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Oxidant-Free Rhodium(I)-Catalyzed Difunctionalization of Acrylamide: An Efficient Approach To Synthesize Oxindoles

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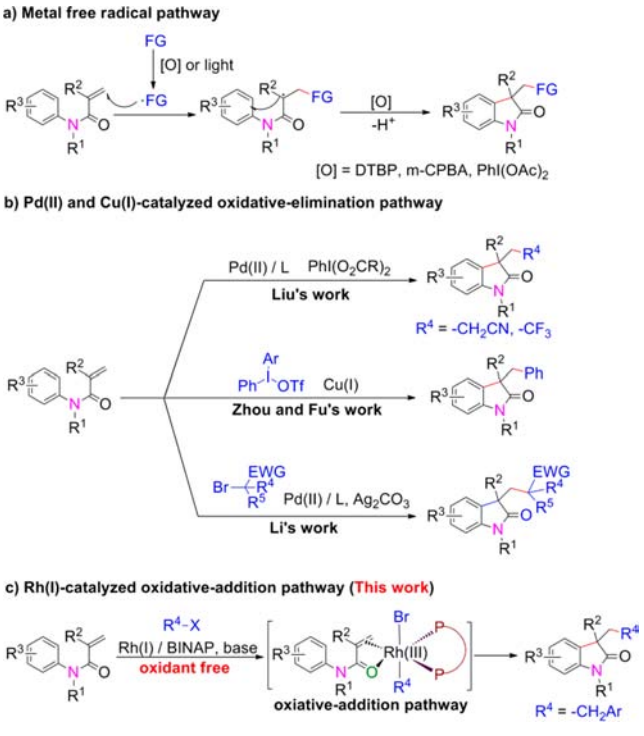
Supporting Information

ABSTRACT: The first rhodium(I)-catalyzed difunctionalization of arylacrylamides to synthesize oxindoles is developed, and it does not require the assistance of an oxidant. This method provides an efficient approach to generate various useful functionalized oxindoles, some of which cannot be easily accessed by previous approaches.

Oxindoles are an important class of heterocycles prevalent in numerous biologically active compounds and natural products, and they have also been widely used as important intermediates in organic synthesis.[1] Consequently, efficient assembly of oxindoles from readily available precursors remains a prominent objective of chemical research.[2] Recently, research has proven the direct difunctionalization[3] of the *N*-phenylacrylamide to be the most efficient approach to generate oxindoles, given the abundance and accessibility of starting materials. In general, this strategy mainly involves two different mechanisms: one is a radical process that includes either metal[4] or metal-free[5] catalyzed cascade radical cyclizations, and different kinds of functionalized oxindoles were achieved (Scheme 1a); the second involves the transition metal-catalyzed oxidative-elimination pathway through which only a few examples have been performed (Scheme 1b).[6] For example, Liu's group has recently reported a hypervalent iodine-assisted Pd(II)/Pd(IV)-catalyzed aryltrifluoro methylation and arylalkylation.[6a,b] Zhou and Fu's groups independently disclosed a Cu(I)/Cu(III)-catalyzed arylation- and vinylation-carbocyclization.[6c,d] In particular, Li's group has developed a unique palladium-catalyzed oxidative difunctionalization of acrylamides with α-carbonyl alkyl bromides toward oxindoles by a radical process in 2014.[4b] Overall, these aforementioned methods require an equivalent oxidant in order to assist in the formation of the oxindoles.[4−6] Herein, we report an oxidant-free rhodium(I)-catalyzed difunctionalization of *N*-phenylacrylamide in order to synthesize oxindole derivates (Scheme 1c). This reaction successfully avoids the use of the oxidant and provides various functionalized oxindoles, some of which cannot be easily accessed by established methods.

Initially, we chose *N*-methyl-*N*-phenylmeth acrylamide (**1a**) and benzyl bromide (**2a**) as the substrates in order to achieve

Scheme 1. Different Difunctionalization of Alkenes To Synthesize Oxindoles



alkylation of the oxindole in the presence of the Rh(I) catalyst. We chose this because the Rh(I) works more easily with

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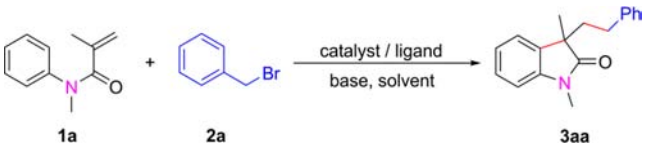
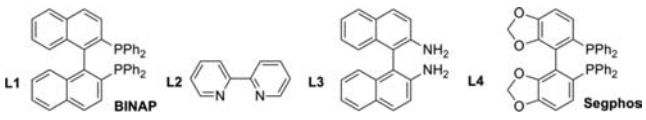
haloalkanes by the oxidative addition[7] and is usually used in activation of alkenes.[8] Disappointingly, however, no desired product was observed. However, we added 10 mol % ligand BINAP (**L1**) in the reaction system and, at the same time, tested different kinds of solvents for this reaction (Table 1 entries 2−5).

Table 1. Reaction Conditions Screening[a]



1a 2a 3aa

entry	catalyst (mol %)	ligand	solvent	base	t (°C)	yield (%)[b]
1	$[Rh(COD)Cl]_2$ (2.5)		PhMe	KOH	80	trace
2	$[Rh(COD)Cl]_2$ (2.5)	L1	PhMe	KOH	80	22
3	$[Rh(COD)Cl]_2$ (2.5)	L1	CH_3NO_2	KOH	80	0
4	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	KOH	80	24
5	$[Rh(COD)Cl]_2$ (2.5)	L1	THF	KOH	80	25
6	$Pd(PPh_3)_4$ (5)	L1	THF	KOH	80	trace
7	$[Ir(COD)Cl]_2$ (2.5)	L1	THF	KOH	80	10
8	$[Rh(COD)Cl]_2$ (2.5)	L2	THF	KOH	80	0
9	$[Rh(COD)Cl]_2$ (2.5)	L3	THF	KOH	80	trace
10	$[Rh(COD)Cl]_2$ (2.5)	L4	THF	KOH	80	22
11	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	KOH	120	46
12[c]	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	KOH	120	45
13[d]	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	KOH	120	0
14	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane		120	trace
15	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	K_2CO_3	120	75
16	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	Na_2CO_3	120	73
17	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	DBU	120	0
18	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	DABCO	120	trace
19	**$[Rh(COD)Cl]_2$ (2.5)**	**L1**	**dioxane**	**$NaHCO_3$**	**120**	**82**
20[e]	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	$NaHCO_3$	120	82
21	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	$NaHCO_3$	100	62
22	$[Rh(COD)Cl]_2$ (2.5)	L1	dioxane	$NaHCO_3$	80	36



[a]The reaction was carried out with catalyst, ligand (10 mol %), base (1.0 equiv), **1a** (0.20 mmol), and **2a** (0.40 mmol) in solvent (2.5 mL) for 24 h under argon. [b]Yield of isolated product. [c]The reaction was carried out in standard conditions with the solvent degassed. [d]The reaction was carried out in standard conditions under oxygen. [e]The reaction was carried out in standard conditions for 30 h.

Fortunately, a significant amount of the target product **3aa** was obtained by the catalysis of $[Rh(COD)Cl]_2$ with BINAP and KOH in PhMe, THF, and dioxane. Next, we also examined other low valences of transition metal catalysts such as $Pd(PPh_3)_4$ and $[Ir(COD)Cl]_2$ (entries 6−7). Results showed that $[Rh(COD)Cl]_2$ was still the best choice. Exploration of the other ligands revealed that BINAP (**L1**) and Segphos (**L4**) gave comparatively better yields (entries 8−10). For economic considerations, we chose BINAP as the ligand in this reaction. Increasing the reaction temperature also proved beneficial for the reaction: a better yield of 46% was obtained (entry 11). Following this part, the influence of oxygen in this reaction was also examined, and results indicated that an oxygen atmosphere would inhibit this reaction (entries 12−13). A series of base screening showed that the best yield (82%) was obtained in the presence of $NaHCO_3$ (entries 14−19). Further study of the reaction conditions indicated that prolonging the reaction time or reducing the temperatures did not help to improve product yield (entries 20−22).

With optimized conditions in hand, we turned our study to the scope of the substrates. First we tested the effect of the *N*-protecting group. We found that *N*-phenylacrylamide with different nitrogen-protecting groups all gave the product in comparatively good yields (**3aa**−**3fa**, Scheme 2). To our surprise, even when the nitrogen protecting group was acetyl, the reaction also proceeded well and afforded the desired product (**3da**) in moderate yield, which was a breakthrough for this type of reaction. However, when *N*-free acrylamide was used as a substrate, no desired product was detected. Then, we discovered that substrates with substituents on the para-position of the arylacrylamide reacted well and the majority of products were obtained with high yields (**3oa**−**3sa**), but when the substituent group was nitro (**3oa**), the substrate provided the product in just a 34% yield. Similarly, the products could be produced in considerable yield when different substituent groups were located at the ortho- (**3fa**−**3ia**) and meta-positions (**3ma**−**3na**) of aromatic ring, whereas when there was a halogen substituent, such as bromine at the ortho-position, the yield of product (**3ia**) was quite low and the reaction system became very complex. Then, substituent alkenes were tested. We found that just a trace amount of product (**3la**) was observed when using a monosubstituted olefin as a substrate. When the substituent group (R_2) was methyl (**3aa**) or benzyl (**3ka**), the reaction could produce the product in an excellent yield and a hydroxymethyl substituent gave a lower yield (**3ja**).

Subsequently, we investigated the reactivity of different kinds of halogenated hydrocarbons. The results indicated that the benzyl bromide and some of its derivatives could react well and provide the product in a high yield. The substituted allyl bromide (**3ai**−**3aj**) and aryl halides (**3ab**), however, did not work in this reaction. The halogenated alkanes could give only trace amounts of product (**3af**). Among the substituted benzyl bromide, aromatic ring-substituted benzyl bromide (**3ac**−**3ae**) afforded desired products in comparatively high yield, especially with electron-withdrawing substituents (**3ad**). However, possibly because of the steric problems, the reaction barely occurred if a substituent was present at the benzyl position (**3ag**−**3ah**). Finally, we tested the reactivity of different kinds of halogen and results showed that benzyl chloride gave the product (**3aa**) in a much lower yield than benzyl bromide.

Next, we focused our study on investigating the mechanism. We tested first if this was a free radical reaction; see Scheme 3 for proof that the addition of 0.5 equiv of TEMPO suppresses the

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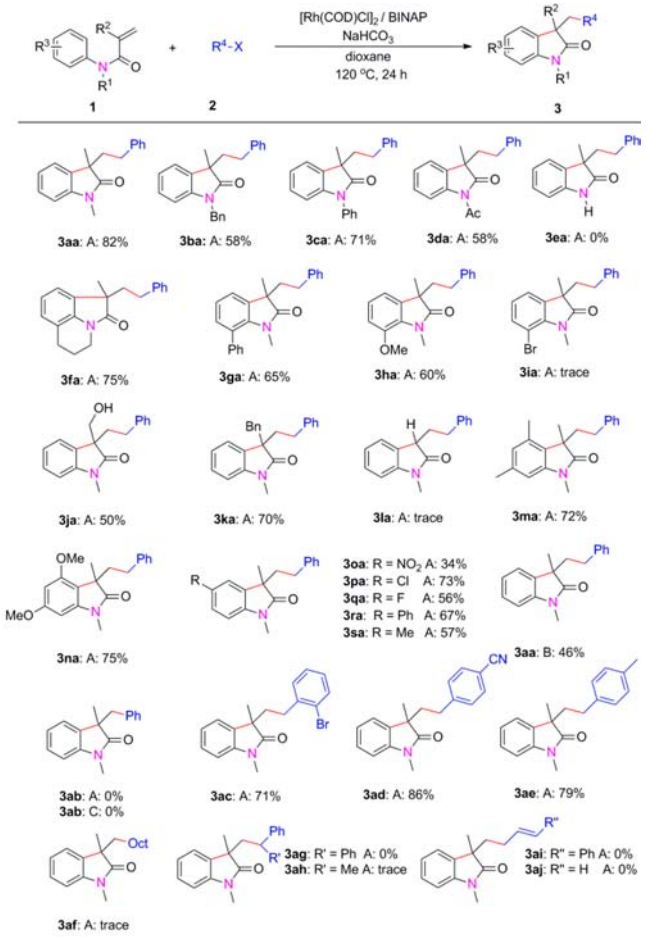
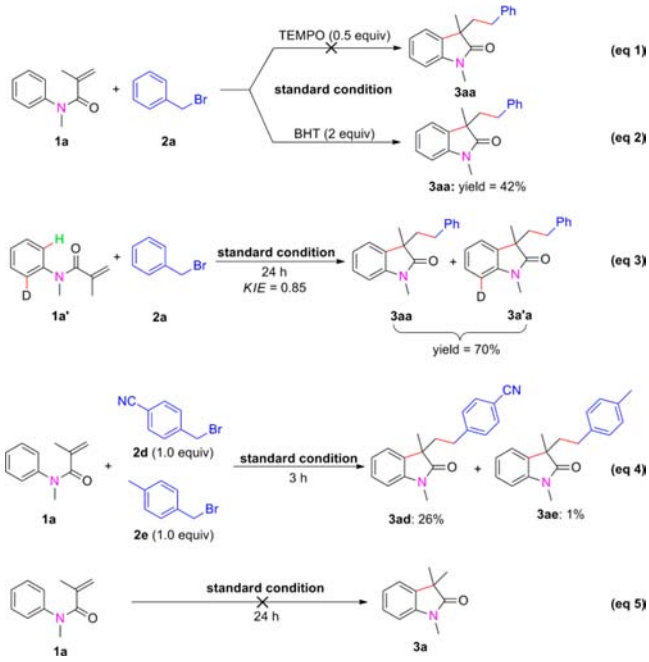
Scheme 2. Representative Example of Difunctionalization of Alkenes Leading to Oxindoles[a,b]



[a]The reaction was carried out with $[Rh(COD)Cl]_2$ (2.5 mol %), BINAP (10 mol %), $NaHCO_3$ (1.0 equiv), **1** (0.25 mmol), and **2** (0.50 mmol) in dioxane (3.1 mL) at 120 °C for 24 h under argon. Conditions A: X = Br. Conditions B: X = Cl. Conditions C: X = I. [b]Yield of the isolated product.

reaction (eq 1). However, with 2 equiv of BHT added, the reaction (eq 2) still proceeded although the yield of the desired product was a bit lower and capture of the free radical species was detected in neither reaction systems. In addition, we did not add any oxidant to this reaction system, which does not agree with the mode of mechanism for this type of reaction.[9] We were therefore able to rule out the radical mechanism for this reaction, subsequently performing an intermolecular kinetic isotope effect experiment with **1a**′ with no kinetic isotope effect ($k_H/k_D = 0.85$) observed (eq 3). This result indicates that the process of C−H rupture is not the rate-determining step.[10] We then added 1 equiv of **1a**, 1 equiv of **2d**, and 1 equiv of **2e** and allowed the reaction to occur under standard conditions for 3 h (eq 4), after which we detected 26% yield of **3ad** but just 1% yield of **3ae**. These results indicate that the rate-determining step might involve the oxidation addition, and then cyclization and reductive elimination may therefore explain the mechanism of this reaction. Finally, as a unique substrate, **1a** reacted in the presence of 2.5 mol % $[Rh(COD)Cl]_2$ and 10 mol % BINAP in dioxane at 120 °C for 24 h. However, C−H functionalization did not occur, and the product **3a** was not observed (eq 5), which

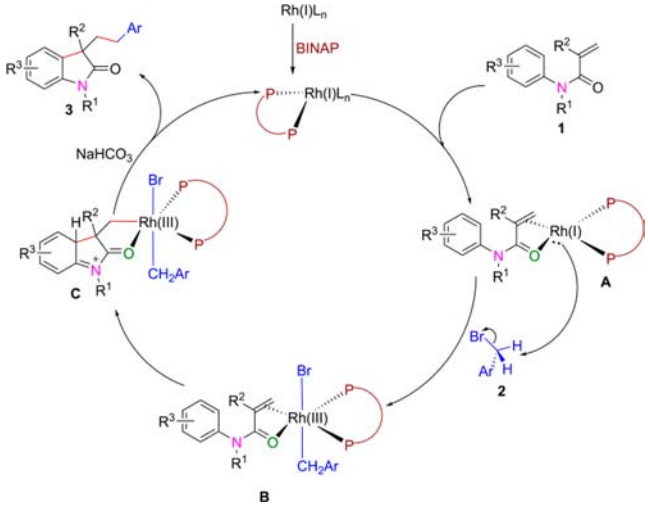
Scheme 3. Experiments to Determine the Mechanism



indicates that the initiation of halogenated hydrocarbons is necessary for this reaction.

Based on the analysis above and previous work, we illustrate a possible catalytic cycle in Scheme 4.[11] This reaction may be

Scheme 4. One Possible Mechanism of Rhodium(I) Catalyzed Intermolecular Difunctionalization of Alkenes



initiated by the coordination of the olefin in order to generate the Rh(I) complex **A**. Then, the rhodium(I) goes on to attack the halogenated hydrocarbons **2** in order to complete the process of oxidative addition in order to give complex **B**. After that, the electrophilic substitution reaction of the aromatic ring is carried out to give **C**. Finally, after the reductive elimination and proton leaving with the help of the base, the target product **3** is formed.

In conclusion, we have developed rhodium(I)-catalyzed intermolecular difunctionalization of arylacrylamides to synthesize oxindoles. This reaction successfully avoids the use of oxidant so that the method can be compatible with many oxidizable substrates. Furthermore, as this reaction is not based

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on a mechanism of free radicals, it provides a possibility for asymmetric synthesis of oxindoles, which continues to represent a difficulty for chemists.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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