Copper-Catalyzed Diarylation of Activated Alkenes with Diaryliodonium Salts

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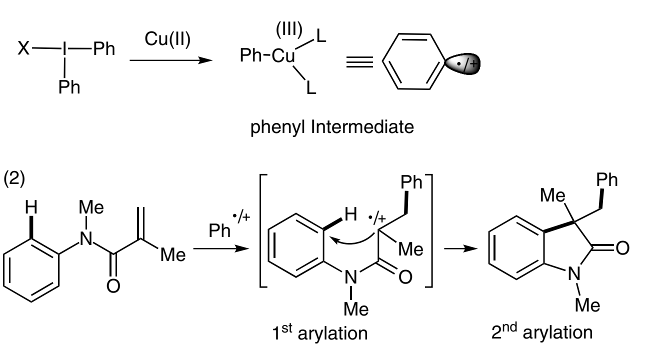
Received: 24.02.2014; Accepted after revision: 07.04.2014

Abstract: $Cu(OTf)_2$-catalyzed diarylation of activated alkenes by using diaryliodonium(III) salts has been developed. With this method, arylated oxindoles can be easily accessed in good yields. Insights into the mechanism of copper-catalyzed arylations are discussed, and the findings are expected to help increase the level of understanding of catalytic arylations with diaryliodonium salts.

Key words: alkene activation, arylation, diaryliodonium salts, oxindoles, copper triflate

Direct arylation, which allows efficient incorporation of arenes into functional molecules, has been one of the most important synthetic methodologies to have been developed in modern organic chemistry. In particular, arylation of alkenes such as the well-known Mizoroki–Heck reactions,[1] Meerwein coupling reactions,[2] and conjugate additions of activated alkenes with aryl boronic acid or organometallic reagents,[3] have been widely investigated. Among the available approaches, the use of diaryliodonium salts ($Ar_2I^+X^-$) as electrophilic arylating agents has recently been developed for use in aryl-transfer reactions with olefins. In this context, several groups have made major contributions in the field of alkene arylation for Heck-type coupling reactions by using hypervalent iodine(III) reagents in a straightforward way.[4] Very recently, Gaunt et al. also developed an electrophilic carbofunctionalization of allylic amides with diaryliodonium salts for the preparation of oxazines under copper catalysis.[5]

Oxidative difunctionalization of activated alkenes for rapid access to oxindoles has also received much attention because of the potential application of the products of such reactions in pharmaceutical research.[6] A wide range of function groups including trifluoromethyl (CF_3), azide (N_3), halogen (Br and I), diphenylphosphine oxide [$Ph_2P(O)$], carbonyl [RC(O)], nitro (NO_2), substituted alkane, trifluoromethylthio (CF_3S), sulfonyl (Ts) and oxaspirocycles have been introduced into oxindole frameworks through the application of a difunctionalization strategy[7,8] since the elegant report of arylacetoxylation of alkenes described by Zhu and co-workers in 2010.[9] However, reports on the direct arylation of alkenes for the synthesis of arylated oxindoles are scarce.[10] As outlined in Scheme 1, the use of metal catalysts in combination with diaryliodonium salts can catalytically generate electrophilic arylating species [Scheme 1, Eq. (1)], and the resulting aromatic electrophiles can be used to arylate a range of nucleophiles in an efficient way; for example, in the arylation of polyfluoroarenes reported by us recently.[11] We therefore envisioned that initial arylation of alkenes with arylating species would result in an activated electrophilic intermediate that could conduct a second arylation through a C–H functionalization cascade process [Scheme 1, Eq. (2)].



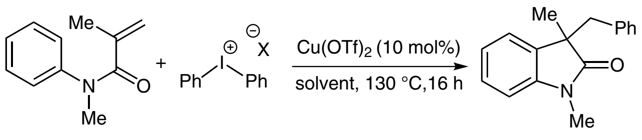
Scheme 1 Copper-catalyzed diarylation with diaryliodonium salts

Herein, we present our primary results on the copper-catalyzed diarylation of activated alkenes by using diaryliodonium(III) salts to mediate the simultaneous formation of two carbon–carbon bonds.

Our investigation began with an examination of the reaction of *N*-arylacrylamide **1a** with diphenyliodonium tetrafluoroborate in the presence of various copper catalysts in dichloroethane (DCE) at 130 °C. It was found that both copper(I) and copper(II) salts could catalyze this reaction, and that the use of 10 mol% $Cu(OTf)_2$ gave the desired product **3a** in 82% yield; the use of CuCl, CuI, $Cu(OAc)_2$ or copper thiopenecarboxylate (CuTC) resulted in decreased yields (Table 1, entries 1–5). An evaluation of the effect of counter-anions of the diphenyliodonium salts

SYNLETT 2014, 25, 1419–1424
Advanced online publication: 19.05.2014
DOI: 10.1055/s-0033-1339004; Art ID: st-2014-w0159-l

Table 1 Optimization of Reaction Conditions[a]



1a 2 3a

Entry	X	Catalyst	Solvent	Yield (%)[b]
1	BF_4	CuI	DCE	71
2	BF_4	CuCl	DCE	70
3	BF_4	$Cu(OAc)_2$	DCE	48
4	BF_4	$Cu(OTf)_2$	DCE	82
5	BF_4	CuTC[c]	DCE	50
6	OTs	$Cu(OTf)_2$	DCE	trace
7	OTf	$Cu(OTf)_2$	DCE	72
8	BF_4	$Cu(OTf)_2$	MeCN	trace
9	BF_4	$Cu(OTf)_2$	DMF	trace
10	BF_4	$Cu(OTf)_2$	EtOH	trace
11	BF_4	$Cu(OTf)_2$	toluene	52
12	BF_4	$Cu(OTf)_2$	dioxane	62
13[d]	PhI	$Cu(OTf)_2$	DCE	0

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), cat. (0.05 mmol), solvent (2 mL), 130 °C, 16 h.

[b] Isolated yield.

[c] Copper thiopenecarboxylate.

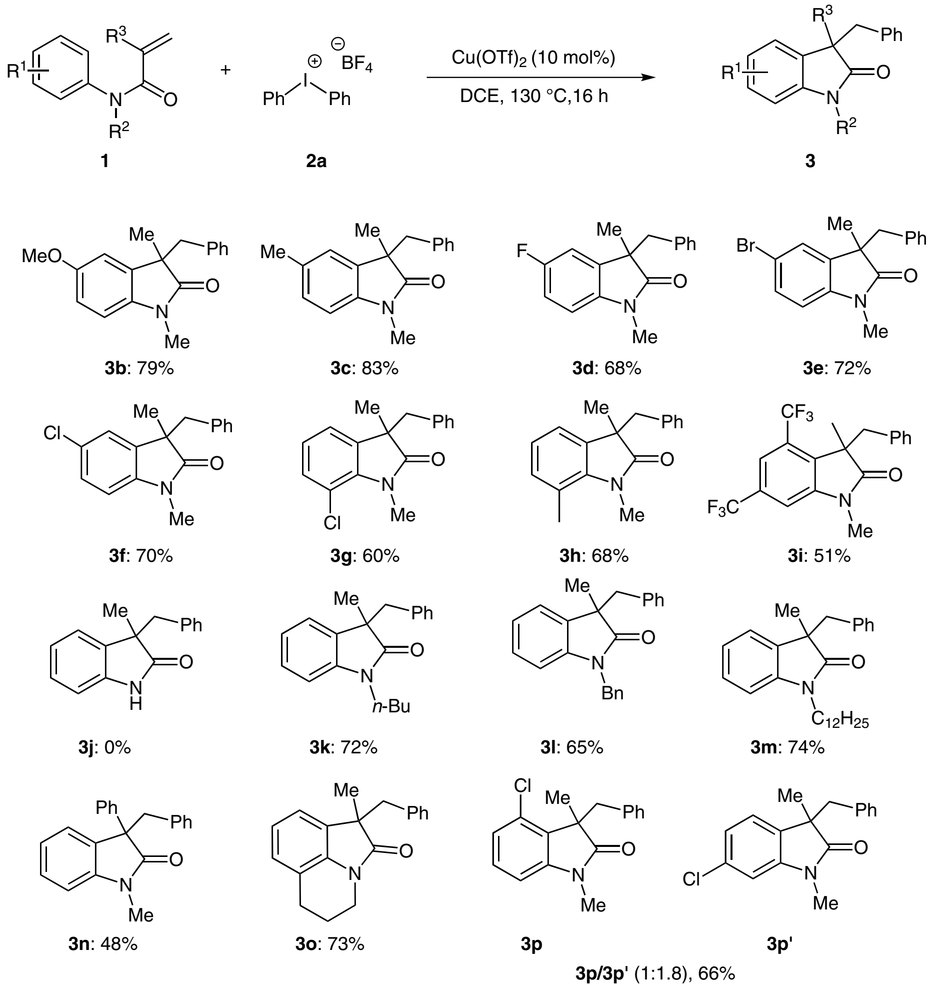
[d] Iodobenzene in place of diphenyliodonium salt.

showed that $[Ph_2I]OTf$ give **3a** in 72% yield, but $[Ph_2I]OTs$ gave no product. In the case of $[Ph_2I]OTs$, a large amount of phenyl *para*-toluenesulfonate (PhOTs) was isolated as a byproduct, which was presumably produced from decomposition of iodonium salts. The influence of solvent on the reaction was also examined. The results showed that DCE was the best choice and that only a trace amount of the desired product was observed in polar solvents such as MeCN, DMF, or ethanol (Table 1, entries 8–10). Notably, when iodobenzene was used in place of diphenyliodonium salts, no product at all was obtained.

With the optimized reaction conditions in hand, we investigated the scope of the reaction with a range of substrates **1** with diphenyliodonium tetrafluoroborate **2a**. As shown in Scheme 2, substrates with various substituents on the *ortho*-, *meta*-, and *para*-positions of arylacrylamides reacted well, and the desired products **3b**–**i** were obtained in yields of 51–83%. However, no desired product was found in the case of N-free arylacrylamides. Nevertheless, substrates with N-protecting groups *n*-butyl, benzyl and a long chain ($C_{12}H_{25}$) afforded **3k**–**m** in good yields of 65–74%. Substituted olefin **1n**, bearing a phenyl group, was also converted into the desired product in 48% yield. Tricyclic arylated oxindole **3o** was prepared in 73% yield from the corresponding acrylamide under the developed conditions. The use of *meta*-substituted acrylamide **1p** provided a mixture of products in 66% yield with a regioselectivity of 1:1.8.

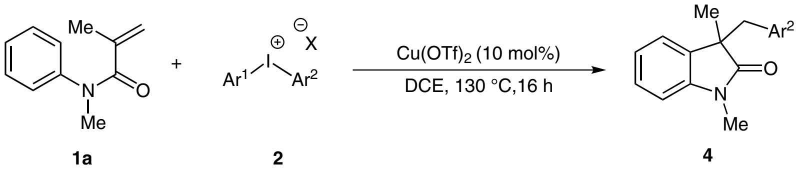
Subsequently, we examined the structural diversity of the various diaryliodonium salts **2** as arylating partners (Table 2). Notably, regardless of the electronic nature of the substituents, a wide variety of functionalities were tolerated in the diarylation of *N*-arylacrylamide. Some diaryliodonium triflates were also applied in this protocol because of their availability in the laboratory and, as expected, the desired products were obtained in good yields (entries 3–5). Steric factors severely affected the reactivity, and almost no reaction took place with bis(2,4,6-trimethylphenyl)iodonium triflate (**2f**) as arylating reagent. Unsymmetrical aryl-mesityl iodonium reagents were also employed in the diarylation of **1a**, and we were delighted to find that salts with either electron-rich or -deficient groups worked well; moreover, a broad range of *ortho*-, *meta*-, and *para*-substituted aryl rings could be readily transferred to give the desired products (entries 7–15). It is worth mentioning that the unsymmetrical salt $[(4\text{-}MeOC_6H_4)(Ph)I]BF_4$ selectively transferred the Ar group to give the desired products **3a**/**4e** in a yield of 75% with a ratio of 2.5:1 (entry 16). When [(2-thienyl)(Ph)I]OTf was employed under the standard conditions, **3a** was formed exclusively; disappointingly, the heteroatomic ring was not transferred to give the desired product (entry 17).

We then analyzed in more detail the impurities formed in this reaction and found that, in several cases, trace amounts of the undesired diarylated product were observed by LC–MS spectrometry experiments. During the synthesis of **3j**, although none of the desired product was formed, arylated and diarylated products were obtained in 21 and 39% yield, respectively [Scheme 3, Eq. (1)]. The by-products were finally identified as **5** and a double arylated product **6**, which is consistent with the *meta*-selectivity observed in the copper-catalyzed C–H bond arylation by Gaunt et al.[12a] Moreover, when olefin **7** was subjected to the reaction conditions [Scheme 3, Eq. (2)], *para*-arylation of the aromatic ring of **7** was found, but no cyclized product was observed.[12b] It was clear that the reaction site on the aromatic ring or on the olefin (Scheme 3, **A**, **B**, or **C**) was determined by the directing groups (amide or ester) on the substrates; as a result, the product outcomes differ significantly using this procedure.



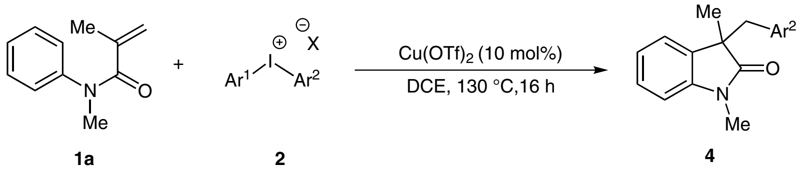
Scheme 2 Scope of the reaction with *N*-arylacrylamides. *Reagents and conditions*: **1** (0.5 mmol), **2a** (1 mmol), $Cu(OTf)_2$ (0.05 mmol), and DCE (2 mL), 130 °C, 16 h; Isolated yields are given.

Table 2 Scope of Reaction with Diaryliodonium Salts[a]



Entry	2	X	Ar^1	Ar^2	Product	Yield (%)[b]
1	**2a′**	BF_4	2-MeC_6H_4	2-MeC_6H_4	**4a**	56
2	**2b**	BF_4	4-ClC_6H_4	4-ClC_6H_4	**4b**	70
3	**2c**	OTf	4-FC_6H_4	4-FC_6H_4	**4c**	55
4	**2d**	OTf	4-*t*BuC_6H_4	4-*t*BuC_6H_4	**4d**	57
5	**2e**	OTf	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**4e**	60
6	**2f**	OTf	mesityl	mesityl	**4f**	–
7	**2a″**	BF_4	mesityl	Ph	**3a**	75
8	**2p**	BF_4	mesityl	2-MeC_6H_4	**4a**	49

Table 2 Scope of Reaction with Diaryliodonium Salts[a] (continued)

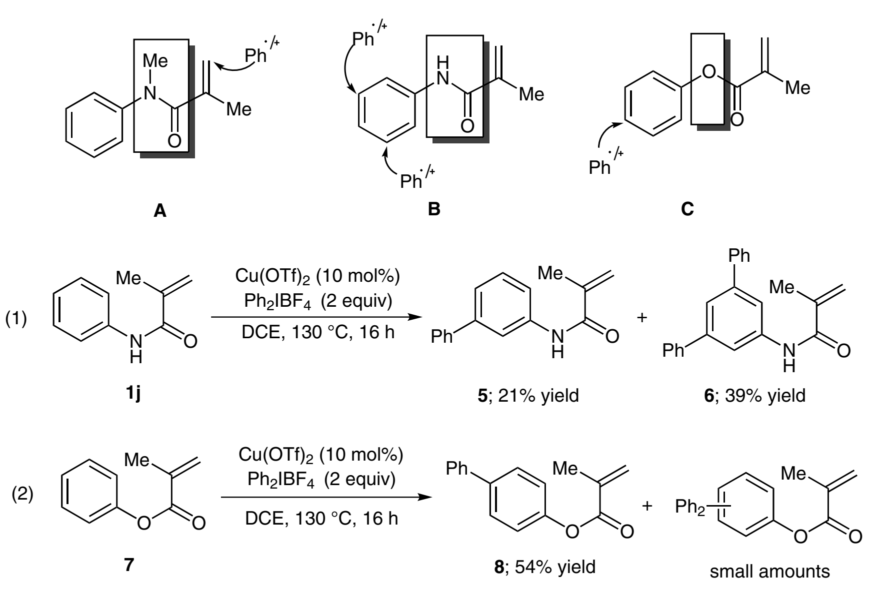


Entry	**2**	X	Ar¹	Ar²	Product	Yield (%)[b]
9	**2g**	BF_4	mesityl	4-MeC_6H_4	**4g**	59
10	**2h**	BF_4	mesityl	$4\text{-EtO}_2C\text{-C}_6H_4$	**4h**	67
11	**2i**	OTf	mesityl	3-MeC_6H_4	**4i**	61
12	**2j**	OTf	mesityl	2-BrC_6H_4	**4j**	40
13	**2k**	OTf	mesityl	4-BrC_6H_4	**4k**	58
14	**2l**	OTf	mesityl	3-FC_6H_4	**4l**	56
15	**2m**	OTf	mesityl	2-ClC_6H_4	**4m**	48
16	**2n**	BF_4	4-MeOC_6H_4	Ph	**3a**/**4e**	54/21
17	**2o**	OTf	2-Thienyl	Ph	**3a**	53

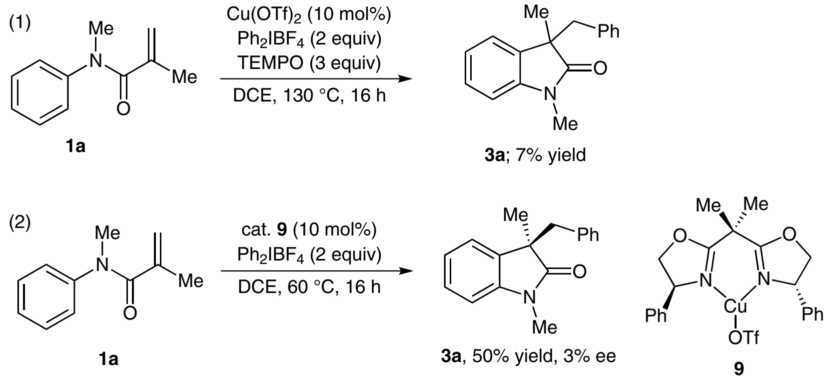
[a] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), $Cu(OTf)_2$ (0.05 mmol), DCE (2 mL), 130 °C, 16 h.
[b] Isolated yield.

We next sought to investigate the mechanism of this reaction. On the basis of previous reports,[7] the possible presence of radical intermediates[4d] in the oxidative difunctionalization of *N*-arylacrylamides was examined. A control experiment to establish the involvement of radical species in the reaction was carried out with the inclusion of the radical inhibitor 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO; 3 equiv) in the reaction of **1a** and **2a** under the same reaction conditions; in this case only 7% yield of the desired product **3a** was obtained [Scheme 4, Eq. (1)].

Gaunt and Macmillan have pioneered the development of enantioselective arylations by employing Cu-PhBox catalyst **9**.[13] Thus, an asymmetric version of the diarylation of **1a** was also attempted by using the same chiral catalyst **9**; however, only 3% ee of **3a** was obtained in 50% yield at a temperature of 60 °C [Scheme 4, Eq. (2)]. Although it is premature to draw precise conclusions on the existence of radicals or carbocations in the reaction at this stage, the above results together with control experiments imply a possible radical mechanism in the diarylation of activated alkenes **1**.



Scheme 3 The site reactivity of the copper-catalyzed arylation



Scheme 4 Control experiment and an asymmetric version of the diarylation of **1a**

In summary, the copper-catalyzed diarylation of activated alkenes by using diaryliodonium(III) salts has been developed.[14] Arylated oxindoles were synthesized in yields of 40–83%. A broad applicability of this method for the construction of relevant chemical entities is anticipated, and further studies on the reaction mechanism and asymmetric catalysis in this reaction are ongoing in our laboratory.

Acknowledgment

This work was supported by the National Nature Science Foundation of China (NSFC, 21272069, 21202186) and the Fundamental Research Funds for the Central Universities, Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(14) **Cascade Reaction of N-Arylacrylamide with Diaryliodonium Salts; General Procedure:** Cu(OTf)$_2$ (0.05 mmol, 0.1 equiv), *N*-arylacrylamide (0.5 mmol, 1.0 equiv) and diphenyliodonium salt (1.0 mmol, 2.0 equiv) were added to a dried Schlenk tube. The tube was degassed with nitrogen three times, then DCE (2.0 mL) was added by using a syringe. The mixture was heated and stirred at 130 °C for 16 h, then cooled to r.t. and the solvent was evaporated in vacuum. The crude products were directly purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 10:1) to afford the desired oxindole.