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Aza-oxindole synthesis by oxidative coupling of C_{sp^2}–H and C_{sp^3}–H centers†

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A Cu(II) mediated oxidative C_{sp^2}–H and C_{sp^3}–H coupling protocol gives access to aza-oxindoles in good to excellent yield in the presence of NaO*t*Bu as base and toluene as solvent.

Compounds containing the aza-oxindole structural motif exhibit biological activities such as oral anti-inflammatory activity, and potent TrkA kinase and JAK 3 kinase inhibition.[1] Literature protocols for the synthesis of aza-oxindoles[2] include the oxidation of azaindoles,[2a] radical cyclization reactions,[2b] Pauson–Khand type [2+2+1] cycloadditions,[2c] Pd-catalyzed intramolecular α-pyridination of amides,[2d] photo cyclizations,[2e] and cyclization of aminopyridineacetic acids.[2f] All the aforementioned methods require a specifically functionalized precursor; for instance an *ortho* pyridyl halogen, an α-xanthate group or an α-hydroxy group, or a preexisting bicyclic ring system.

Oxidative inter- and intramolecular radical coupling protocols are powerful tools for the construction of C–C bonds.[3] We here communicate a simple, robust protocol for the preparation of aza-oxindoles. It involves an oxidative C_{sp^2}–H/C_{sp^3}–H coupling using cheap $CuCl_2$ as oxidant. We discovered this reaction sequence while working on Pd catalyzed asymmetric intramolecular arylations of aryl amides to give highly enantiomerically enriched 3,3-disubstituted oxindoles.[4] Attempting to couple the reaction with an *ortho*-palladation step under oxidative conditions led to the finding that Pd is not involved and that oxindoles are formed *via* a radical process under these conditions.[5] Shortly following our publication, Taylor and coworkers published similar findings leading to oxindoles with ester, nitrile and phosphonate functions in the 3-position.[6] The key step of this transformation is an intramolecular radical cyclization reaction.

Radical addition to pyridines is known as the Minisci reaction.[7,8] Literature shows that it works best when the reaction is carried out in acidic media. Recently, intramolecular variants of the Minisci reaction have come to the fore.[9] To the best of our knowledge, there is no literature precedent for the synthesis of aza-oxindoles *via* the oxidative coupling method described here.

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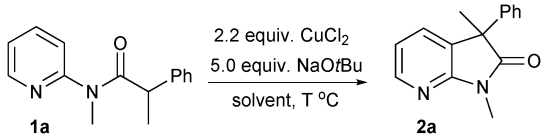
Table 1 Optimization of reaction conditions for the intramolecular radical addition/oxidation of **1a**[a]



Entry	Solvent	Temp/°C	Time/h	Yield[b] (%)
1	DMF	110	3	50
2[c]	DMF	180	0.15	51
3	PhMe	110	2.5	68
4	Xylene	110	2.5	64
5	*n*Bu_2O	110	2.5	58
6	Mesitylene	110	2.5	64
7	PhMe	140	2	67
8	Xylene	140	2	61
9	Diglyme	140	2	62
10[d]	PhMe	110	2.5	40
11[e]	PhMe	110	2.5	59
12[f]	Mesitylene	165	20	Trace

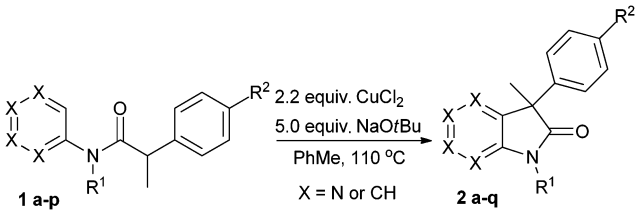
[a] 0.2 mmol scale in 4.0 mL solvent. [b] Isolated yield. [c] Microwave irradiation. [d] 2.2 equiv. $Cu(OAc)_2$ was used. [e] 5.0 equiv. KO*t*Bu was used. [f] 5 mol% $Cu(OAc)_2{\cdot}H_2O$ was used, no base added.[6]

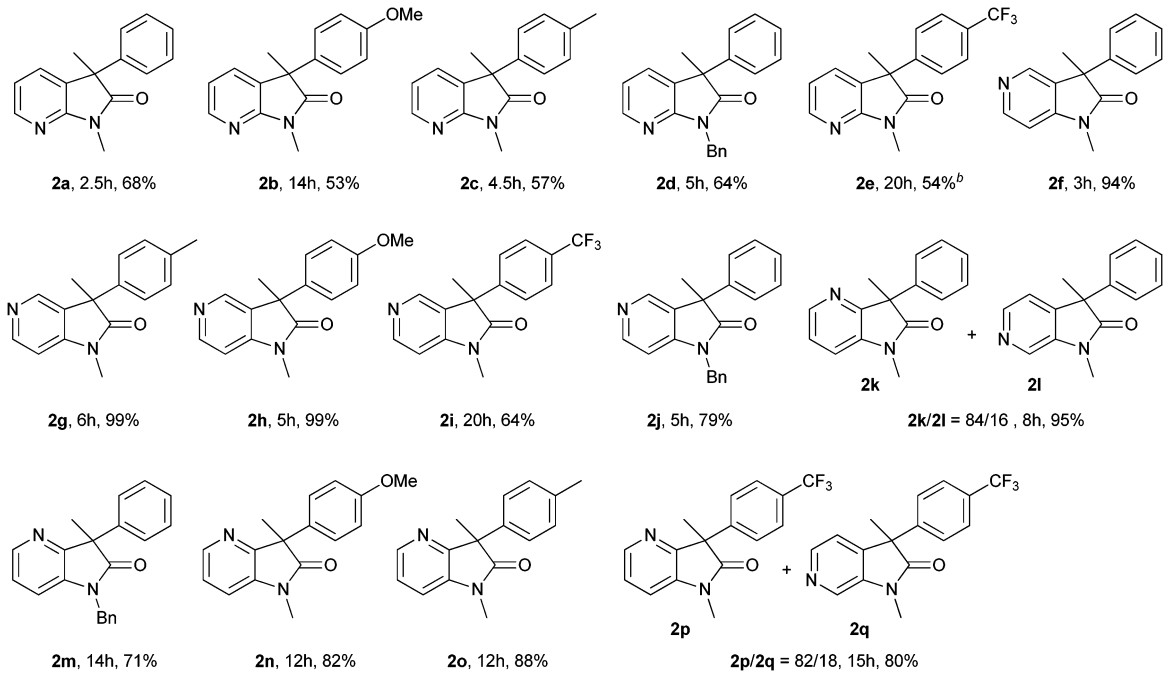
N-Methyl-2-phenyl-*N*-(pyridin-2-yl)propanamide (**1a**) was prepared by reaction of 2-amino pyridine with 2-phenyl propanoyl chloride followed by N-methylation. Reaction with 2.2 equiv. of $CuCl_2$ and 5 equiv. of NaO*t*Bu in DMF at 110 °C for 3 h afforded aza-oxindole **2a** in 50% yield (Table 1, entry 1).[10] Microwave heating cuts the reaction time to 10 min but did not improve the yield (entry 2). Solvent screening revealed toluene to be the best choice (entries 3–6). Higher reaction temperatures did not improve the yield (entries 7–9).

Different oxidants and bases were probed but $CuCl_2$ and NaO*t*Bu proved to be the best combination (entry 3 *vs.* entries 10 and 11). This has precedence in the synthesis of oxindoles.[5] The use of catalytic quantities of Cu(II) in refluxing mesitylene for 20 h[6] returned mainly starting material **1a** (Table 1, entry 12). In all other reactions, **1a** was consumed completely, the mass balance being made up of intractable materials.

Using the optimized conditions found for **2a**, the reaction was extended to other *ortho*-, *meta*-, and *para*-pyridyl substrates and to precursors with substituted aryl groups (Table 2). Reaction with substrate **1e**, containing a *p*-trifluoromethyl required a

Table 2 Scope of aza-oxindole synthesis *via* intramolecular oxidative coupling[a]





[a] 0.4 mmol scale for **1b–e**, **g–j**, **m–p** in toluene (8.0 mL), 0.8 mmol scale for **1a**,**f**,**k**. Yields given are those of the isolated pure products. [b] **2e** was obtained together with an inseparable, unidentified impurity (~15%).

longer reaction time. Yields with *para*-pyridyl substrates **1f–h** were considerably higher than with *ortho*-pyridyl substrates. A similar increase in efficiency was reported by Harrowven and coworkers for intramolecular addition of phenyl radicals to pyridines.[11] The origin may simply be one of statistics given that for the *para*-pyridyl substrates there are two positions for cyclization whereas for *ortho*-pyridyl substrates there is only one. The reaction times for the synthesis of 7- and of 5-aza-oxindoles were shorter than the synthesis of oxindoles (2.5–3 h *cf.* 5 h[5]) due to the faster addition of the amidyl radical to pyridine over that to a phenyl ring.

The data in Table 2 show the product yields to be usually good to excellent. The reactions worked well with both electron-rich and electron-poor aryl rings but the latter require longer reaction times. *N*-Benzyl protected substrates afforded aza-oxindoles **2d**, **2j**, and **2m** in 64, 79 and 71% yields respectively. As expected, the oxidative coupling reaction of 3-pyridyl amide substrates **1k–1p**, affords two regioisomeric products with the one resulting from addition *ortho* to the pyridyl N being largely favoured or (for **2m–o**), the exclusive product. A similar trend of regioselectivity of radical addition to a 3-pyridyl substrate under Lewis acidic conditions was also reported by Harrowven and co-workers and may be linked to enhanced electrophilicity at the *o*-position due to pyridyl-N-coordination to Cu(II).[12]

In summary, we have developed a simple, cheap and efficient method for the synthesis of 3,3-disubstituted aza-oxindoles by the direct intramolecular oxidative coupling of pyridyl C_{sp^2}–H and C_{sp^3}–H centers. This method has been applied to a range of substrates. The rate and yield of the reaction depend on the position of the nitrogen atom in the pyridine ring and on the aryl substituents.

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