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Atom Economical Synthesis of Oxindoles by Metal-Catalyzed Intramolecular C-C Bond Formation under Solvent-Free and Aerobic Conditions

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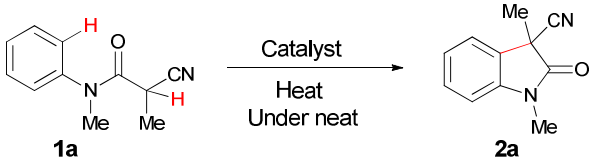
Diversely substituted oxindoles were obtained from atom economical direct C-C bond formation reactions of various substituted anilides and pyridinylamides with metal salts and oxides. The catalysts include CuO, Cu_2O, $FeCl_3$, Fe_2O_3, TiO_2, ZnO, and Ag_2O and their nanoparticles. The reaction proceeds under solvent-free and aerobic condition in excellent yields. The reaction mechanism was proved to be a single electron transfer pathway with oxygen as the re-oxidant of the metal catalysts.

Substituted oxindole scaffolds are found in many biologically active molecules including several natural products.[1] Therefore, much effort has been made to develop a more efficient method for the synthesis of the heterocyclic oxindole cores. Representative examples are Pd-catalyzed C-C bond formations with halogen substituted aromatic compounds.[2,3] All of these reactions require pre-functionalized trifluoromethanesulfonate or halogen substituted aromatic compounds for bond activation by palladium at the initiation step of the reaction with limited substrate versatility. Recently, Bolm reported transition metal free base promoted intramolecular cyclization and it also required *ortho*-halogen-activated anilides.[4] Taylor reported intramolecular C-H activation route of non-activated anilides to provide oxindoles with 5 mol % of $Cu(OAc)_2$•H_2O as a catalyst in mesitylene as a solvent at high temperature (165 ºC).[5a] Most of those previously reported methods[5] required organic solvents, extra additives, an inert atmosphere, and a limited scope of substrates. Therefore, a further extensive investigation is needed to seek more efficient catalysts under milder and environmentally benign conditions with a wider scope of substrates other than simple anilides. In this report we describe the synthesis of diverse oxindoles with small amount of nano-sized metal particles[6] as the active catalyst in solvent-free[7] and aerobic environments as a showcase of the atom economical and environmentally benign synthesis of organic molecules.

Table 1. Reaction conditions for oxindole (**2a**) synthesis from the representative substrate **1a**.



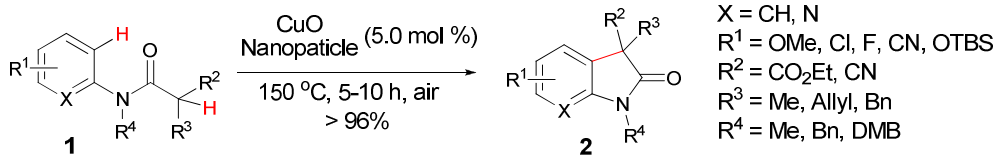
1a **2a**

Entry[a]	Catalyst[b]	Temp. (℃)	Time (h)	Yield (%)
1	$Cu(OAc)_2·H_2O$	175	8	98
2	$Cu(OAc)_2$	175	6	98
3	CuO	175	5	98
4	Cu_2O	175	5	96
5	$CuCl_2$	175	10	NR
6	$CuBr_2$	175	10	NR
7	$FeCl_3$	175	3	95
8	Fe_2O_3	175	3	98
9	$Fe(OAc)_2$	175	5	97
10	TiO_2	175	18	96
11	ZnO	175	3	98
12	Ag_2O	175	5	98
13	CuO (NP)[c]	175	16	98
14	Cu_2O (NP)	175	1	99
15	Cu_2O (NP)	150	5	98
16	Cu_2O (NP)	100	20	NR
17	Cu_2O (NP), 2 mol%	175	2	98
18	Cu_2O (NP), 1 mol%	175	6	96
19	Cu_2O (NP), Under N_2	175	12	NR
20	Cu_2O (NP) (0.5 mol%) Under O_2[d]	175	8	98
21	Cu_2O (NP), TEMPO(1.2 equiv.)[e]	175	5	NR

[a] The catalyst was added to the vial containing starting substrate **1a**. Then, the vial was heated at the specified temperature until all the stating material was consumed. [b] 5 mol % of a catalyst was used otherwise specified. [c] NP means nanoparticle. [d] Oxygen was charged prior to heating. [e] TEMPO was added prior to heating.

At first we started a metal-catalysed direct intramolecular Csp^3-H/Csp^2-H coupling reaction based on Taylor's intramolecular C-H activation route[5d] without any prerequisite functionalization of the aromatic ring (Table 1). The reaction was performed with 5 mol % of $Cu(OAc)_2•H_2O$ and its anhydrous form under solvent-free condition to yield the expected product in more than 98% yield (entries 1 and 2). In the same manner CuO and Cu_2O catalysts were as active as their acetate salts (entries 3 and 4). However, $CuCl_2$ and $CuBr_2$ did not provide the expected product at all (entries 5 and 6). Interestingly, the same halide salts of iron such as $FeCl_3$ had similar abilities to catalyze the reaction as its oxide and acetate salt such as Fe_2O_3 and $Fe(OAc)_2$ (entries 7, 8 and 9). The transition metal oxides including TiO_2, ZnO and Ag_2O were efficient catalysts to yield the expected oxindole in high yield (entries 10, 11 and 12). Then we turned our attention to the nanoparticles of oxide and expected higher catalytic activity than its bulk material. Cuprous oxide (Cu_2O) nanoparticles (NP) were better than cupric oxide (CuO) which is highly active and expected to carry the reaction within an hour at 175 ºC (entries 13 and 14). Therefore, increasing the surface area of the catalyst also increases the catalytic activity of Cu_2O. When we carried out the reaction at lower temperature at 150 ºC the reaction was a bit sluggish (entry 15). The reaction at 100 ºC with the same amount of Cu_2O (NP) catalyst did not produce the expected product at all (entry 16) even after 20 hrs. The reaction still worked with smaller amounts of the catalyst i.e. 2 and 1 mol % Cu_2O (NP) in a bit longer reaction time at 2 and 6 hrs (entries 17 and 18). Since we set up the reaction with 5 mol % of Cu_2O (NP) catalyst, we evaluated the efficacy of the catalyst with the known substrates and investigated expanding the reaction scope with more diverse substrates.

The substrates (**1b**) bearing carboxylate instead of nitrile in **1a** was used to yield the expected product in almost quantitative yield up to 1.0 g scale (yield: 94%). Other oxindoles **2c** and **2d** with benzyl and allyl substituents were also obtained without any difficulty. We also carried out the reactions from the starting materials that originated from substituted aniline. 3-Methylanilide (**1e**) yielded the expected product in 97% yield as a non-separable region-isomeric mixture of **2e** and **2e′** with the ratio of 1:2 which was measured by ^{1}H NMR integration. The reactions with anilides generated from *p*-chloro, *o*-fluoro and *p*-methoxyanilines yielded the expected oxindole products (**2f**, **2g**, and **2h**) in almost quantitative yield. Particularly, the product **2i** with allyl substituent at C3 is a valuable synthetic precursor for the preparation of anticancer analgesic alkaloid (±)-horsfiline.[8] However, with the starting substrate bearing the methoxy substituent at the *ortho*-position of the anilide to yield **2j**, the reaction is very sluggish by requiring 40 hours of heating to yield 30% with most of the starting material remaining in the reaction vessel. In addition to widening the scope of this reaction with various electron-donating and electron-withdrawing substituents in aryl ring, a great functional group tolerance was also observed getting the cyclized products (**2k** and **2l**) with nitrile and *t*-butyldimethylsilyloxy substituents on the aryl ring.[9] These successful reaction protocols also resulted in the same extension of efficiency for 2-pyridinylamides instead of anilides with representative examples of **1m**, **1n** and **1o**. All successful substrates had electron withdrawing substituents as nitrile and carboxylate for the reaction to proceed.



Scheme 1. Syntheses of various oxindoles (**2**) from amides (**1**).

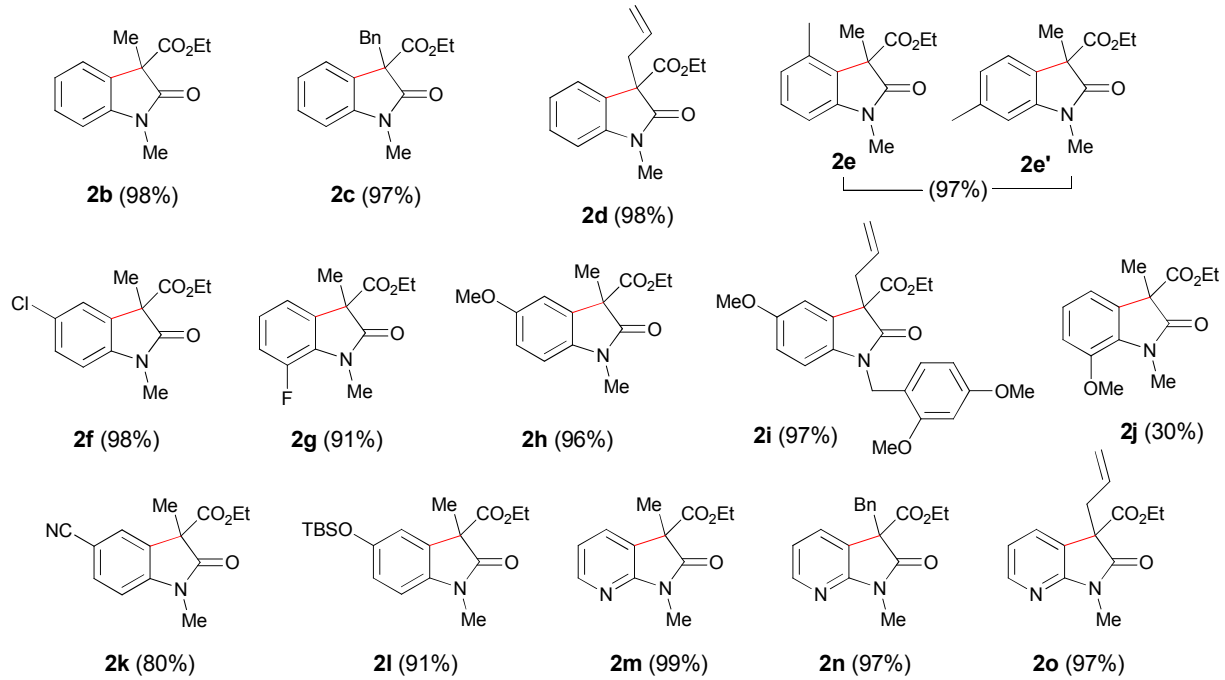


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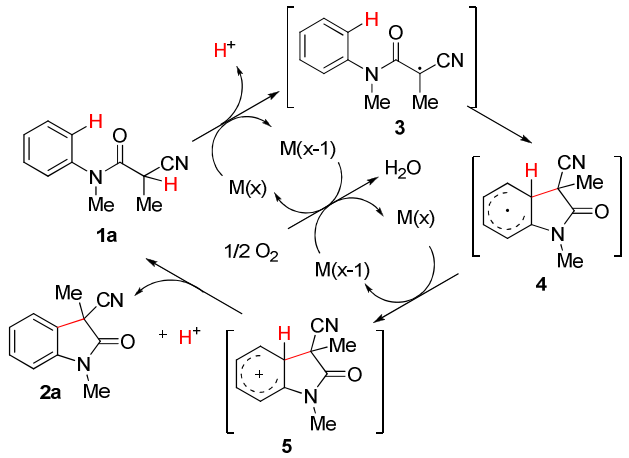
Figure 1. Oxindole (**2**) synthesized either from anilide (**1**, X=C) or 2-pyridinylanilide (**1**, X=N)



Scheme 2. Possible mechanism for metal ion-mediated oxindole (**1a**) synthesis from **2a**.

Regarding the reaction mechanism the proton abstraction step to generate a carbanionic intermediate is the initiation step for the reaction to proceed. All successful substrates had electron withdrawing substituents as nitrile and carboxylate for the reaction to proceed. When the substituent was changed to phenyl (R^2 = Ph) instead of nitrile in (R^2 = CN) or carboxylate in (R^2 = CO_2Et), we were not able to obtain the expected cyclic product at all. This result implies that the acidity of the α-proton is crucial for the reaction to proceed. When we carried out the reaction under the same optimized conditions with all necessary requirements but in a glove box under nitrogen atmosphere, no cyclized product was obtained with all starting material unreacted (Table 1, entry 19). However, for the same reaction under oxygen atmosphere the reaction proceeded to yield the expected product **2a** from the starting anilide **1a** (Table 1, entry 20). This result indicates that oxygen is essential to re-oxidize the catalyst and we also found that extra oxygen pressure did not affect the reaction rate.

The introduction of the radical scavenger, TEMPO, completely shut down the reaction (Table 1, entry 21) and this result indicates a radical intermediate is involved in the reaction mechanism[10] with the possible catalytic system as shown in Scheme 2. The initially deprotonated anionic specie was one electron oxidized by the catalyst to generate the radical (**3**) at which point the cyclization proceeds via a possibly aryl copper intermediate.[11] Then the cyclized radical (**4**) was further oxidized to the cationic specie (**5**). The final step is the release of a proton from the cationic specie (**5**) to yield the expected oxindole **2a**. The key of this catalytic system is the regeneration of the catalyst from the reduced state after the catalytic cycle by oxygen as the re-oxidant.[12] Thereby, the reaction to provide various oxindoles from the starting substrates bearing the acidic proton can be catalysed by various metal oxides.

Conclusions

We described the syntheses of diversely substituted oxindoles by treatment of various substituted anilides and pyridinylamides with various metal salts and oxides as catalysts including CuO, Cu_2O, $FeCl_3$, Fe_2O_3, TiO_2, ZnO, and Ag_2O and their nanoparticles under solvent-free and aerobic conditions in excellent yields. We also showed that the reaction mechanism was a single electron transfer pathway with oxygen as the re-oxidant of the metal catalysts. This report describes a representative example of the atom economical and environmentally benign catalytic synthesis of organic molecules.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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