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# Oxidative [4+2] Cycloaddition of α-(*N*-Arylamino) Carbonyls with Aryl Alkenes by Multiple C−H Functionalizations and [1,2]-Aryl Shifts

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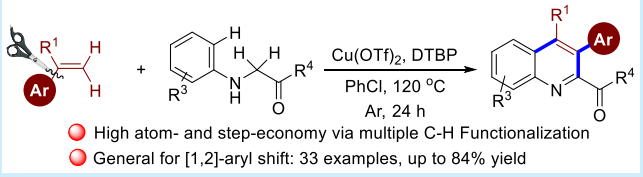
Supporting Information

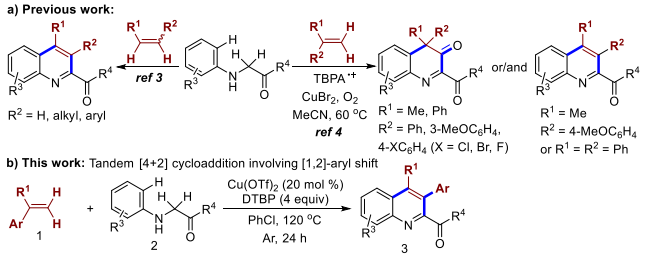
**ABSTRACT:** A new, general copper-catalyzed oxidative tandem [4+2] cycloaddition of α-(*N*-arylamino) carbonyl compounds with aryl alkenes to produce highly substituted quinolines has been developed, which allows the formation of three new C−C bonds through a sequence of multiple C−H functionalizations, annulation, and [1,2]-aryl shifts.






Quinolines represent an important class of heterocycles that occur widely as natural products, pharmaceuticals, and functional materials and serve as useful synthetic building blocks in synthesis.[1,2] The construction of quinoline scaffolds is arguably one of the most important goals of the synthetic community and continues to attract the attention of synthetic chemists.[2−4] Attractive methods include the catalytic annulation reactions of aromatic compounds with 2π components (e.g., alkenes and alkynes) involving C($sp^2$)−H functionalization for targeting these skeleton constructions.[3,4] Among them, the oxidative tandem [4+2] cycloaddition of α-(*N*-arylamino) carbonyl compounds with alkenes has proven to be particularly efficient, which allows the formation of substituted quinolines via multiple C−H functionalization and annulation cascades (Scheme 1a).[3,4] However, available examples are less abundant, and a majority of them concern a limited olefin scope (e.g., monosubstituted and 1,2-disubstituted alkenes). Mancheño and co-workers first reported an $FeCl_3$-promoted TEMPO oxoammonium salt-mediated dehydrogenative Povarov/oxidative tandem reaction of *N*-alkyl anilines with olefins for the one-pot synthesis of quinolines.[3a,b] Jia, Wang, and co-workers have established a similar version for quinolines via a domino C−H functionalization/annulation of glycine derivatives with olefins using the trisarylaminium salt/$InCl_3$/$O_2$ catalytic system.[3c,d] Recently, Jia and co-workers[3e] extended the oxidative tandem annulation method to readily available 1,1-disubstituted olefins, where 3,4-dihydro-quinoline-3-ones were formed by a consecutive C−H functionalization/C−H oxidation of various glycines and *N*-benzylanilines. Although the construction of the [1,2]-aryl shift products has been reported, the [1,2]-aryl shift process relied on two special aryl alkenes. While 1,1-diphenylethylene gave a minor 1,2-Ph shift product, the other aryl alkene, 1-methoxy-4-(prop-1-en- 2-yl)benzene, was exclusively converted to the 1,2-aryl (4-methoxyphenyl) shift product (Scheme 1a). Thus, discovery of new, general catalytic oxidative strategies for achieving tandem [4+2] cycloaddition of α-(*N*-arylamino) carbonyl compounds with aryl alkenes involving [1,2]-aryl shifts is highly desirable.

**Scheme 1. [4+2] Cycloaddition of α-(*N*-Arylamino) Carbonyl Compounds with Olefins**




Herein, we report a new oxidative tandem [4+2] cycloaddition of α-(*N*-arylamino) carbonyl compounds with aryl alkenes by means of a copper oxidative catalysis, in which an unprecedented [1,2]-aryl shift occurs (Scheme 1b).[5] The method is general for various terminal aryl alkenes and provides new access to highly substituted quinolines through multiple C−H oxidative functionalization, annulation, and [1,2]-aryl shift cascades.

Our studies began with the [4+2] cycloaddition of 1,1-diphenylethylene **1a** with 1-phenyl-2-(phenylamino)ethanone **2a** for optimization of reaction conditions (Table 1). Gratifyingly, the reaction of alkene **1a** with substrate **2a**,

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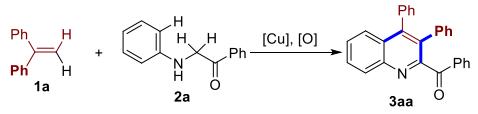
**Table 1. Optimization of the Reaction Conditions**[a]



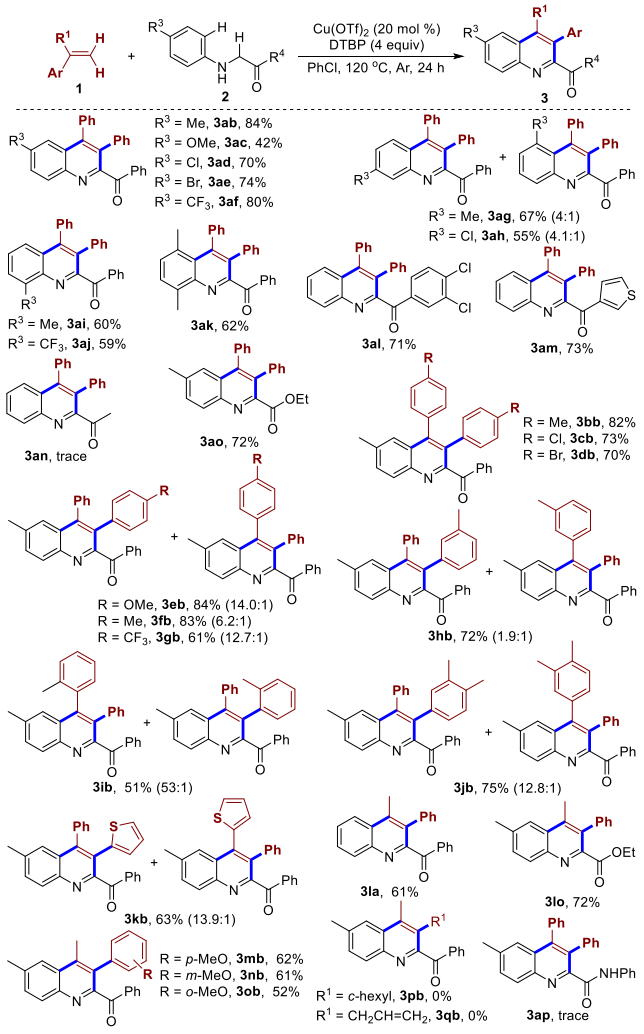

| entry | [Cu] (mol %) | [O] | solvent | $T$ (°C) | yield (%) |
|---|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ (20) | DTBP | MeCN | 120 | 69 |
| 2 | $CuCl_2$ (20) | DTBP | MeCN | 120 | 10 |
| 3 | $CuBr_2$ (20) | DTBP | MeCN | 120 | 12 |
| 4 | $Cu(OAc)_2$ (20) | DTBP | MeCN | 120 | 51 |
| 5 | CuOTf (20) | DTBP | MeCN | 120 | 10 |
| 6 | $Fe(OTf)_3$ (20) | DTBP | MeCN | 120 | 10 |
| 7 | – | DTBP | MeCN | 120 | 0 |
| 8 | $Cu(OTf)_2$ (10) | DTBP | MeCN | 120 | 23 |
| 9 | $Cu(OTf)_2$ (40) | DTBP | MeCN | 120 | 68 |
| 10 | $Cu(OTf)_2$ (20) | DTBP | DMF | 120 | 6 |
| 11 | $Cu(OTf)_2$ (20) | DTBP | toluene | 120 | 42 |
| 12 | $Cu(OTf)_2$ (20) | DTBP | PhCl | 120 | 72 |
| 13 | $Cu(OTf)_2$ (20) | TBHP | PhCl | 120 | 10 |
| 14 | $Cu(OTf)_2$ (20) | TBPB | PhCl | 120 | 62 |
| 15 | $Cu(OTf)_2$ (20) | $PhI(OAc)_2$ | PhCl | 120 | 0 |
| 16 | $Cu(OTf)_2$ (20) | $O_2$ | PhCl | 120 | 0 |
| 17 | $Cu(OTf)_2$ (20) | – | PhCl | 120 | 0 |
| 18 | $Cu(OTf)_2$ (20) | DTBP | PhCl | 130 | 70 |
| 19[b] | $Cu(OTf)_2$ (20) | DTBP | PhCl | 100 | 23 |
| 20[c] | $Cu(OTf)_2$ (20) | DTBP | PhCl | 120 | 68 |

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), [M], [O] (4 equiv), solvent (1 mL), argon, 24 h. [b]Recovery of **1a** of >67%. [c]**1a** (1 g, 5.56 mmol) and PhCl (5 mL) for 48 h.

$Cu(OTf)_2$, and di-*tert*-butyl peroxide (DTBP) in MeCN at 120 °C for 24 h unexpectedly afforded the [1,2]-Ph shift product **3aa**[6] in 69% yield (entry 1). Although other Cu and Fe salts, including $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, CuOTf, and $Fe(OTf)_3$, displayed catalytic activity, they were less efficient than $Cu(OTf)_2$ (entries 2–6, respectively). Both the Cu catalyst and the peroxide oxidant are crucial, as omission of each led to no cycloaddition reaction (entries 7 and 17). While a smaller amount (10 mol %) of $Cu(OTf)_2$ had a negative effect (entry 8), a larger amount (40 mol %) of $Cu(OTf)_2$ gave no obvious improvement in yield (entry 9). Screening the effect of solvents revealed that the use of DMF and toluene showed lower reactivity (entries 10 and 11, respectively) but the use of the PhCl solvent slightly increased the yield from 69% (entry 1) to 72% yield (entry 12). Other peroxides, *tert*-butyl hydroperoxide (TBHP) and *tert*-butyl perbenzoate (TBPB), were inferior to DTBP (entries 13 and 14, respectively), and $PhI(OAc)_2$ and $O_2$ were inert (entries 15 and 16, respectively). The effect of the reaction temperature was found to affect the reaction. Using 130 °C did not improve the yield (entry 18), but at 100 °C, the yield of **3aa** decreased dramatically (entry 19). The reaction could be applied to a 1 g scale of alkene **1a**, furnishing **3aa** in good yield (entry 20).

Under the optimal reaction conditions, the scope of this [4+2] cycloaddition protocol with regard to both alkenes **1** and α-(*N*-arylamino) carbonyl compounds **2** was next investigated (Scheme 2). The generality of α-(*N*-arylamino) carbonyl compounds **2** in the presence of alkyne **1a**, $Cu(OTf)_2$, and DTBP was initially explored (Scheme 2). Several substituents, namely, Me, MeO, Cl, Br, and $CF_3$, on the aromatic ring of the *N*-aryl moiety were well tolerated, and the position effect had a fundamental influence on reactivity

**Scheme 2. Variation of the Aryl Alkenes (1) and α-(*N*-Arylamino) Carbonyl Compounds (2)**[a]




[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), $Cu(OTf)_2$ (20 mol %), DTBP (4 equiv), PhCl (1 mL), 120 °C, argon, 24 h.

(**3ab**–**ak**). While *p*-Me-substituted substrate **2b** furnished **3ab** in 84% yield, *m*- and *o*-Me-substituted substrates **2g** and **2i** afforded **3ag** and **3ai** in 67% and 60% yields, respectively. Interestingly, halogen-substituted substrates **2d**, **2e**, and **2h** were highly reactive, giving halo-possessing products **3ad**, **3ae**, and **3ah**, respectively, in moderate to good yields. Substrates **2f** and **2j** with an electron-withdrawing $CF_3$ group were smoothly converted to **3af** and **3aj**, respectively. The bulky 2,5-diMe-substitued substrate **2k** also produced **3ak** in 62% yield. The reaction with 1-(3,4-dichlorophenyl)-2-(phenylamino)-ethanone **2l** or 2-(phenylamino)-1-(thiophen-2-yl)ethanone **2m** was performed successfully (**3al** or **3am**, respectively). Unfortunately, 1-(phenylamino)propan-2-one **2n** had no reactivity (**3an**). The optimal conditions were found to be applicable to α-(*N*-phenylamino) ester **2o**, giving **3ao** in 72% yield.

The [4+2] cycloaddition protocol was subjected to a wide range of 1,1-disubstituted olefins **1b**–**p** (Scheme 2). For symmetrical 1,1-disubstituted olefins **1b**–**d** that possess the same two aryl groups, the reaction with substrate **2b**, $Cu(OTf)_2$, and DTBP selectively afforded **3bb**–**db**, respectively, in high yields. In the case of unsymmetrical 1,1-



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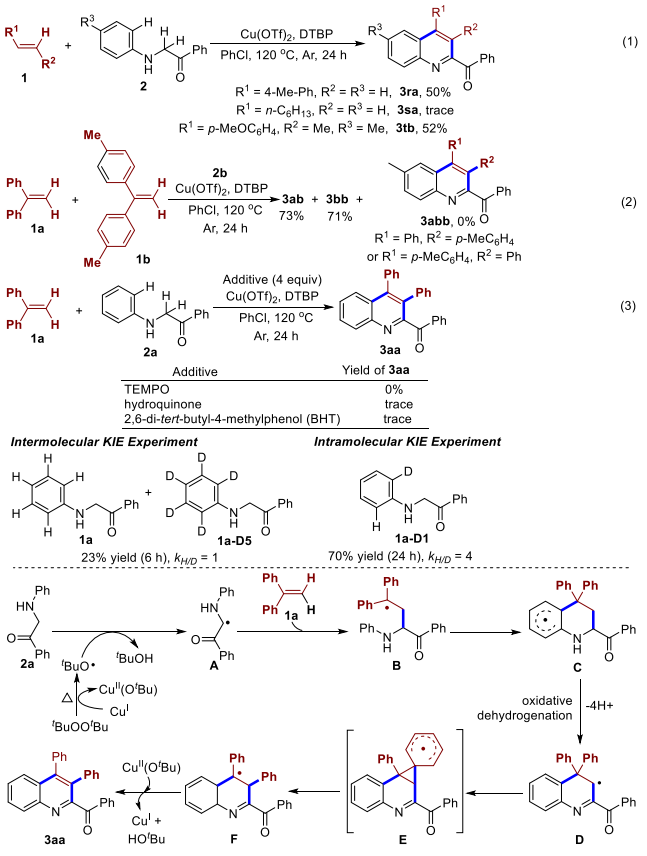
disubstituted olefins **1e**–**k** with two different aryl groups, which aryl group undergoes the [1,2] shift depends on the electronic and steric hindrance properties: electron-deficient aryl groups > electron-rich aryl groups > Ph, and *p*- and *m*-substituted aryl group > Ph > *o*-substituted aryl groups (**3eb**–**kb**). For example, olefins **1e**, **1f**, and **1g**, bearing a Ph group and a *p*-substituted aryl group, mainly gave the *p*-substituted aryl-migration products **3eb**, **3fb**, and **3gb**, respectively, as the major products. Although the *m*-substituted aryl-migration product **3hb** was the major product from olefin **1h** having a Ph group and an *m*-substituted aryl group, the ratio of two isomers was decreased to 2:1. The same version of migration was observed in the reaction with 1-phenyl-1-(3,4-dimethylphenyl)ethylene **1j** and 1-phenyl-1-(thiophen-2-yl)-ethylene **1k**, which provided selectivity toward **3jb** and **3kb**, respectively, mainly through the migrating 3,4-dimethylphenyl group or the migrating thiophen-2-yl group. Because of the steric hindrance effect, the migration of the Ph group had precedence over the *o*-Me-substituted-aryl group with a 53:1 ratio (**3ib**). Gratifyingly, a variety of 1-methyl-1-arylethylenes **1l**–**o** worked well and exclusively afforded aryl-migration products **3la**, **3lo**, and **3mb**–**ob** in moderate to good yields. Unfortunately, 1,1-dialkyl alkenes **1p** and **1q** and *α*-(*N*-arylamino) amide **2p** were not viable for the reaction.

As shown in Scheme 3, the optimal conditions were also consistent with terminal and internal aryl olefins **1r** and **1t**, giving the corresponding products **3ra** and **3tb**, respectively, in moderate yields (eq 1).[3] However, aliphatic olefin **1s** had no reactivity for the reaction (**3sa**).

**Scheme 3. Other Alkenes, Control Experiments, and Possible Mechanism**




To understand the mechanism for the current reaction, control experiments were performed (Scheme 3). A mixture of two different 1,1-diaryl olefins **1a** and **1b** reacted with substrate **2b** afforded products **3ab** and **3bb**, respectively, in which no cross aryl-migrating products were observed (eq 2). The results suggest that the [1,2]-aryl shift proceeds via an intramolecular process. The reaction of olefins **1a** with substrate **2a** was completely suppressed when a stoichiometric amount of the radical inhibitor was used (4 equiv), including TEMPO, hydroquinone, and BHT (eq 3). The results imply that the current reaction includes a free radical process, which was also supported by the intermolecular kinetic isotope effect experiment ($k_H/k_D$ = 1.0).[7] Notably, a strong high kinetic isotope effect ($k_H/k_D$ = 4.0) in the intramolecular experiment supported the idea that the aromatic C($sp^2$)–H functionalization step is rate-limiting.[7]

The mechanism for this oxidative [4+2] cycloaddition protocol was proposed (Scheme 3).[3−5,8] Initially, the splitting of an *α*-C($sp^3$)–H bond in substrate **2a** with the active $Cu^I$ species and DTBP affords alkyl radical **A**, the $Cu^{II}(O^tBu)$ species, and $HO^tBu$ under heating.[5] Subsequently, the addition of alkyl radical **A** across the C=C bond in 1,1-diphenylethylene **1a** produces radical intermediate **B**, followed by cyclization with the *N*-aryl ring that gives radical intermediate **C**. Single-electron oxidation and continuous oxidative deprotonation of intermediate **C** afford intermediate **D**,[8] which would subsequently undergo an intramolecular 1,2-Ph shift that occurs via spiro[2,5]octadienyl radical **E** to deliver intermediate **F**.[5] Finally, intermediate **F** is converted to **3aa** through the single-electron oxidation by the $Cu^{II}(O^tBu)$ species.

In summary, we have developed a novel, general copper-catalyzed oxidative [4+2] cycloaddition of *α*-(*N*-arylamino) carbonyl compounds with aryl alkenes for producing highly substituted quinolines involving functionalization of multiple C–H bonds and [1,2]-aryl shifts. This method enables an unprecedented [1,2]-aryl shift with excellent levels of selectivity and high atom and step economy and provides general access to diverse substituted quinoline scaffolds using a multiple-C–H oxidative radical functionalization strategy.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02169.

Experimental details, NMR spectra, and details of the experiments (PDF)

### Accession Codes

CCDC 1417836 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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