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Copper-Catalyzed Direct Arylation of Cyclic Enamides Using Diaryliodonium Salts

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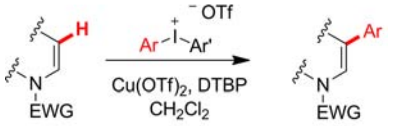
ABSTRACT



19 examples
up to 80% yield

A convenient method for the copper(II)-catalyzed direct arylation of cyclic and nonaromatic enamides using diaryliodonium salts has been developed. The reaction demonstrates large functional group tolerance, good yields, and total regioselectivity with a C(3)-functionalization. The synthetic potential of this coupling was explored by using a range of readily accessible diaryliodonium salts and enamides.

Carbon–carbon bond-forming reactions mediated by direct carbon–hydrogen bond functionalization remain a crucial challenge in organic chemistry and currently represent a powerful tool for the formation of complex building blocks.[1] Addressing this issue will thus not only improve atom economy but also increase the overall efficiency of multistep synthetic sequences.

Consequently, the direct copper-catalyzed functionalization of various derivatives by using iodonium salts has been recently extensively studied.[2] Iodonium salts are indeed extremely appealing as they are air- and moisture-stable and can be easily prepared in one step from commercially available starting materials.[2d,3] Among some recent significant studies, a major contribution was made by Gaunt's research group who reported the selective copper-catalyzed arylation of indoles,[2k] aromatic compounds,[2h–j] and alkenes.[2c] Independently, MacMillan and co-workers described an elegant enantioselective α-arylation[2g] or α-vinylation[2d] of carbonyl groups.

In our quest to generate libraries of nitrogen-containing derivatives for biological screening,[4] we sought to apply

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(1) For recent reviews of transition-metal-catalyzed C–H activation: (a) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236–10254. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879–5918. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083. (d) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991. (e) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885–1898. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169.

(2) For recent or significant examples: (a) Liu, C.; Zhang, W.; Dai, L.-X.; You, S.-L *Org. Lett.* **2012**, *14*, 4525–4527. (b) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815–10818. (c) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773–10776. (d) Skucas, E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 9090–9093. (e) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 13782–13785. (f) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778–13781. (g) Allen, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260–4263. (h) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 463–466. (i) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458–462. (j) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597. (k) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174. (l) Jalalian, N.; Petersen, T. B.; Olofsson, B. *Chem.—Eur. J.* **2012**, *18*, 14140–14149.

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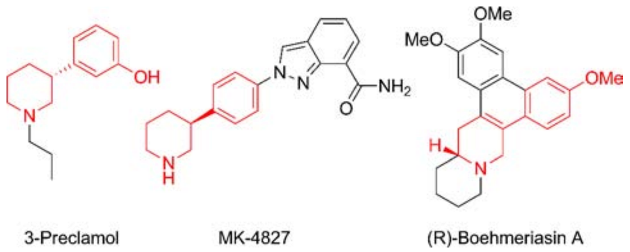
this powerful copper-catalyzed direct arylation to cyclic nonaromatic enamides. Despite their poor reactivity in comparison to enamine species, they have seen much recent use notably as nucleophiles in various processes.[5] While the direct C-2 arylation of enamides has been extensively explored,[6] only a few examples of their C-3 arylation have been reported. For instance, Rutjes developed a two-step sequence involving halogenation followed by a subsequent Pd(0) catalyzed cross-coupling reaction;[7] Loh and co-workers also described the first palladium-catalyzed direct C-3 arylation of acyclic enamides with simple arenes.[8] Inspired by these pioneering studies, we envisioned that a copper-catalyzed direct arylation reaction of nonaromatic enamides in the presence of diaryliodonium salts would afford 3-arylpiperidine backbones prevalent in a wide range of bioactive compounds (Figure 1).[9]

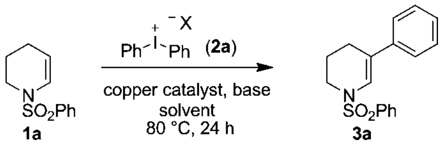
At the outset of the study, six-membered cyclic enamide **1a** and diphenyliodonium triflate **2a** were chosen as model substrates to establish the best reaction conditions (Table 1). In light of recent advances in this area, the feasibility of the direct coupling reaction was first examined using 20 mol % $Cu(OAc)_2$ as a catalyst and 2 equiv of 2,6-di-*tert*- butylpyridine (DTBP) as a base in dioxane at 80 °C (entry 1). Under these conditions, the attempted C3-arylated enamide **3a** was isolated albeit in 19% yield. Modifying the nature of the copper source identified $Cu(OTf)_2$ as the most efficient catalyst (entries 1−3). It is noteworthy to mention that the reaction is not effective in the absence of copper triflate (entry 4).



3-Preclamol MK-4827 (R)-Boehmeriasin A

Figure 1. Representive examples of 3-arylpiperidine.

Table 1. Optimization of Direct Arylation onto Enamide **1a**[a]



entry	X	Cu catalyst (20 mol %)	base (2 equiv)	solvent	yield **3a** (%)[b]
1	OTf	$Cu(OAc)_2$	DTBP	dioxane	19
2	OTf	CuCl	DTBP	dioxane	34
3	OTf	$Cu(OTf)_2$	DTBP	dioxane	67
4	OTf	none	DTBP	dioxane	12
5[c]	OTf	$Cu(OTf)_2$	DTBP	dioxane	41
6[d]	OTf	$Cu(OTf)_2$	DTBP	dioxane	41
7[e]	OTf	$Cu(OTf)_2$	DTBP	dioxane	32
8[f]	OTf	$Cu(OTf)_2$	DTBP	dioxane	30
9	OTf	$Cu(OTf)_2$	pyridine	dioxane	0
10	OTf	$Cu(OTf)_2$	Et_3N	dioxane	0
11	OTf	$Cu(OTf)_2$	DTBP	DCE	43
12	OTf	$Cu(OTf)_2$	DTBP	CH_2Cl_2	76
13	PF_6	$Cu(OTf)_2$	DTBP	CH_2Cl_2	73
14	BF_4	$Cu(OTf)_2$	DTBP	CH_2Cl_2	80
15	OTs	$Cu(OTf)_2$	DTBP	CH_2Cl_2	0
16	Br	$Cu(OTf)_2$	DTBP	CH_2Cl_2	0

[a] Reaction conditions: **1a** (1 equiv), **2a** (2 equiv), copper catalyst, and base in solvent at 80 °C for 24 h. [b] Yield of pure product after purification by column chromatography. [c] The reaction was conducted for 12 h. [d] $Cu(OTf)_2$ (10 mol %) was used. [e] Base (1 equiv) was used. [f] **2a** (1 equiv) was used.

Considering that processes have to be carried out rapidly with high atom economy and using inexpensive reagents, we next explored different parameters such as reaction time and loadings of base, diaryliodonium salt, or catalyst (entries 5−8). Unfortunately, despite all our attempts the yield of C−H arylation was not improved. Further studies highlighted the crucial role of DTBP as a base in our catalytic system (entries 9−10).[10] Pleasingly, a study of the nature of the solvent revealed that good results were obtained by using CH_2Cl_2 (entry 12); the desired adduct **3a** was thus isolated in 76% yield. Diaryliodonium salts **2** bearing different counteranions (entries 13−16) were next examined. Among all the tested reagents, triflate, hexafluorophosphate, and tetrafluoroborate diaryliodonium salts showed similar behavior, while either *p*-toluenesulfonate or bromide diaryliodonium salt was unreactive in our reaction conditions, as decomposition was observed.[21] To our

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(3) For recent reviews, see: (a) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052–9070. (b) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924–1935. See also: (c) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602–4607. (d) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610–2618.

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(5) For recent reviews: (a) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599–4657. (b) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292–301. (c) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455–3460.

(6) (a) Liu, Y.; Li, D.; Park, C.-M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7333–7336. (b) Ruan, J.; Iggo, J. A.; Berry, N. G.; Xiao, J. *J. Am. Chem. Soc.* **2010**, *132*, 16689–16699. (c) Hyder, Z.; Ruan, J.; Xiao, J. *Chem.—Eur. J.* **2008**, *14*, 5555–5566. (d) Mo, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4152–4157. (e) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751–760.

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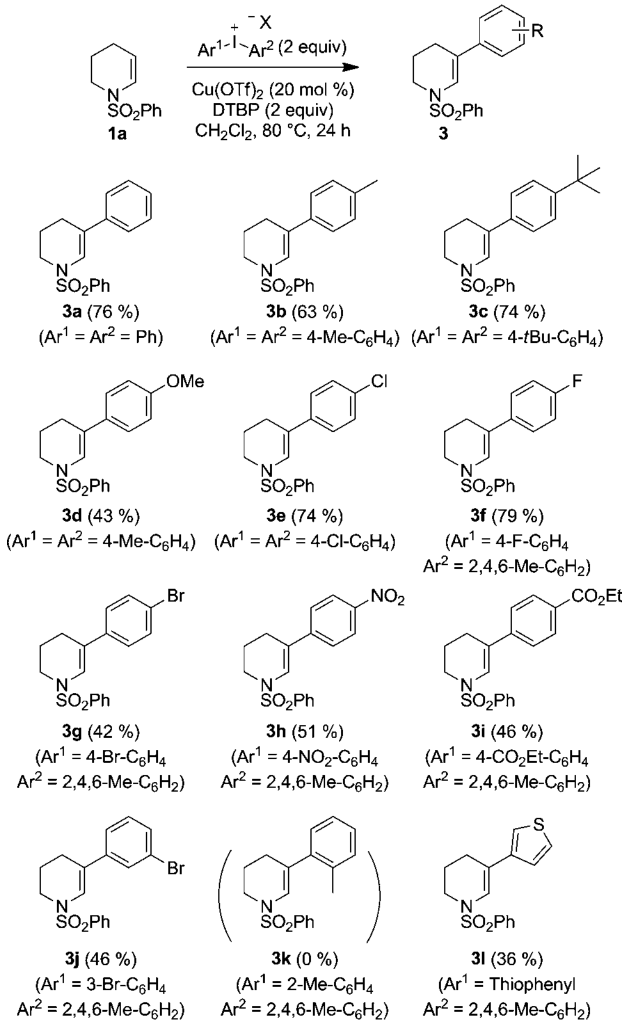
(10) Presumably a less hindered base might poison the copper catalyst and inhibit the reaction.

knowledge, this is the first report on the copper-catalyzed direct regioselective C-3 arylation of nonaromatic enamides using diaryliodonium salts.

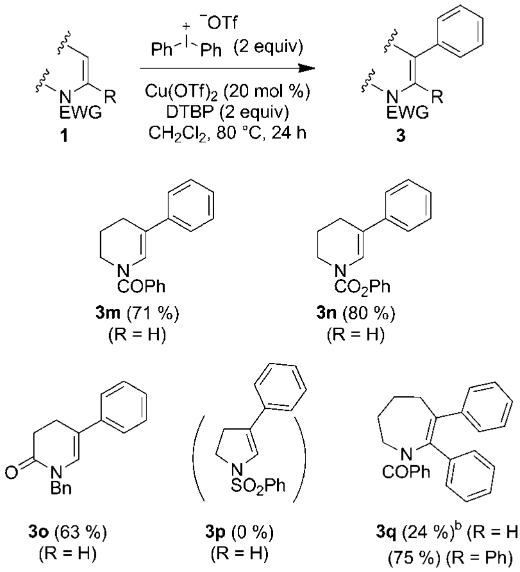
Scheme 1. Direct Coupling of Enamide **1a** with Various Diaryliodonium Salts[a]



[a] Reaction conditions: **1a** (1 equiv), **2a** (2 equiv), Cu(OTf)$_2$ (20 mol %), and DTBP (2 equiv) in CH$_2$Cl$_2$ at 80 °C for 24 h. Yield of pure product after purification by column chromatography.

Having established the optimal conditions, we next examined the scope of the transformation (Scheme 1). Gratifyingly, symmetrical diaryliodonium salts were successfully employed, and either electron-rich or -deficient arenes were found to be suitable coupling partners in this protocol, affording C3-arylated enamides **3a**–**e** in good yields. Furthermore, unsymmetrical diaryliodonium salts, containing the desired aryl group and a more voluminous second aryl unit that would not transfer in the catalytic process,[11] were tested. In this case despite moderate yields, either halogen or other electron-withdrawing substituents were well-tolerated under these conditions, demonstrating the potential of this process (**3f**–**i**). Interestingly the substituent on the aryl group could then be further functionalized, a critical consideration for the elaboration of more complex derivatives. Noteworthy, the transformation is also compatible with meta-substituted diaryliodonium salt **3j**; unfortunately the sterically more hindered enamide **3k** could not be isolated. A heteroaromatic aryliodonium salt afforded the desired enamide **3l** albeit with moderate yield. It is noticeable that a competing substrate decomposition was observed prior to the complete consumption of the starting material.

Scheme 2. Direct Coupling of Diaryliodonium Salt **2a** with Various Enamides[a]



[a] Reaction conditions: **1a** (1 equiv), **2a** (2 equiv), Cu(OTf)$_2$ (20 mol %), and DTBP (2 equiv) in CH$_2$Cl$_2$ at 80 °C for 24 h. Yield of pure product after purification by column chromatography. [b] 5 equiv of **2a** were used.

To assess the effectiveness of our reaction, different enamides were then screened by focusing on six-membered ring systems found in the 3-arylpiperidine framework (Scheme 2). The efficiency of the process was demonstrated whatever the nitrogen-protecting group employed, affording arylated enamides **3a** and **3m**–**n** in good yields.[12] The protocol was also amenable to *endo*-enamide (**3o**). Unfortunately, the five-membered enamide **3p** could not be delivered; the constrained structure is presumably responsible for the lack of reactivity. Seven-membered cyclic enamides **1q** afforded an inseparable mixture of mono- and diarylated products. However, performing the reaction with 5 equiv of diaryliodonium salt **2a** led to the diarylated enamide **3q** isolated as a sole compound in only 24% yield. In addition, we were pleased to isolate with a good yield the same difunctionalized enamide **3q** starting from the corresponding ramified substrate (R = Ph).

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[11] (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973. (b) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924–1935.

[12] The use of the *N*-Boc protecting group was unsuccessful.

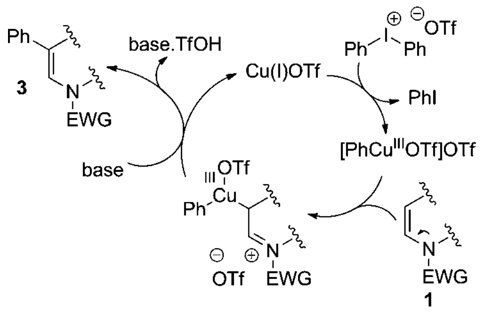
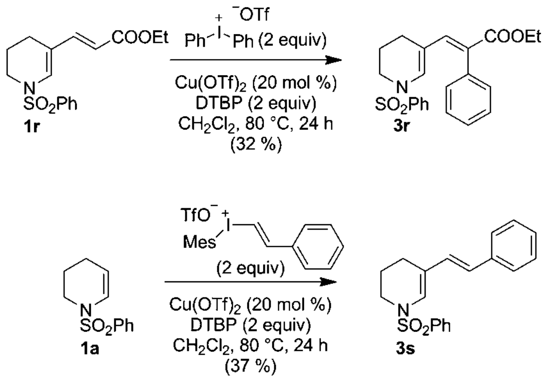


Figure 2. Proposed catalytic cycle for the direct arylation of enamide **1**.

Regarding the mechanism of the reaction, we assume, in agreement with previous reports by Gaunt and co-workers, that an oxidative insertion of Cu(OTf) into the diaryliodonium salt will afford an electrophilic Cu(III)-aryl intermediate (Figure 2).[2] The latter Cu(III)-aryl species undergoes electrophilic addition at the electron-rich C3 position of the enamide **1**. Then a reductive elimination, followed by regeneration of the enamide moiety, affords the desired framework **3**. Although this mechanism is commonly admitted, we cannot rule out the possibility that the copper catalyst might induce dissociation of the triflate anion to form an activated aryliodonium species. Then a new λ^3 iodane is generated after attack by the enamide **1** and undergoes a rapid reductive elimination to deliver the corresponding intermediate.[13] The formation of the diarylated enamide **3q** can be rationalized by a first regioselective arylation sequence at the C3 position accompanied by a second one at the C2 position. As previously described by Gaunt,[2k] a C3 to C2 migration of the C–Cu bond promoted by the *N*-benzoyl group of the seven-membered intermediate iminium ion could be envisaged.

Finally, we were delighted to find that this methodology is amenable to the more complex enamide **1r** leading to the substituted conjugated diene **3r** in moderate yield (Scheme 3).[14] In addition, vinylphenyliodonium salts[2a,d] also appeared to be interesting partners for this direct CH functionalization, albeit with low yields (**3s**). These results again highlight the potential of this process in combination with further conventional transformations.

Scheme 3. Direct Coupling of Enamides with Various Iodonium Salts[a]



[a] Reaction conditions: **1a** (1 equiv), **2a** (2 equiv), $Cu(OTf)_2$ (20 mol %), and DTBP (2 equiv) in CH_2Cl_2 at 80 °C for 24 h. Yield of pure product after purification by column chromatography.

In summary, we described herein a straightforward method for the direct copper-catalyzed C-3 arylation of cyclic and nonaromatic enamides using diaryliodonium salts as a coupling partner. The transformation is both general and efficient with respect to a broad range of substrates. To the best of our knowledge, this is the first direct strategy involving nonaromatic enamides and iodonium salts. Further studies focusing on extending the scope of the reaction to synthesize 3-arylpiperidine scaffolds as potential medicinal products will be reported in due course.

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Supporting Information Available. Full characterization details including ^1H and ^{13}C NMR, IR, MS, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(14) 56% of the starting material was recovered.