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Synthesis of oxindole-3-acetates through iron-catalyzed oxidative arylalkoxycarbonylation of activated alkenes

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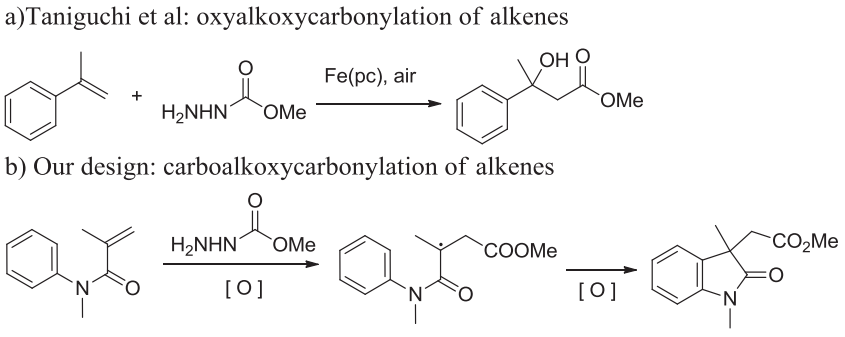
ABSTRACT

An iron-catalyzed alkoxycarbonylation/cyclization reaction of *N*-arylacrylamides with carbazates has been developed. This new alkene difunctionalization reaction provides an efficient and straightforward method to obtain various ester-containing oxindoles.

The direct difunctionalization of alkenes has become an attractive strategy for the assembly of functionalized organic compounds. A number of difunctionalization reactions for alkenes have been developed, such as arylalkylation,[1] carboamination,[2] diamination[3] and dioxygenation.[4] However, examples of alkoxycarbonylative alkene difunctionalization reactions are rare.

Carboxylic esters are valuable commodity chemicals and useful synthetic building blocks.[5] The addition of alkoxycarbonyl radicals to multiple bonds is an efficient way to prepare esters. However, the generation of an alkoxycarbonyl radical often requires the use of toxic reagents and special equipment.[6] Using carbazates as the precursors of alkoxycarbonyl radicals, Taniguchi et al. found that alkoxycarbonyl groups could be easily introduced into α-methylstyrenes under mild conditions (Scheme 1, equation a).[7] These readily available and environmentally friendly materials make alkoxycarbonyl radicals a useful tool for alkoxycarbonylation reactions.[8] Very recent progress on the difunctionalization of *N*-arylacrylamides[1,9] prompted us to envision the addition of an alkoxycarbonyl radical to *N*-phenylacrylamide to generate a new radical that would be trapped by the benzene ring, thus providing



Scheme 1. The introduction of an alkoxycarbonyl group into alkenes.

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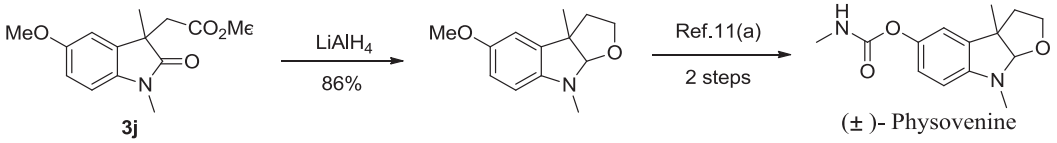
oxindole-3-acetates (Scheme 1, equation b).[10] Oxindole-3-acetates have shown important biological activities and are versatile starting materials for the synthesis of a broad range of polycyclic compounds. For example, the substitution of oxindole-3-acetates can easily produce the acetylcholinesterase inhibitor, (±)-physovenine (Scheme 2).[11]



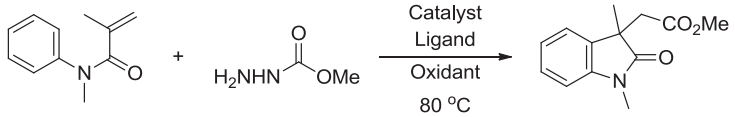
Scheme 2. The utilization of oxindole-3-acetate derivatives.

We initiated our study on the reaction of *N*-methyl-*N*-phenylmethacrylamide (**1a**) with methyl carbazate (**2a**) in ethyl acetate at 80 °C to optimise the conditions (Table 1). In the presence of $FeCl_3$ and TBHP (*tert*-butyl hydroperoxide 70 wt % in water), the desired product, methyl 1,3-dimethyl-oxindole-3-acetate (**3a**), was isolated in low yield (entry 3). Subsequently, we were delighted to discover that the addition of **2a** over 30 min could significantly increase the yield (entry 4 vs entry 3). After screening other catalysts, we found that *n*-Bu_4NI or $Co(OAc)_2{\cdot}4H_2O$ were less effective, whereas $FeCl_2{\cdot}4H_2O$ was as effective as $FeCl_3$. Due to the ease of its handling, $FeCl_2{\cdot}4H_2O$ was chosen as the catalyst (entries 5–7). Only a trace amount of the product was detected in the absence of a catalyst (entry 2). $K_2S_2O_8$ is an alternative oxidant; other oxidants are not suitable for this transformation (entries 8–12). We discovered that ligands could remarkably influence the yields of this transformation. Among the tested ligands, 4-cyanopyridine was the best choice, providing the product in 80% yield (entry 20 vs entries 13–19).[12] The influence of air, water and solvents was also investigated. The results demonstrated that this reaction was not sensitive to air or a small amount of water and that ethyl acetate was the best solvent.

With the optimal reaction conditions in hand, we examined the reaction of **1a** with various carbazates (Table 2). The reactions of methyl, ethyl and propyl carbazates with **1a** gave the corresponding products **3a**–**c** in good yields (entries 1–3). Phenyl carbazates were also good substrates (entry 4). It should be noted that trace amounts of alkylarylation products **4** were often observed. In particular, when *tert*-butyl carbazate was subjected to this reaction, no product **3** was observed. Instead, 10% of alkylarylation product **4a** was isolated (entry 5). This result shows that the *tert*-butyloxycarbonyl radical readily undergoes decarboxylation to produce alkyl radicals.[13]

Next, the scope of *N*-arylacrylamides was investigated, as shown in Table 3. First, the effects of substituents on the benzene ring were studied. *N*-Arylacrylamides bearing an electron-withdrawing or electron-donating group at the *para*-position of the benzene ring always afforded the desired products in good to excellent yields (**3e**–**3m**). Notably, halides, esters, nitro and cyano groups were tolerated and furnished the corresponding products. *N*-Arylacrylamides bearing *meta*-substituents showed good reactivity but poor regioselectivity (**3n**). An *ortho*-substituent had a negative influence on this transformation. For example, *ortho*-fluoro-*N*-phenylacrylamide and *ortho*-phenyl-*N*-phenylacrylamide provided products **3o** and **3p** in 40% and 43% yield, respectively. The effects of

Table 1
Optimisation of reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst	Oxidant	Ligand	Yield (%)
1	$FeCl_3$	—	—	0
2	—	TBHP	—	Trace
3	$FeCl_3$	TBHP	—	10[b]
4	$FeCl_3$	TBHP	—	45
5	*n*-Bu_4NI	TBHP	—	32
6	$Co(OAc)_2{\cdot}4H_2O$	TBHP	—	17
7	$FeCl_2{\cdot}4H_2O$	TBHP	—	45
8	$FeCl_2{\cdot}4H_2O$	DTBP	—	0
9	$FeCl_2{\cdot}4H_2O$	O_2	—	0
10	$FeCl_2{\cdot}4H_2O$	H_2O_2	—	Trace
11	$FeCl_2{\cdot}4H_2O$	$PhI(OAc)_2$	—	Trace
12	$FeCl_2{\cdot}4H_2O$	$K_2S_2O_8$	—	35
13	$FeCl_2{\cdot}4H_2O$	TBHP	18-Crown-6	56
14	$FeCl_2{\cdot}4H_2O$	TBHP	Cyclen	40
15	$FeCl_2{\cdot}4H_2O$	TBHP	TMEDA	Trace
16	$FeCl_2{\cdot}4H_2O$	TBHP	Pyridine	65
17	Fe(pc)	TBHP	—	Trace
18	$FeCl_2{\cdot}4H_2O$	TBHP	Phen	68
19	$FeCl_2{\cdot}4H_2O$	TBHP	2,2′-Bipyridine	40
20	$FeCl_2{\cdot}4H_2O$	TBHP	4-Cyanopyridine	80

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (10 mol %), ligand (20 mol %), oxidant (1.0 mmol) in ethyl acetate (2 mL). After stirring well at 80 °C, **2a** (0.8 mmol) was added in portions over 20 min, and the reaction was exposed to air for 4 h at the same temperature.
[b] **2a** was fed in one batch before the reaction. Cyclen=1,4,7,10-tetraazacyclododecane, TMEDA=tetramethylethyl-enediamine, phen=1,10-phenanthroline.