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Silver-Prompted Carbonitration of Acrylamides for the Synthesis of Nitrating Oxindoles

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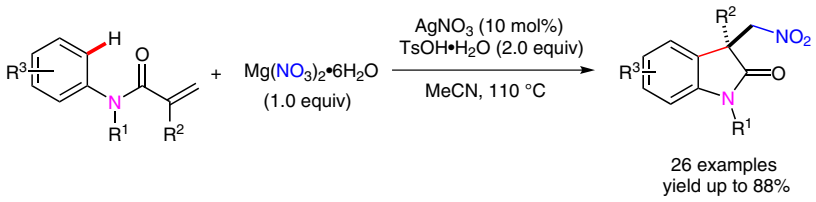

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Abstract A silver-prompted carbonitration of alkenes involving concomitant direct C–H functionalization and C–N bond formation to synthesize nitrating oxindoles has been developed. The CR TH2 receptor antagonist skeleton can be obtained from one of the products with further modification.

Key words silver, *N*-methyl-*N*-arylacrylamide, carbonitration, nitrating oxindoles

Oxindoles play an important role in natural products, pharmaceuticals, agrochemicals, and the key structural motifs of numerous natural products.[1] Additionally, nitro compounds are important synthetic intermediates in pharmaceuticals, chemical industry, and organic synthesis because they can be easily converted into various amines and ketones.[2] Representative oxindole derivatives such as horsfiline, CR TH2 receptor antagonist, and alstonisine (Figure 1) can be easier afforded from nitrating oxindoles. Therefore, the selective assembly of nitrated oxindoles from readily available precursors is a prominent objective in chemical research. Recently, transition-metal-catalyzed simple alkene difunctionalization to synthesize different oxindoles represents a highly attractive alternative. For example, the Grigg group[3] reports the palladium-catalyzed difunctionalization of alkenes with aryl iodides and CO through interamolecular Heck coupling and succeeds in obtaining oxindoles derivatives. Subsequently, the Zhu group applies the intramolecular Heck coupling with *o*-haloaniline to oxindoles synthesis and gets the best advancements.[4] Very recently, a new tactic of direct 1,2-difunctionalization of alkenes for the synthesis of oxindoles by the palladium-catalyzed C–H oxidative activation has been developed firstly by the Liu group.[5] Moreover, an iron-catalyzed oxidative radical cyclization leading to functionalized oxindoles has also been performed by Li and coworkers.[6] Based on this considerable progress, numerous groups have independently developed some new methods of metal-catalyzed or metal-free oxidative carbo–hetero or carbo–carbo difunctionalization of arylacrylamides, which involved all kinds of functional groups, such as trifluoromethyl,[5a,7] alkyl,[6,8] phosphoryl,[7l,m,9] azidyl,[7l,m,10] hydroxyl,[11] carbonyl,[12] nitro,[13] sulfonyl,[14] and (trifluoromethyl)thio[7m,15] in the past few years. We wish to apply this strategy for the selective synthesis of nitrated oxindoles.

In classical methods, the simplest pathway to obtain the aliphatic nitro compounds was through the direct addition of nitrogen dioxide to a C–C multiple bond, but the problem

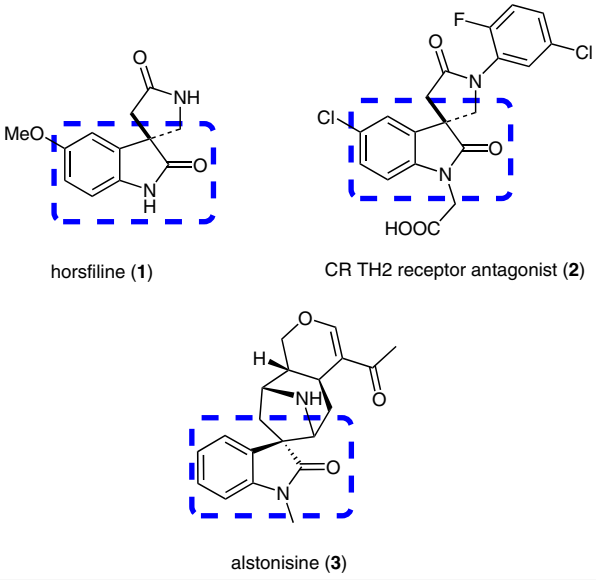
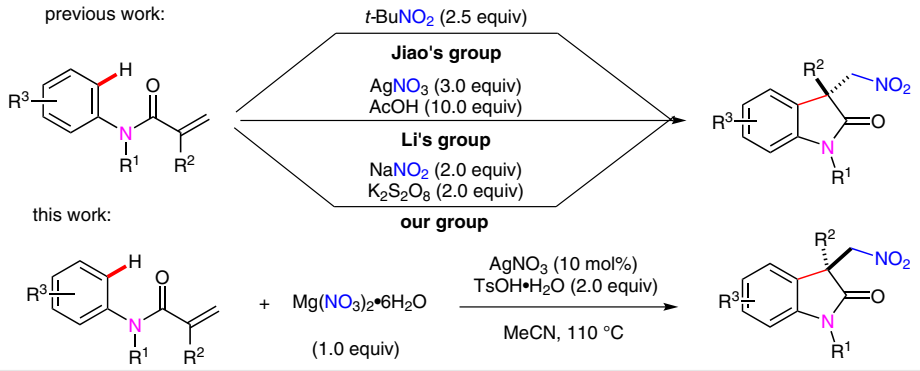
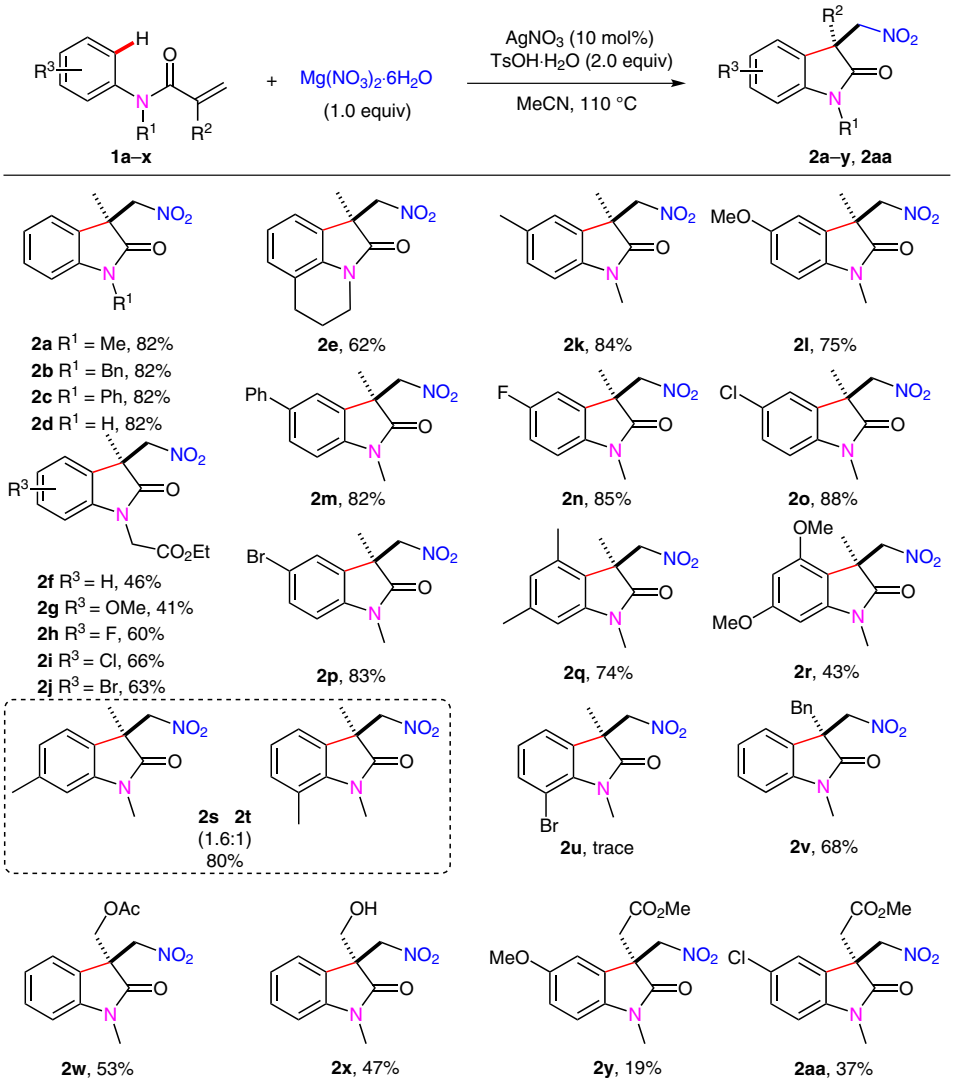


Figure 1 Representative oxindole derivatives



Scheme 1 Different methods related to carbonitration of alkenes



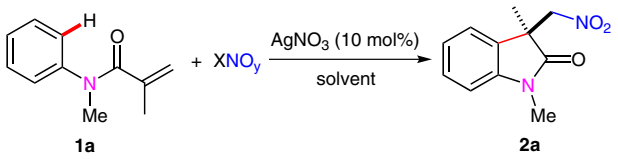
Scheme 2 The scope of substrates investigation; isolated yields are given. *Reagents and conditions*: **1a** (0.2 mmol), $Mg(NO_3)_2·6H_2O$ (1 equiv), $TsOH·H_2O$ (2 equiv) and $AgNO_3$ (0.1 equiv), MeCN (2 mL), 110 °C, 24 h. Yields for **2f–j** are for a 36 h reaction.

is the difficulty of handling NO_2 exhaust and the inefficiency of reaction efficiency.[16] Therefore, the development of an efficient nitrating method is always a considerable challenge. Very recently, the oxidative metal-free difunctionalization of *N*-aryl acrylamides **1** to construct nitro-substituted oxindole derivatives **3** has been reported by Jiao[13b] and Li[13c] groups (Scheme 1). Our group has also disclosed an efficient synthesis of nitro-containing oxindoles and dihydroquinolin-2(1*H*)-ones by oxidative arylnitration of alkenes via nitration and C–H functionalization.[13a] However, these aforementioned methods are the equivalent reactions. Herein, we would like to present a practical and an efficient radical difunctionalization of alkenes to synthesize nitrating oxindoles via silver-prompted carboazidation and C–H functionalization of arylacrylamides. In the scope of what we know, silver-catalyzed difunctionalization of alkenes to form nitrating oxindoles is the first example.

In an initial study, we focused on *N*-methyl-*N*-arylacrylamide **1a** as the model substrate with $Mg(NO_3)_2{\cdot}6H_2O$ as nitrating source, and diphenylphosphinic acid as acid in the presence of 10 mol% $AgNO_3$ in MeCN at 90 °C. To our delight, the carbonitration of alkene really works, and the desired product **2a** was obtained in 62% yield (Table 1, entry 1). When the temperature was increased to 110 °C, the yield of **2a** reached 77% (Table 1, entry 2). Encouraged by these results, we further screened several nitro resources (Table 1, entries 3–12) and found that $Mg(NO_3)_2{\cdot}6H_2O$ is still the best choice. Based on our previous report, we were strongly aware of the vital role of acid playing in the reaction. The best yield (82%) was obtained in the presence of *p*-toluenesulfonic acid (PTSA, Table 1, entries 14–18). Meanwhile, different solvents were also examined, and MeCN was found to be the best choice (Table 1, entries 19–24). Furthermore, the control experiment showed that only 50% yield of the desired product was obtained in the absence of $AgNO_3$ (Table 1, entries 25 and 26).

With the optimal reaction conditions in hand (Table 1, entry 14), the reaction scope was examined as shown in Scheme 2. Varying the different substituent of N-protecting groups with an electron-donating group gave the product in good yield, such as methyl, benzyl, and phenyl (**2a**–**c**), but an N-free substituent under identical conditions failed to produce the desired product **2d**. Moreover, tricyclic oxindole **2e** was transformed from cyclization of tetrahydroquinoline derivative with a moderate yield. Meanwhile, many substrates with arylacrylamide as N-protecting group were also tested; the substituent on the phenyl group with electron-withdrawing or electron-donating groups provided the corresponding oxindoles in moderate to good yields (**2f**–**j**). When the N-protecting group was changed to methyl, different substituent on the aryl ring afforded the desired products in good to excellent yields, which are bearing electron-withdrawing or electron-donating groups (**2k**–**t**). However, trace product was obtained when an *ortho*-substituent was present on the phenyl group (**2u**). Next, various α-substituted groups of alkenes bearing different functional groups were additionally examined. Analogous to substrate **1a**, substrates with benzyl (**2v**), acetoxymethyl (**2w**), hydroxyl (**2x**), and ester (**2y** and **2aa**) groups at this position generated the corresponding products in moderate to good yields.

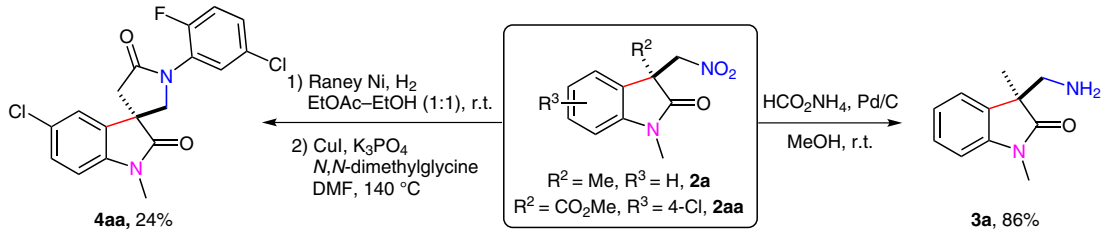
Table 1 Optimization of the Reaction Conditions[a,b]



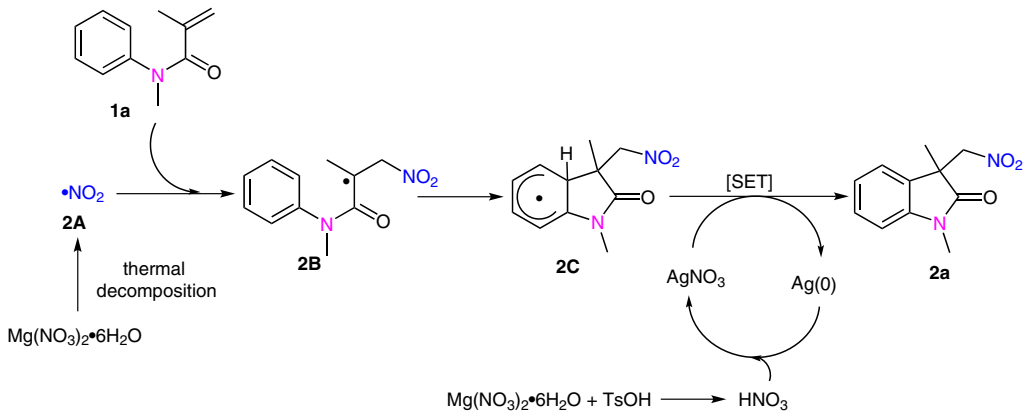
1a **2a**

Entry	XNO$_y$ (1 equiv)	Additive (2 equiv)	Solvent	Yield (%)
1[c]	$Mg(NO_3)_2{\cdot}6H_2O$	$HO(O)PPh_2$	MeCN	62
2	$Mg(NO_3)_2{\cdot}6H_2O$	$HO(O)PPh_2$	MeCN	77
3	KNO_3	$HO(O)PPh_2$	MeCN	23
4	NH_4NO_3	$HO(O)PPh_2$	MeCN	27
5	$NaNO_3$	$HO(O)PPh_2$	MeCN	29
6	$NaNO_2$	$HO(O)PPh_2$	MeCN	25
7	$Y(NO_3)_3{\cdot}6H_2O$	$HO(O)PPh_2$	MeCN	50
8	$Co(NO_3)_3{\cdot}5H_2O$	$HO(O)PPh_2$	MeCN	73
9	$Bi(NO_3)_3{\cdot}5H_2O$	$HO(O)PPh_2$	MeCN	60
10	$Ce(NO_3)_3{\cdot}6H_2O$	$HO(O)PPh_2$	MeCN	11
11	$(NH_4)_2Ce(NO_3)_3{\cdot}6H_2O$	$HO(O)PPh_2$	MeCN	n.d.
12	$Zr(NO_3)_4{\cdot}5H_2O$	$HO(O)PPh_2$	MeCN	52
13	$Mg(NO_3)_2{\cdot}6H_2O$	AcOH	MeCN	61
14	$Mg(NO_3)_2{\cdot}6H_2O$	PTSA	MeCN	82
15	$Mg(NO_3)_2{\cdot}6H_2O$	TFA	MeCN	29
16	$Mg(NO_3)_2{\cdot}6H_2O$	PrivOH	MeCN	37
17	$Mg(NO_3)_2{\cdot}6H_2O$	boric acid	MeCN	46
18	$Mg(NO_3)_2{\cdot}6H_2O$	$H(O)P(OEt)_2$	MeCN	43
19	$Mg(NO_3)_2{\cdot}6H_2O$	PTSA	MePh	29
20	$Mg(NO_3)_2{\cdot}6H_2O$	PTSA	DMF	11
21	$Mg(NO_3)_2{\cdot}6H_2O$	PTSA	DCE	32
22	$Mg(NO_3)_2{\cdot}6H_2O$	PTSA	TFE	55
23	$Mg(NO_3)_2{\cdot}6H_2O$	PTSA	DME	59
24	$Mg(NO_3)_2{\cdot}6H_2O$	PTSA	dioxane	51
25	$Mg(NO_3)_2{\cdot}6H_2O$		MeCN	trace
26[d]	$Mg(NO_3)_2{\cdot}6H_2O$	PTSA	MeCN	50

[a] Reaction conditions: **1a** (0.2 mmol), XNO$_y$ (1 equiv), additive (2 equiv), MeCN (2 mL), 110 °C, 24 h.
[b] Isolated yield.
[c] 90 °C.
[d] No $AgNO_3$.



Scheme 3 Application of our protocol



Scheme 4 Proposed mechanisms

It is worthy of note that the product of **2aa** can be easily converted into spiropyrrolidinyloxoindoles, such as the CR TH2 receptor antagonist skeleton, and nitro compounds can be transferred into amine or amide because they exist in an extensive array of natural products and pharmaceuticals. Our group has been reported that compound **2a** can be reduced by Pd/C to form primary amine **3aa** in moderate yields,[13a] and what is more, spiro-4-pyrrolidinone skeleton **3aa** was obtained through use of the reported method (see the Supporting Information).[17] And then CR TH2 receptor antagonist skeleton **4aa** can be used to synthesize the CR TH2 receptor antagonist with further modification (Scheme 3).

Based on our previous work,[9,13a] a proposed mechanism for silver-catalyzed carbonitration of arylacrylamide is described in Scheme 4. Initially, $Mg(NO_3)_2{\cdot}6H_2O$ decomposed to produce the nitro radical **2A** under heating conditions. Then **2A** was added to alkene **1a** to form the alkyl radical **2B**, which participated in an intramolecular radical cyclization to generate intermediate **2C**. After **2C** was oxidized by $AgNO_3$ to generate **2a** via a single-electron transfer (SET) and release of Ag(0). Finally, Ag(0) was oxidized to Ag(I) again in the presence of HNO_3, which was produced by *p*-toluenesulfonic acid and $Mg(NO_3)_2{\cdot}6H_2O$.

In summary, we have developed a new silver-prompted difunctionalization of alkenes to form C–N and C–C bond to synthesize nitro-group-containing oxindoles by oxidative carbonitration and C–H functionalization. Our transformation employs an inexpensive and nontoxic silver salt as metal catalysts.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380514.

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