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Cu-catalyzed oxidative coupling of alkylarenes with tertiary C(sp^3)–H bonds *via* C–H activation

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An efficient Cu-catalyzed cross-dehydrogenative coupling (CDC) of oxindoles, fluorenes and xanthenes with alkylarenes containing primary and secondary benzylic C–H bonds was developed. The method is capable of forming highly hindered bonds (adjacent quaternary/ternary centers) and permits direct access to highly functionalized oxindoles, fluorenes and xanthenes with good functional group compatibility. This oxidative protocol is operationally simple and the synthetic utility was demonstrated by a gram-scale reaction while maintaining the yield. Further synthetic transformations of this product proceeded in high yield. Based on observations from a radical capture experiment, the transformation is proposed to proceed *via* a radical process.

Introduction

Cross-dehydrogenative coupling (CDC) is a particularly atom-economic and sustainable process to construct new C–C bonds.[1] Direct C–H functionalization provides an especially useful entry to more complex structures from commodity petroleum products including toluene and xylenes.[2] There has been growing interest in directly functionalizing benzylic C(sp^3)–H bonds, which circumvents pre-functionalization steps and improves overall atom economy. In this regard, metal-based (Pd,[3,4] Fe,[5] Co,[6] Ni[7]) C–H activation strategies have been developed to directly functionalize benzylic C–H bonds. The discovery of the Kharasch–Sosnovsky reaction in 1958[8] highlighted the potential of low-cost and abundant copper salts in C–H functionalization and there has been a resurgence in examining the reactivity of these systems. Examples include copper catalyzed couplings of benzylic C(sp^3)–H with trimethylcyanide,[9] *N*-pyrimidylindoles,[10] arenes,[11] arylboronates,[12] amides,[13] 1,3-dicarbonyls,[14] and *N*-oxides.[15] In addition, photo-catalytic C–H functionalization of toluene and its derivatives is emerging as a sustainable process.[16] However, existing methods have intrinsic drawbacks such as requiring significant acidification of the benzylic position through electron-withdrawing groups or the coupling partner is restricted to C–X (X = O, N, S *etc.*) or C(sp^2)–H bonds. To the best of our knowledge, the CDC of C(sp^3)–H systems with C(sp^3)–H bond of toluene derivatives remains limited.[3,17]

Oxindoles with 3,3′disubstitution are found in an array of natural products and bioactive compounds.[18] A number of synthetic methods have been developed to generate this structural type with much attention directed toward formation of the tetrasubstituted C3-center. The C3 nitration,[19] hydroxylation,[20] arylation,[21] chlorination,[22] peroxidation,[23] alkynylation,[24] olefination[25] and sulfonation[26] of 3-substituted oxindoles have been reported. For example, redox neutral Pd-catalyzed allylation of oxindoles has been achieved using alkynes and enynes.[27] A corresponding oxidative method with a palladium NHC catalyst has been reported used allylbenzene as allylic alkyl donor (Scheme 1a).[28] However, reaction of oxindoles or fluorenes with toluene derivatives especially secondary benzylic derivatives cannot be achieved by these methods nor by simple alkylation with secondary halides. Recently, our group discovered a Pd catalyzed oxidative coupling of oxindoles with toluene.[3] However, halogenated toluene and 3-alkyl substituted oxindoles were not applicable with this Pd catalytic system (Scheme 1b). Inspired by precedent from the Kharasch–Sosnovsky reaction and our previous work on oxidative coupling,[29] we disclose herein the discovery of a Cu catalyzed benzylic C(sp^3)–H bond activation that accomplishes CDC with oxindoles, fluorenes, and xanthenes (Scheme 1c).

Results and discussion

Our studies commenced using 1-methyl-3-phenylindolin-2-one (**1a**) and toluene (**2a**) (Table 1). Treatment **1a** with 10 mol% of CuI, 20 mol% of 1,10-phenanthroline (**L1**), and *t*-BuOO*t*-Bu in

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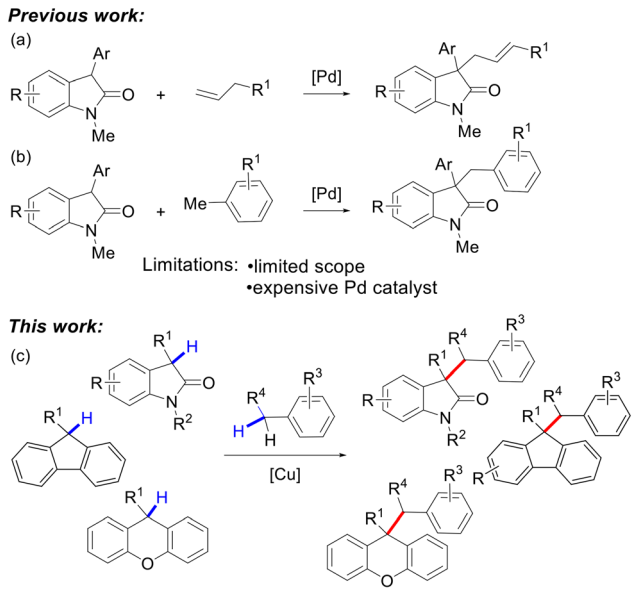
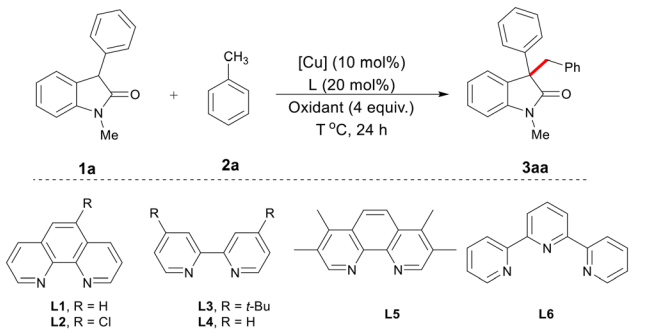


Scheme 1 Transition metal catalysed oxidative alkylation of 3-substituted oxindoles.

toluene (**2a**, 1.5 mL) at 100 °C for 24 h led to product **3aa** in 52% yield (Table 1, entry 1). Subsequently, different copper salts, such as CuCl, CuBr·DMS, $Cu(OTf)_2$, $Cu(OAc)_2$, $CuBr_2$ and CuBr (entries 2–7), were examined. CuBr was found to afford **3aa** in higher yield (62%). Examination of alternate oxidants (entries 8–13) did not lead to an improvement in yield. Assessment of different ligands (entries 14–18) revealed that the initial ligand **L1** provided the best results. Higher temperatures (135 °C, entries 19 and 20) enhanced the product of **3aa** (83%). Finally, controls showed that the yield of **3aa** decreased significantly in the absence of copper catalyst or ligand (entries 21 and 22).

With the optimized conditions, the reactions of toluene with a series of oxindoles was examined (Table 2). When the C3-aryl contained electron-donating or electron-withdrawing substituents (**3ba**, **3ca**, **3ea**, **3fa**, **3ha**), good reactivity was observed. With oxindoles bearing an electron-donating (Me) or electron-withdrawing substituent (Cl) in the 5- and 6-positions, respectively, the corresponding products were achieved in high yields (**3da**, **3ga**). The naphthyl group in the C3-position was also tolerated, affording **3ia** in 55% yield. Replacement of the C3-aryl group with an alkyl group (3-methyl oxindole) led to successful benzylation with toluene (**3ja**), albeit in lower yield (30%). It should be noted that this substrate did not react with our previous Pd system.[3] The *N*-benzyl oxindole congener was equally reactive as the *N*-methyl (**3ka** *vs.* **3aa**). However, the *N*-Boc version was less reactive (**3la**, 22%) indicating that the acidity of the oxindole C–H bond was not the primary contributor to reactivity. Consistent with this trend, an electron-rich *N*-pyrrole substituent at the C3-position of the oxindole also gave rise to high yields with toluene (**3ma**, **3na**, **3oa**).

Table 1 Reaction development[a]

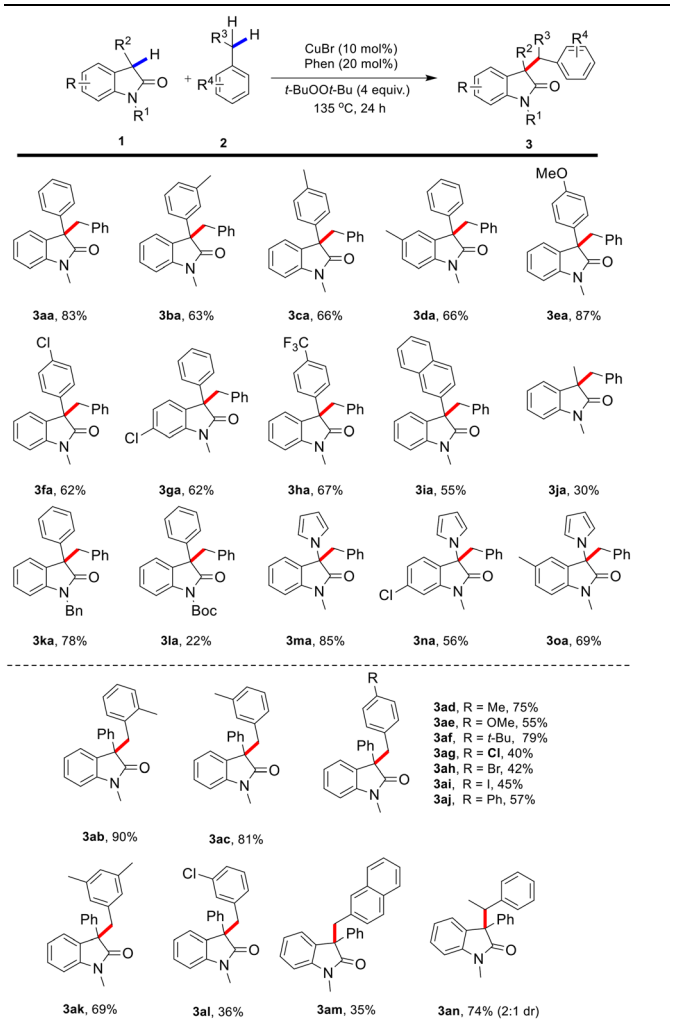


Entry	Catalyst	Ligand	Oxidant	*T* (°C)	Yield (%)
1	CuI	**L1**	*t*-BuOO*t*-Bu	100	52
2	CuCl	**L1**	*t*-BuOO*t*-Bu	100	51
3	CuBr·DMS	**L1**	*t*-BuOO*t*-Bu	100	27
4	$Cu(OTf)_2$	**L1**	*t*-BuOO*t*-Bu	100	23
5	$Cu(OAc)_2$	**L1**	*t*-BuOO*t*-Bu	100	31
6	$CuBr_2$	**L1**	*t*-BuOO*t*-Bu	100	30
7	CuBr	**L1**	*t*-BuOO*t*-Bu	100	62
8	CuBr	**L1**	*t*-BuOOH	100	0
9	CuBr	**L1**	BzOOBz	100	36
10	CuBr	**L1**	CHP[b]	100	0
11	CuBr	**L1**	NFSI[b]	100	0
12	CuBr	**L1**	*t*-BuOOBz	100	56
13	CuBr	**L1**	$K_2S_2O_8$	100	0
14	CuBr	**L2**	*t*-BuOO*t*-Bu	100	27
15	CuBr	**L3**	*t*-BuOO*t*-Bu	100	34
16	CuBr	**L5**	*t*-BuOO*t*-Bu	100	43
17	CuBr	**L5**	*t*-BuOO*t*-Bu	100	44
18	CuBr	**L6**	*t*-BuOO*t*-Bu	100	50[c]
19	CuBr	**L1**	*t*-BuOO*t*-Bu	120	67[c]
20	CuBr	**L1**	*t*-BuOO*t*-Bu	135	83[c]
21	—	**L1**	*t*-BuOO*t*-Bu	135	6
22	CuBr	—	*t*-BuOO*t*-Bu	135	30

[a] Reaction conditions: **1a** (0.15 mmol) and **2a** (0.1 M), at the indicated temperature for 24 h under argon. Yields determined by ^{1}H NMR spectroscopic analysis of the mixture relative to 4,4′-di-*tert*-butylbiphenyl as an internal standard. [b] CHP = cumene hydroperoxide, NFSI = *N*-fluorobenzenesulfonimide. [c] Isolated yields.

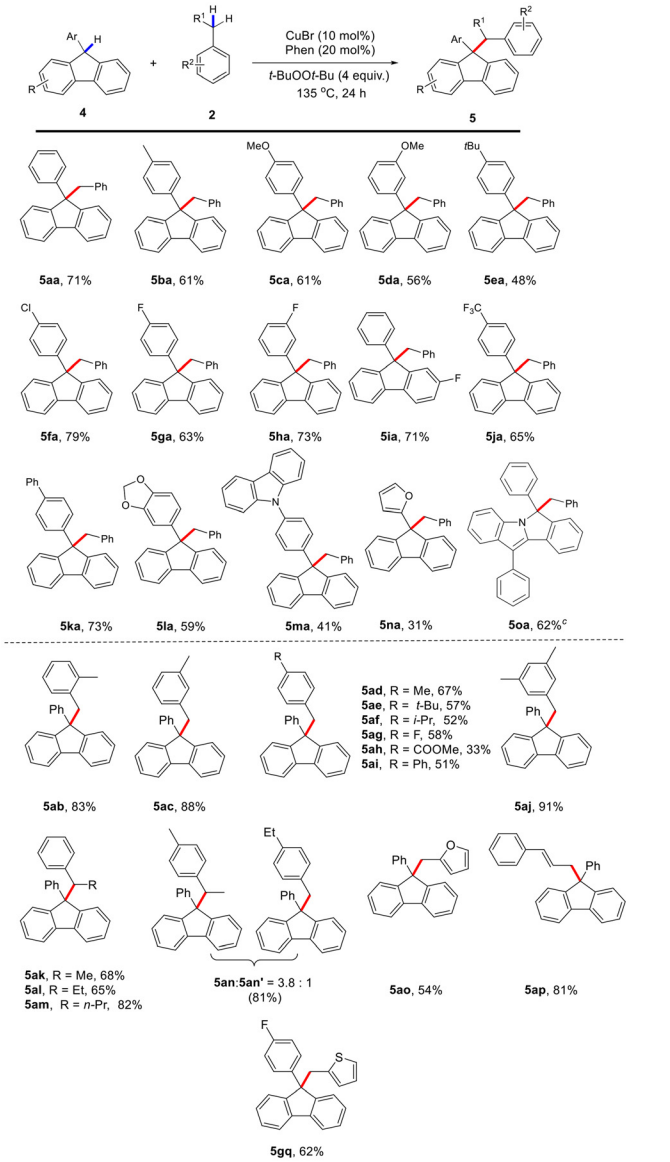
The scope of the benzylic hydrocarbons was next examined with **1a** (Table 2). Various xylenes (*p*-, *m*-, *o*-) were effective giving high yields of the corresponding products (75–90%). Alkylarenes bearing an electron-donating methoxy or *tert*-butyl group afforded products **3ae** and **3af** in 55% and 79% yields, respectively. Even substrates such as mesitylene, halo-substituted toluene, which were not reactive in the previous Pd system,[3] smoothly coupled with **1a** to afford corresponding products in 36–69% yields (**3ag–ai**, **3ak**, **3al**), reflecting the high potential for further synthetic transformations. Further, 4-methybiphenyl and 2-methyl-naphthalene underwent reaction to give the target products **3aj** and **3am** in 57% and 35% yields, respectively. As for ethylbenzene, instead of the activation in the terminal CH_3 position,[3] the benzylic position was activated in this protocol to afford oxindole **3an** with adjacent quaternary and tertiary centers in 74% yield. The potential to generate highly hindered arrays is particularly notable.

Table 2 Cu-catalyzed benzylation of oxindoles[a,b]



[a] Reaction conditions: **1** (0.15 mmol), CuBr (10 mol%), phenanthroline (20 mmol%), *t*-BuOO*t*-Bu (4 equiv.) in tolyl analogs **2** (1.5 mL, 0.1 M), 135 °C, 24 h. [b] Isolated yield.

Table 3 Cu-catalyzed benzylation of flourenes[a,b]



[a] Reaction conditions: **4** (0.15 mmol), CuBr (10 mol%), phenanthroline (20 mmol%), *t*-BuOO*t*-Bu (4 equiv.) in tolyl analogs **2** (1.5 mL, 0.1 M), 135 °C, 24 h. [b] Isolated yield. [c] Run under 105 °C for 20 h.

Since efficient methods to prepare of highly substituted fluorenes are limited, we next examined whether fluorenyl substrates would be effective in these transformations.

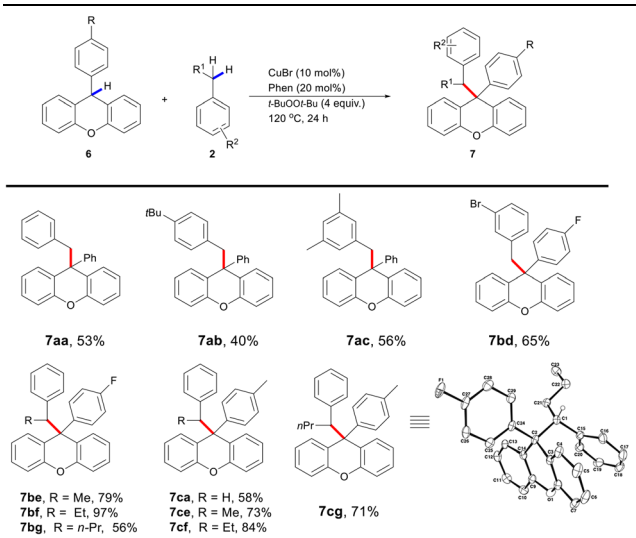
Fluorenes are widely used in pharmaceuticals, dyes, organic light emitting diodes, polymer light emitting diodes, solar cells, fuel cells, *etc*.[30] With our previously reported Pd system,[3] over 95% of fluorene **4a** was unreacted when subjected toluene. However, fluorenes (**4**) underwent surprisingly robust reaction with a series of alkylbenzenes (**2**) under the present copper catalyzed conditions (Table 3). Little difference was observed between substrates with electron-neutral (**5aa**), electron-donating (**5ba–5ea**), and electron-withdrawing (**5fa–5ja**) groups regardless of their position. Notably, fluorene derivatives containing additional conjugation (**4k**) or heterocycle groups (**4l–4n**) also provided the corresponding products in good yields (**5ka–5na**). Moreover, this CDC system even worked well with a heterocyclic isoindoline analog (**5oa**).

Subsequently, a variety of benzylic hydrocarbons was investigated under the optimized conditions with fluorenes (Table 3, bottom). Methylarenes bearing both electron-donating and electron-withdrawing substituents were successfully incorporated in similar yields to afford the corresponding products (**5ab–5ai**). The results with the electron-withdrawing substituents (**5ag–5ah**) is notable as such systems fail with other protocols.[3] Of particular note, mesitylene only gave the monobenzylation product in 91% yield (**5aj**). When the secondary benzylic versions of **2** were explored, products arising from coupling at the benzylic position were obtained in 65–82% yields (**5ak–5am**), which is quite different from our developed

Pd system.[3] With *p*-ethyltoluene, inseparable regioisomers (**5an**, **5an′**) were obtained in 81% overall yield. The predominance of reaction at the more hindered secondary *vs.* the primary position in this substrate foreshadows a radical mechanism where the bond strength of the substrate determines the relative reactivity. Remarkably, methylheteroarenes including 2-methylfuran, 2-methylthiophene also performed well under the optimized conditions, providing the desired products in 54% and 62% yields, respectively (**5ao**, **5gq**). Another highlight is the efficiency of the Cu catalytic system in allylic C–H activation, delivering **5ap** from allylbenzene in 81% yield without observation of any branched product which likely reflects formation of the least hindered allyl copper intermediate.

Remarkably, the benzylation process also allows 9-aryl xanthenes to serve as the cross-coupling partner; this moiety is a common skeleton in perovskite solar cells and dyes.[31] By decreasing the temperature to 120 °C with toluene, product **7aa** was obtained in 53% yield (Table 4). Three different xanthenes afforded the products in good to excellent yields (**6a**, **6b**, **6c**, 40–97%). A particularly broad range of benzylic hydrocarbons were highly effective including *para*-*tert*-butyltoluene (**7ab**, 40%), mesitylene (**7ac**, 56%), and *meta*-bromotoluene (**7bd**, 65%); the presence of bromo substituent in the latter was compatible with the reaction conditions and allows for additional future functionalization. Reactions at secondary benzylic centers were even more effective: ethylbenzene (**7be**, 79%; **7ce**, 73%), propylbenzene (**7bf**, 97%; **7cf**, 84%), butylbenzene (**7bg**, 56%; **7cg**, 71%). And **7cg** was obtained in 65% yield in a 2 mmol scale. The formation of these hindered bonds generating contiguous quaternary and tertiary centers is expected to lead to novel conformationally defined materials.

Table 4 Cu-catalyzed benzylation of xanthenes[a,b]

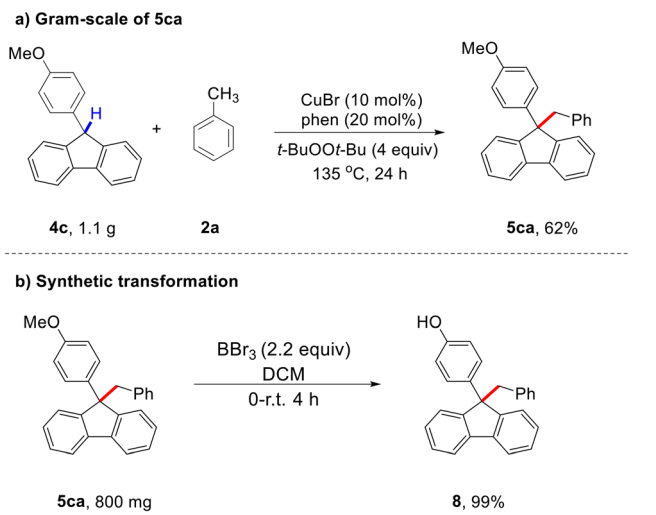


[a] Reaction conditions: **6** (0.15 mmol), CuBr (10 mol%), phenanthroline (20 mmol%), *t*-BuOO*t*-Bu (4 equiv.) in tolyl analogs **2** (1.5 mL, 0.1 M), 120 °C, 24 h. [b] Isolated yield.

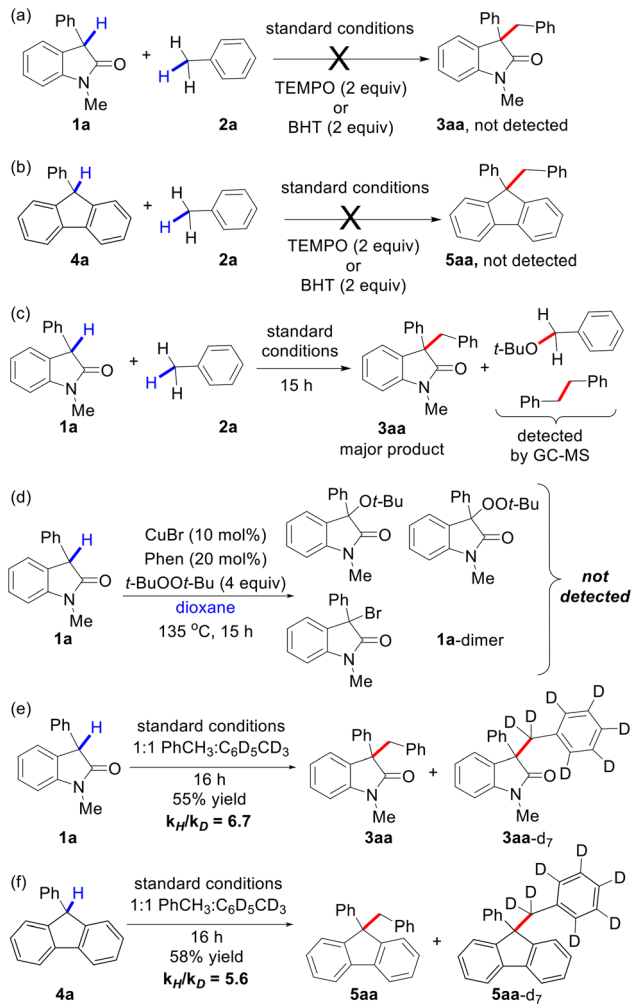
This hypothesis is supported by the X-ray crystallographic structure of **7cg** (Table 4) which shows an antiperiplanar arrangement of the xanthyl and *n*-propyl groups. This conformation persists in solution as determined from ^{1}H NMR coupling constants (see SI). Unfortunately, 1-methylindolin-2-one was not compatible under our catalytic conditions and benzylic hydrocarbons bearing electron withdrawing groups (–COOMe, –CN) failed to deliver any detectable products indicating that the current catalytic system is sensitive to the electronic and structural features of the coupling partner. When other potential coupling partners such as tetrahydrofuran, dioxane, cyclohexane were attempted with oxindole under optimized conditions, they did not give desired products. Further details regarding unsuccessful substrates are provided in the SI. Despite these limitations, this work represents a crucial contribution for copper-catalyzed oxidative coupling of alkylarenes with tertiary C(sp^3)–H Bonds, and is complementary to our previously developed Pd catalytic system.[3]

The practicality of this methodology was further demonstrated by a gram scale up. A 1.1 g scale reaction of **4c** under standard conditions afforded desired product **5ca** in 62% yield (Scheme 2a). Treatment of the obtained product **5ca** (800 mg) with BBr_3 smoothly effected demethylation to furnish fluorene **8** in 99% yield, providing a useful building block for further fluorene functionalization with reactive phenolic hydroxyl group.

To gain insight into the mechanism, additional experiments were undertaken (Scheme 3). Radical scavengers such as TEMPO or BHT (2,4-di-*tert*-butyl-4-methylphenol) completely inhibit the reaction with both the oxindole and fluorene substrates (Scheme 3a and b). GC-MS analysis of the reaction mixture after 15 h revealed the formation of two byproducts 1,2-diphenylethane and (*tert*-butoxymethyl)benzene (Scheme 3c). No radical initiated adduct was observed when reaction was conducted in dioxane instead of toluene (Scheme 3d).[32] These results imply that any stabilized oxi-



Scheme 2 Scale up reaciton and synthetic transformation.

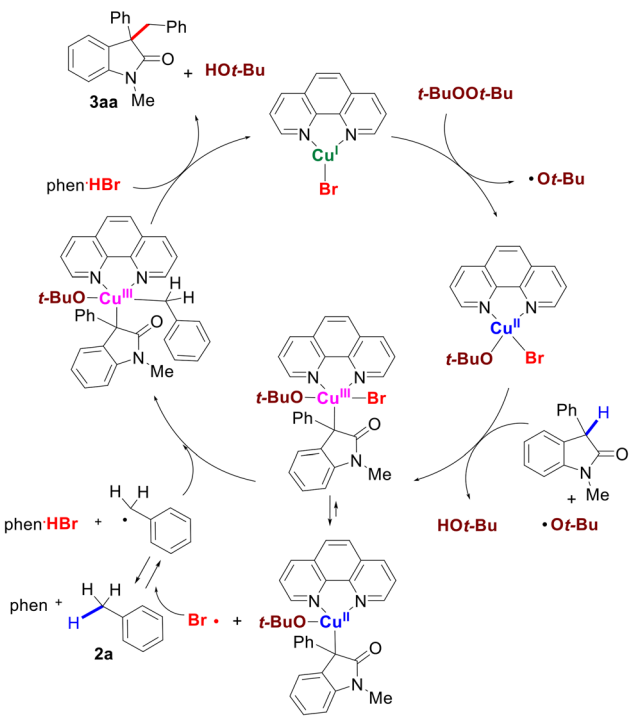


Scheme 3 Mechanistic experiments.

ndole/fluorene/xanthene radicals formed are sequestered by copper from which C–C reductive elimination is more favorable than C–O reductive elimination.

Intermolecular competing kinetic isotope effect (KIE) experiments were carried out and significant kinetic isotopic effects were observed (k_H/k_D = 6.7 for oxindole **1a**, and k_H/k_D = 5.6 for fluorene **4a**) (Scheme 3e and f). A somewhat lower KIE value (1.6) was observed in a parallel KIE experiment for the benzylation of **1a** (see SI for details). The results from these experiments suggest that C(sp^3)–H bond cleavage to form the benzylic radical is only partly rate-limiting and that another mechanistic step may also contribute to the catalytic turnover rate (*e.g.*, generation of the reactive radical *via* activation of DTBP by Cu^I or solvent cage effects that partially mask the intrinsic isotope effect in the parallel experiment).[9,33] The high reactivity of the *tert*-butoxy radical is expected to lead to no KIE, but complexation to species present or formation of less reactive radicals (*i.e.* those from 1/4/6 or bromine atom) that subsequently react with toluene would give rise to a modest parallel KIE of the magnitude seen here.[34]

From these control experiments and previous reports,[12,35] a plausible mechanism for this Cu catalyzed CDC with benzylic C(sp^3)–H is proposed in Scheme 4, with the reaction of oxindole (**1a**) and toluene (**3a**) shown as an example. At the temperatures utilized, homolysis of *t*-BuOO*t*-Bu is expected to provide *tert*-butoxyl radicals. This species would likely first react with the (phen)CuIBr to form a (phen)CuIIBr(O*t*-Bu) adduct.[36] Of the organic species, the oxindoles/fluorenes/xanthenes have the weaker bonds (≤72 kcal mol^{-1}) **3b** and would likely undergo radical abstraction first as *tert*-butoxyl radicals form. The higher yields observed with more electron rich substrates (*e.g.* **3aa** and **3ka** *vs.* **3la**) is consistent with formation of this radical species. The resultant stabilized radicals could combine with the Cu^{II} adduct which may be accompanied by bromine atom release.[37,38] Either this bromine atom or an additional *tert*-butoxyl radical could then abstract the stronger C–H bond of the alkyl arene to generate a Cu^{III} intermediate.[35] Steric hindrance would disfavor coordination of two equivalents of the oxindole/fluorene/xanthene to the copper center. If two of the oxindole/fluorene/xanthene radicals did combine, they would give rise to a dimer that would serve as a source of the respective radicals.[3] Recombination of two benzylic radicals *via* the copper center (or in solution) is expected to be less likely as the concentration of this species will be lower due to the stronger bond dissociation energy of the benzylic C–H bonds (90 kcal mol^{-1} for toluene, 78 kcal mol^{-1} for ethylbenzene),[39] but was observed to some extent (Scheme 3c). Reductive elimination from the Cu^{III} intermediate[35]is expected to be rapid giving rise to the observed adducts such as **3aa**.



Scheme 4 Proposed mechanism.

Conclusions

In conclusion, a copper-catalyzed cross-dehydrogenative coupling of oxindoles/fluorenes/xanthenes with benzylic hydrocarbons has been discovered. This discovery adds a new dimension to oxidative copper reaction by permitting the union of two sp^3 C–H centers to form highly hindered bonds. Additional highlights include straightforward construction of quaternary centers by addition of primary and secondary benzylic hydrocarbons. Considering the importance of the fluorene, oxindole and xanthene frameworks in medicinal, synthetic organic chemistry, and material science, this transformation is expected to find further applications.

Author contributions

G. H. and M. C. K. conceived of the project. G. H. and P. D. N. designed the experiments. G. H., P. D. N., and W. G. P. performed the research. G. H., P. D. N., and M. C. K. wrote the manuscript. M. C. K. Supervised the project and reviewed the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information (SI): all experimental data, procedures for data analysis, and pertinent data sets. See DOI: https://doi.org/10.1039/d6ob00723f.

CCDC 1939223 contains the supplementary crystallographic data for this paper.[40]

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