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Silver-Catalyzed Intramolecular C-2 Selective Acylation of Indoles with Aldehydes: An Atom-Economical Entry to Indole-Indolone Scaffolds

Xiaoxia Wang,[+a] Zhongfeng Li,[+a] Shengli Cao,[a] and Honghua Rao[a,*]

[a] Department of Chemistry, Capital Normal University, Beijing 100048, People's Republic of China
Fax: (+86)-10-6890-2493; e-mail: honghua.rao@gmail.com

[+] These authors contributed equally to this work.

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Abstract: A direct annulation reaction of *N*-(2-formylaryl)indoles has been developed, which can provide a new entry to biologically and medicinally important indole-indolone scaffolds *via* a silver-catalyzed direct oxidative coupling between aldehyde C–H and sp^2 C–H bonds for the first time. Remarkably, this strategy displayed excellent functional group compatibilities, thereby suggesting its wide potential for applications in developing and synthesizing new drug-like compounds containing indole-indolone frameworks.

Keywords: C–H bond oxidative coupling; indole-indolone hybrids; silver-catalyzed reaction; single-electron-transfer process (SET); sulfate radical anion

The indole moiety is a privileged structural constituent of numerous natural products and pharmacological entities.[1] In addition, the indolone motif is also embedded in several biologically active molecules, including the potent cholecystokinin antagonist asperlicin[2] and the antifungal fumiquinazolines.[3] Consequently, the diverse array of biological and medicinal activities has stimulated synthetic chemists and medicinal chemists to pursue new drug-like compounds by introducing chemical functional groups to the indole or indolone core.[1c,4–6] In this context, a most promising strategy is to assemble these two biologically and medicinally interesting substructures into one skeletal structure, especially the indole fused indolone scaffold.[7] In 2009, the Larock group thereby first presented a rapid synthesis of the indole-indolone hybrid through [3+2] annulation of arynes with methyl indole-2-carboxylates in moderate to good yields,[8] which has been serving as the sole strategy for establishing this biologically important skeleton for a long time (Figure 1a).[9] Only very recently, another strategy *via* an HFIP-promoted intramolecular Friedel–Crafts acylation was proposed for the construction of the indole-indolone scaffold (but only one example was given) (Figure 1b).[10]

As is well-known, catalytic C–H activations and subsequent C–C bond formations have witnessed a meteoritic development during the past decades and are now routinely employed as a powerful tool in both academia and industry.[11] In particular, direct couplings between C–H bonds utilizing transition metal catalysis or organocatalysis can provide an unprecedented opportunity for the development of novel retrosynthetic disconnections, thus promising the construction of useful molecular frameworks in an atom-economical and straightforward manner from

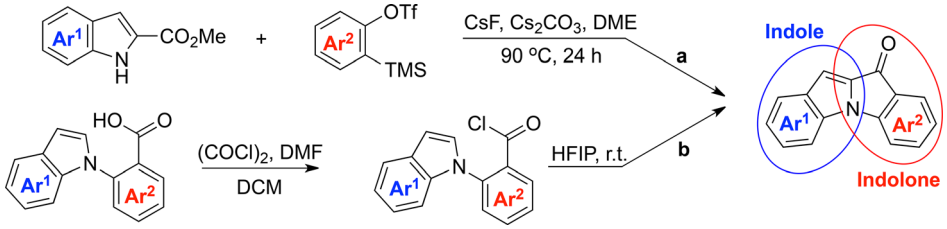
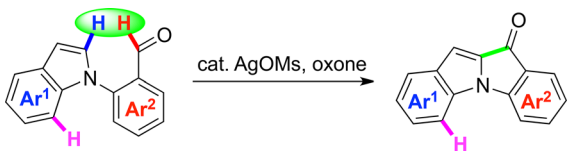


Figure 1. Reported protocols for indole-indolone hybrid construction.

less functionalized substrates.[12] Unfortunately, no such catalysis has been developed for establishing indole-indolone hybrids through direct coupling of aldehyde C–H and sp^2 C–H bonds, even though direct activation of aldehyde C–H bonds has been realized *via* either oxidative insertion of Rh[13] or Pd catalysts[14] to aldehyde C–H bonds (generating acyl-metal moieties) or direct hydrogen abstraction from aldehyde C–H bonds utilizing Cu,[15] Fe catalysts,[16] quaternary ammonium salts,[17,18] or even under simple oxidative conditions (generating acyl radicals).[19] Following this tendency and regarding to retrosynthetic analysis of indole-indolone motif, we herein report the design of a variety of *N*-(2-formylaryl)indoles that can efficiently and highly selectively deliver the indole fused indolone scaffolds *via* a silver-catalyzed aldehyde C–H bond activation (Scheme 1). This strategy accommodates a broad range of catalytically reactive functional groups, and to the best of our knowledge, can serve as a new entry to indole-indolone hybrids.

Our study commenced by subjecting *N*-(2-formylphenyl)indole (**1a**) to the TBAX/TBHP organocatalytic system, which was previously developed by our group to realize the intramolecular oxidative coupling between sp^2 C–H bonds.[17] However, it only leads to the consumption of **1a** without any detection of the desired acylation product **2a** (Table 1, entry 1). Cu[15] or Fe catalysis[16] that has been developed for cross-coupling of aldehyde C–H and sp^2 C–H bonds afforded only trace amounts of **2a** (Table 1, entry 2). Fortunately, use of Ag_2SO_4 as the catalyst, $K_2S_2O_8$ as the oxidant, and *p*-dioxane as the solvent can deliver product **2a** in 39% yield (entry 5). Among the oxidants examined, oxone provided the best yield (66%) of the desired product **2a**, and 10% of the undesired C-7 acylation product (entries 3–6). To improve the yield of C-2 acylation product **2a**, as well as to suppress the C-7 acylation process, a series of different solvents and catalysts were thereby screened. Remarkably, the reaction efficiency and selectivity show a strong dependency on the solvent: when the reaction was carried out in THF, DME, or CH_3CN, the yield of desired product **2a** was slightly reduced by approximately 10% (entries 6–9), but decreased dramatically in $(n\text{-Bu})_2O$, *t*-BuOH, toluene or DMF (entries 11–14); notably, DCE as solvent nearly inhibited

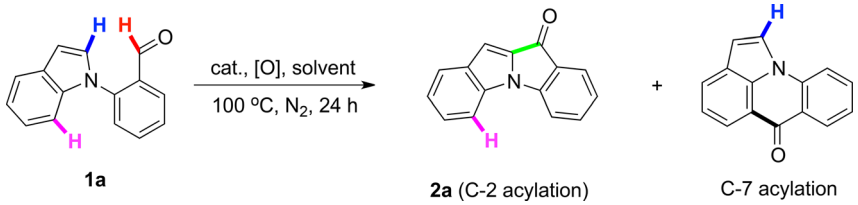


Scheme 1. Indole-indolone hybrid formation *via* silver-catalyzed intramolecular C-2 selective acylation of indoles with aldehydes.

the C-7 acylation process completely,[20] albeit affording product **2a** in diminished yield (entry 10). Likewise, the use of different silver catalysts had a drastic impact in catalyzing this oxidative coupling reaction. By using AgOMs as the catalyst, product **2a** was obtained in 87% yield, together with only 3% of C-7 acylation product (entry 15). Other silver catalysts having different counterions (such as SO_4^{2-}, OTf^-, BF_4^-, NO_3^-, or OAc^-) exhibited much lower catalytic activities and selectivities than AgOMs (entries 6, 16–19). Interestingly, a trace amount or 21% of the desired product **2a** was obtained without either oxidant or catalyst, respectively (entries 20 and 21). Nevertheless, when a substrate with an electron-donating groups, such as 5-methoxy group on indole ring, was subjected to the above optimized reaction conditions (*p*-dioxane as solvent, 5.0 mol% of AgOMs as catalyst, and 2.0 equiv. of oxone as oxidant), it afforded only 75% of the C-2 selective acylation product **2o**, with 10% of C-7 acylation product (entry 22). Further optimizations were hence conducted, and the results revealed that *p*-dioxane/DCE (10:1 v/v ratio) as co-solvent and 4.0 mol% of AgOMs as catalyst are crucial to the obtention of exclusive C-2 acylation product for substrates with electron-donating groups (entry 23; see Table S1 in the Supporting Information), while *p*-dioxane/DCE (8:1, v/v ratio) as co-solvent, 7.5 mol% of AgOMs as catalyst and 3.0 equiv. of oxone as oxidant are required for substrates with electron-withdrawing groups (entry 24; see Table S2 in the Supporting Information).

With the optimized reaction conditions in hand, we probed the substrate scope at 100 °C under a nitrogen atmosphere by using AgOMs (4.0–7.5 mol%) as the catalyst, oxone (2.0–3.0 equiv.) as the oxidant. As summarized in Scheme 2, the AgOMs-catalyzed intramolecular oxidative cross-coupling between C–H bonds displays broad substrate capacity and is tolerant of a range of substituents in different positions of the indole ring. On the other hand, the presence of various substituents with different electronic properties results in drastic reactivity and selectivity differences. For example, substrates bearing electron-withdrawing groups permit exclusive C-2 acylation on the indole ring (**2b–j**), although higher catalyst loading (7.5 mol% AgOMs) and longer reaction time (36 h) are required to achieve higher reaction efficiency (comparing the yields of **2b** under conditions **A** and **C**). In contrast, electron-sufficient substrates (e.g., reactant **1o**) can facilitate higher conversions of the starting materials, but afford considerable yields of the undesired C-7 acylation byproducts under conditions **A**. Gratifyingly, when reactions of substrates with electron-donating groups are conducted in the previously optimized reaction conditions **B**, the corresponding C-2 acylation products are obtained in good to excellent yields with nearly no detection of the C-7

Table 1. Screening of the reaction conditions.[a]

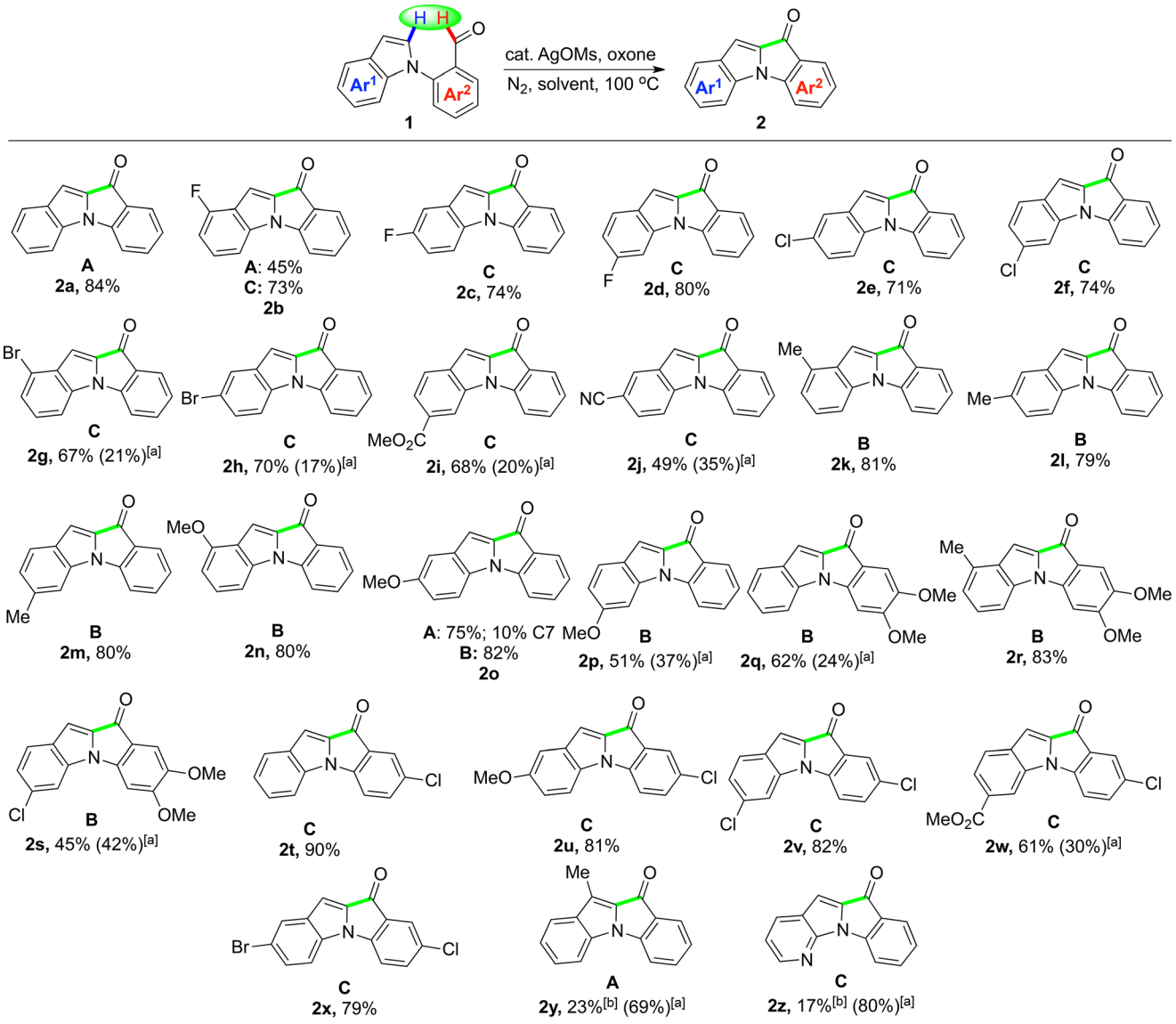


Entry	Cat. (mol%)	[O] (equiv.)	Solvent	Yield [%][b]	
				2a	C-7
1	TBAX (10.0)	TBHP (2.0)	CH_3CN	0	0
2	"Cu" or "Fe"	TBHP (2.0)	CH_3CN	trace	0
3	Ag_2SO_4 (5.0)	$Na_2S_2O_8$ (2.0)	*p*-dioxane	trace	0
4	Ag_2SO_4 (5.0)	$(NH_4)_2S_2O_8$ (2.0)	*p*-dioxane	trace	0
5[c]	Ag_2SO_4 (5.0)	$K_2S_2O_8$ (2.0)	*p*-dioxane	39	12
6	Ag_2SO_4 (5.0)	**oxone (2.0)**	***p*-dioxane**	66	10
7	Ag_2SO_4 (5.0)	oxone (2.0)	THF	53	16
8	Ag_2SO_4 (5.0)	oxone (2.0)	DME	59	14
9	Ag_2SO_4 (5.0)	oxone (2.0)	CH_3CN	52	15
10	Ag_2SO_4 (5.0)	oxone (2.0)	DCE	45	3
11	Ag_2SO_4 (5.0)	oxone (2.0)	nBu_2O	38	17
12	Ag_2SO_4 (5.0)	oxone (2.0)	*t*BuOH	30	0
13	Ag_2SO_4 (5.0)	oxone (2.0)	toluene	19	0
14	Ag_2SO_4 (5.0)	oxone (2.0)	DMF	0	0
15	**AgOMs (5.0)**	oxone (2.0)	*p*-dioxane	87	3
16	AgOTf (5.0)	oxone (2.0)	*p*-dioxane	33	0
17	$AgBF_4$ (5.0)	oxone (2.0)	*p*-dioxane	55	10
18	$AgNO_3$ (5.0)	oxone (2.0)	*p*-dioxane	28	15
19	AgOAc (5.0)	oxone (2.0)	*p*-dioxane	51	16
20	AgOMs (5.0)	–	*p*-dioxane	trace	0
21	–	oxone (2.0)	*p*-dioxane	21	0
22[c]	AgOMs (5.0)	oxone (2.0)	*p*-dioxane	75	10
23[c,d]	**AgOMs (4.0)**	**oxone (2.0)**	***p*-dioxane/DCE (10:1)**	**84**	<1
24[e,f]	**AgOMs (7.5)**	**oxone (3.0)**	***p*-dioxane/DCE (8:1)**	**74**	<1

[a] *Reaction conditions:* **1a** (0.10 mmol), [O] (2.0 equiv.), solvent (2.0 mL), 100 °C, under nitrogen for 24 h unless otherwise noted.
[b] Yield determined by ^1H NMR spectroscopy with mesitylene as the internal standard.
[c] *N*-(2-Formylphenyl)-5-methoxyindole (**2o**) as the substrate.
[d] AgOMs (4.0 mol%), *p*-dioxane/DCE (2.0 mL; 10:1, v/v ratio).
[e] *N*-(2-Formylphenyl)-6-chloroindole (**2f**) as the substrate.
[f] AgOMs (7.5 mol%), oxone (3.0 equiv.), *p*-dioxane/DCE (2.0 mL; 8:1, v/v ratio), 36 h. [O] = oxidant, TBAX = $(n\text{-Bu})_4NI$ or $(n\text{-Bu})_4Br$, TBHP = *tert*-butyl hydroperoxide, THF = tetrahydrofuran, DME = 1,2-dimethoxyethane, DCE = 1,2-dichloroethane, DMF = *N,N*-dimethylforamide, Tf = trifluoroacyl, Ms = methanesulfonyl.

acylation by-products (**2k–p**). To expand the substrate scope, the benzaldehyde units bearing either electron-donating groups (e.g., methoxy group; **2q–s**) or electron-withdrawing groups (e.g., chloro group; **2t–x**) were tested, and all of them readily produce the desired C-2 acylation products in reasonable to excellent yields. Surprisingly, 3-methylindole (**2y**) and 7-azaindole (**2z**) display poor reactivities under the optimized reaction conditions. Particularly noteworthy is the tolerance toward a range of functionally diverse substituents in both indole and benzaldehyde units, such as halogen (**2b–h** and **2s–x**), ester (**2i** and **2w**), cyano (**2j**), methyl (**2k–m** and **2r**), and methoxy groups (**2n–s** and **2u**), which remain unaffected during the reaction; these examples demonstrate that the silver-catalyzed intramolecular C–H cross-coupling provides a complementary platform for further elaboration of the indole-indolone hybrid *via* transition metal-catalyzed or even traditional chemical functional group transformations.

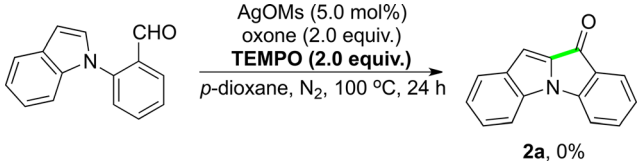
When investigating the mechanism for this silver-catalyzed direct oxidative coupling between C–H bonds, the single-electron-transfer (SET) process is a favorable consideration because it has already been proved that silver(II) species, formed from the oxidation of silver(I) salts with peroxydisulfate, may facilitate a hydrogen-abstraction process to generate the reactive carbon-centered radical.[21] Therefore, a radi-



[a] Yields of recovered starting materials **1** are given in parentheses.
[b] NMR yields with mesitylene as the internal standard are given.

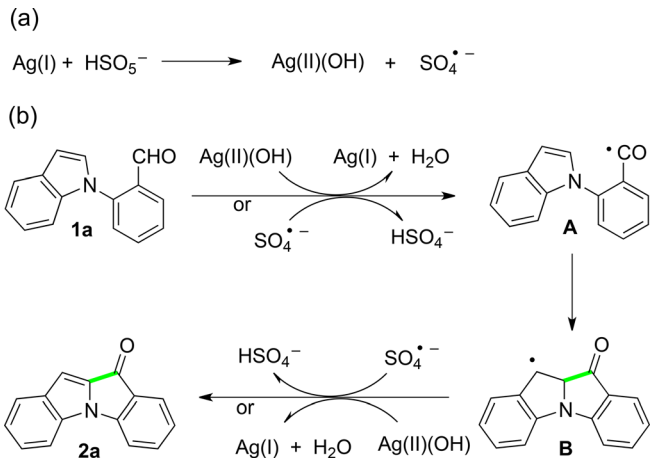
Scheme 2. Silver-catalyzed indole-indolone scaffold formation. *General reaction conditions:* **1** (0.10 mmol), 100 °C, under nitrogen atmosphere. ***Conditions A****:* AgOMs (5.0 mol%), oxone (2.0 equiv.), *p*-dioxane (2.0 mL), 24 h. ***Conditions B****:* AgOMs (4.0 mol%), oxone (2.0 equiv.), *p*-dioxane/DCE (2.0 mL, 10:1 v/v ratio), 24 h. ***Conditions C****:* AgOMs (7.5 mol%), oxone (3.0 equiv.), *p*-dioxane/DCE (2.0 mL, 8:1 v/v ratio), 36 h. Average isolated yields of two runs are given.

cal-trapping experiment was carried out by introducing TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) into the standard reaction conditions. The desired reaction did not occur (Scheme 3), thus indicating that this transformation most likely involves a radical intermediate (for reaction details in the presence of TEMPO and the exclusion of intramolecular C-2 addition to aldehyde, please refer to the Supporting Information, pp S3–S5).



Scheme 3. Investigation of the reaction mechanism.

Based on the above result, a tentative mechanism for this silver-catalyzed intramolecular cross-coupling reaction between C–H bonds is proposed in Scheme 4. In the first step, peroxymonosulfate anion disproportionates into a hydroxide anion and a sulfate radical anion in the presence of silver(I) salt; meanwhile, the silver(I) salt is oxidized to silver(II) species



Scheme 4. Plausible mechanism for this AgOMs-catalyzed indole-indolone hybrid construction.

(Scheme 4a).[22] After oxidizing the aldehyde C–H bond in **1a** with silver(II) species,[23] or abstracting a hydrogen atom from the aldehyde group with sulfate radical anion,[18c] an acyl radical **A** is thereby generated, and subsequently undergoes an intramolecular radical addition to the indolyl C=C bond. The resulting radical **B** is believed to undergo direct oxidation by either sulfate radical anion or silver(II) species and deprotonation to release the final product **2a** (Scheme 4b).

In summary, we have developed a direct annulation reaction of *N*-(2-formylbenzaldehyde)indoles, which first utilizes the silver-catalyzed oxidative coupling between aldehyde C–H and sp^2 C–H bonds to produce biologically and medicinally important indole-indolone hybrids in an atom-economic and straightforward manner. Remarkably, this method is well-suited to both electron-donating and electron-withdrawing substituents on the indole and benzaldehyde rings, and can afford the C-2 acylation products exclusively. Moreover, the good tolerance toward a diverse range of catalytically reactive functional groups promises further modifications of the end product, and will be of broad utility for the development and synthesis of new medicinal and pharmaceutical agents containing indole-indolone frameworks.

Experimental Section

Typical Procedure

An oven-dried round-bottom reaction vessel was charged with AgOMs (1.01 mg, 0.005 mmol, 5.0 mol%), **1a** (0.1 mmol) and oxone (61.5 mg, 0.2 mmol, 2.0 equiv.). After the vessel was filled with nitrogen, dry *p*-dioxane (2.0 mL) was added by syringe under nitrogen, and the reaction mixture was stirred at room temperature for 5 min. Then the vessel was sealed, placed into an oil bath and heated to 100 °C. After 24 h, the resulting mixture was cooled to room temperature, filtered through a short silica gel pad and washed with ethyl acetate. The above solution was evaporated under vacuum, and the residue was purified by silica gel column with petroleum ether/ethyl acetate as the eluent to give the analytically pure product **2a**.

Acknowledgements

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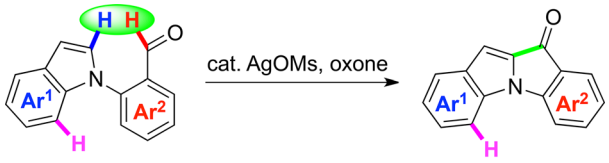

- **24 examples**
- **up to 90% isolated yields**
- **exquisite regioselectivity**
- **excellent functional-group compatibility**