17a**–**b** and ±**18** in 62–64% yields from ±**16a**–**c** (Figure 3).[16] We believe that these compounds have potential for the regioselective and enantioselective Tsuji-Trost decarboxylative prenylation/reverse-prenylation, geranylation/reverse-geranylation in the presence of suitable chiral Pd(0) complexes.[17] Especially compound ±**17b** could be a potential intermediate for the total synthesis of **12a**–**b** and **13a**–**b** via enantioselective decarboxylative prenylation reaction.

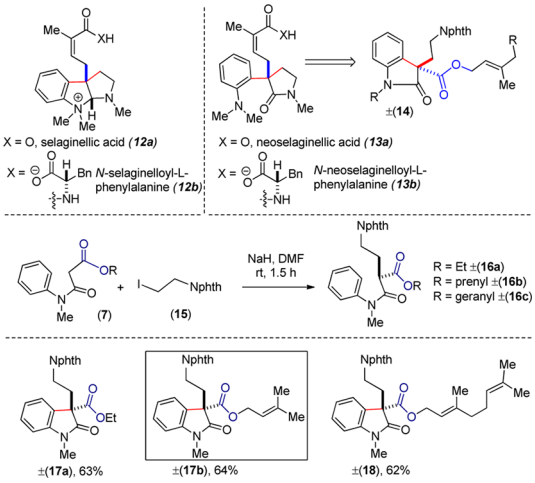


Figure 3. Potential utility of 2-oxindoles.

In addition, fascinated by their striking polycyclic molecular architectures and wide spectrum of physiological activities, we targeted to synthesize tetracyclic ergoline structure (**20**) of the ergot alkaloids (Figure 4), such as lysergic acid (**19a**), lysergol (**19b**), ergometrine (**19c**) and ergocristam (**19d**).[18] We reasoned that the tetracyclic core

(14) (a) Williams, R. M.; Sanz-Cervera, J. F.; Sancenón, F.; Marco, J. A.; Halligan, K. *J. Am. Chem. Soc.* **1998**, *120*, 1090. (b) Finefield, J. M.; Frisvad, J. C.; Sherman, D. H.; Williams, R. M. *J. Nat. Prod.* **2012**, *75*, 812 and references therein.

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(16) One-pot alkylation of β-*N*-arylamido esters **7** with **15** in presence of KO^{t}Bu were found inefficient. Therefore, IDC was carried out using C-alkylated ±**16a-c**.

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

(18) (a) Inuki, S.; Iwata, A.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 2072. For a discussion on structure diversity, and biosynthetic gene of ergot alkaloids, see: (b) Wallwey, C.; Li, S. -M. *Chem. Soc. Rev.* **2011**, 496.

(19) For synthesis of 3-monosubstituted-2-oxindoles from IDC product of the type ±**4**, see: Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010**, 934.

similar to that of tetracyclic 2-oxindoles **20** could serve as an advanced intermediate[19] to access various structures of ergot alkaloids with a unified strategy. Compound **20** in turn could be accessed from 2-oxindole **21** via a direct biaryl coupling.

Remarkably, 2-bromo-pseudo benzylbromides also appeared to be good candidates for an electrophilic partner in a one-pot C-alkylation. A variety of 2-oxindoles (**21a** and **23a**−**c**),[20] having suitable bromo functionality for biaryl-coupling, could be easily accessed in high yields thus highlighting the usefulness of our methodology (Figure 4).

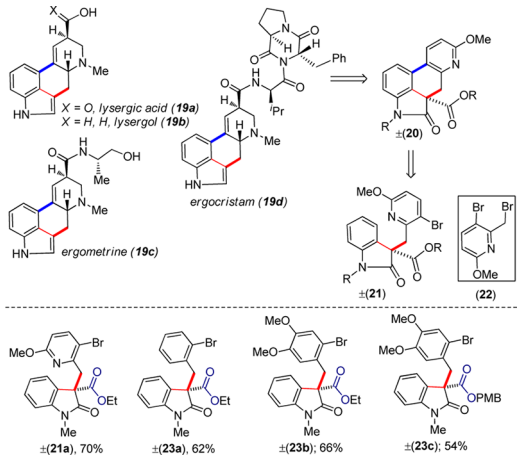
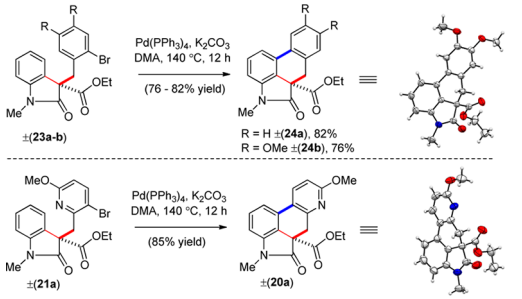


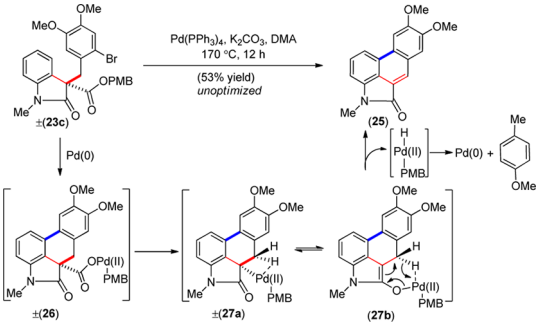
Figure 4. Further utility of 2-oxindoles.

With a synthetically viable route to the 2-oxindoles in hand, we were inclined to synthesize the advanced intermediate **20** featuring a pyridine annulated tetracyclic 2-oxindole. All efforts to optimize the biaryl-coupling of **23a** as a model substrate to afford **24a** using KO^{t}Bu promoted homolytic aromatic substitution (HAS)[21] led to multitude of products. However, on subjecting **23a** to a Pd(0)-catalyzed direct arylations,[22] we found that the direct arylation product **24a** can be achieved in 82% yield (Scheme 5). Under optimized conditions, **23b** and **21a** also afforded the expected biaryl-coupling products without event. The X-ray crystal structures of **24b** and **20a** unambiguously proved the formation of ergoline type skeletons. Interestingly, we found that if the reaction was carried out at 170 °C, compound ±**23c** afforded directly to the olefin **25** in 53% unoptimized yield in one-pot sequence (Scheme 6), which represents an unprecedented one-pot Pd(0)-catalyzed direct biaryl-coupling, activation of *p*-methoxybenzyl (PMB) ester followed by a decarboxylative depalladation reaction presumably through the intermediacy of ±**26** and **27a**−**b**.

Scheme 5. Synthesis of Tetracyclic Core (X-ray of **24b** and **20a**)



Scheme 6. One-pot Synthesis of Tetracyclic 2-Oxindole **25**



In summary, we report an efficient DDQ-mediated 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 DDQ. This study not only offers a vital method for the oxidative C−C bond construction but also clearly demonstrates the potential of the modular 2-oxindole scaffolds. Further exploration of this strategy as well as its application in the synthesis of complex alkaloids is currently under active investigation in our laboratory.

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Supporting Information Available. General experimental procedures and characterization of all new compounds, including CIF files of compounds **24b** and **20a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(20) For use of 5-bromo-2-methoxy-6-picolylbromide **22**, see: Bisai, V.; Sarpong, R. *Org. Lett.* **2010**, *12*, 2551.

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