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**To be cited as:** *Chem. Asian J.* 10.1002/asia.202001032

**Link to VoR:** https://doi.org/10.1002/asia.202001032

A Journal of
ACES Asian Chemical Editorial Society

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

10.1002/asia.202001032

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COMMUNICATION

# $CuCl_2$-Mediated Oxidative Intramolecular α-Arylation of Ketones with Phenolic Nucleophiles via Oxy-Allyl Cation Intermediates

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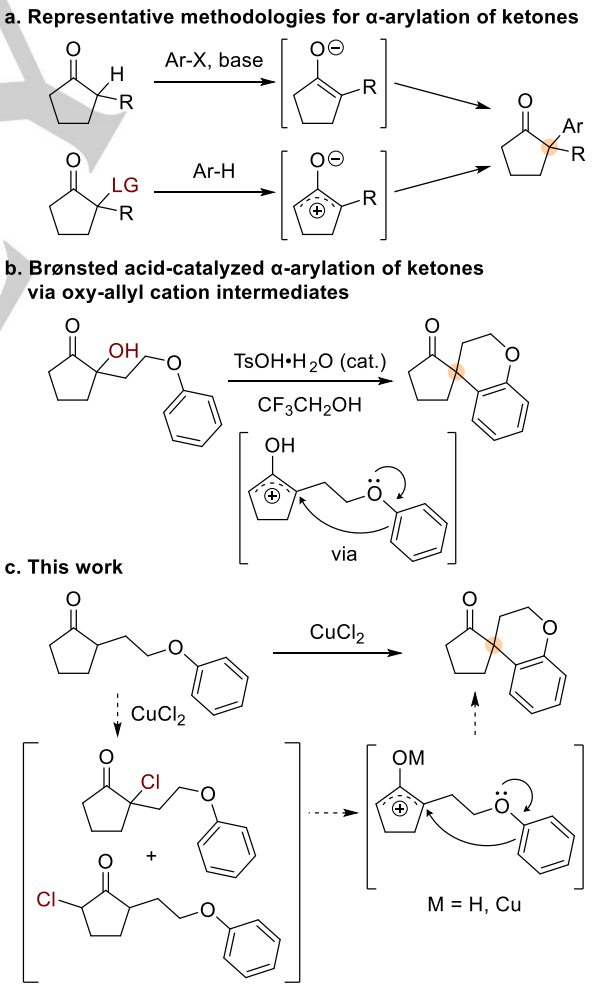
**Abstract:** α-Functionalization of ketones in an umpolung fashion can be achieved by nucleophilic addition to the oxy-allyl cation intermediate. However, applicable carbon nucleophiles are limited to ones with high nucleophilicity. Additionally, introduction of a leaving group to the α-position of ketone substrates is required beforehand. Herein, we report the $CuCl_2$-mediated oxidative intramolecular α-arylation of ketones with less nucleophilic phenolic moieties as carbon nucleophiles via α-chlorination of ketones and the subsequent generation of the oxy-allyl cation intermediates, giving ketones with a quaternary carbon center at the α-position.

α-Arylated carbonyl compounds are found in natural products and pharmaceuticals and considered as one of important building blocks.[1] Among them, ketones with a quaternary carbon center at the α-position are valuable synthetic intermediates, while their synthesis is quite difficult.[2] To date, a number of synthetic methods have been developed to prepare such motifs.[3] In general, α-arylketones are prepared from a nucleophilic enolate and an electrophilic arylating agent (Scheme 1a, upper).[4,5]

In an umpolung strategy, on the other hand, addition of a nucleophilic aromatic compound to an electrophilic α-carbon of ketones has been significantly less investigated (Scheme 1a, lower).[6] Recently, a number of nucleophilic additions to the oxy-allyl cation intermediates derived from ketones have been investigated.[7,8] In the presence of a base or an acid, ketones having a leaving group at the α-position can be converted to highly reactive electrophilic oxy-allyl cation intermediates, which are known to react with various nucleophiles. However, less nucleophilic aromatic compounds such as phenol derivatives are not suitable nucleophiles for this type of reaction.




**Scheme 1.** Strategies for α-Arylation of Ketones via Oxy-allyl Cation Intermediates.

10.1002/asia.202001032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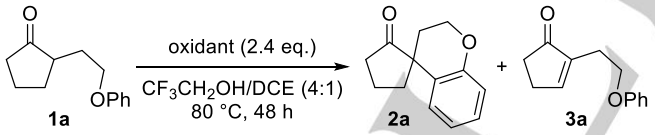
Recently, we have reported the Brønsted acid-catalyzed intramolecular α-arylation of ketones with phenolic nucleophiles via oxy-allyl cation intermediates (Scheme 1b).[6k] However, ketone substrates require a hydroxy group as a leaving group at the α-position to generate the oxy-allyl cation intermediate, and the difficulty in their synthesis limits the synthetic utility of this transformation. In this context, we became interested in developing an intramolecular α-arylation of simpler ketones via introduction of a leaving group in-situ and the subsequent generation of the oxy-allyl cation intermediate. Since copper(II) halides are known to be an α-halogenating agent of ketones as well as a Lewis acid,[9] such tandem sequence might be realized (Scheme 1c). Herein, we describe $CuCl_2$-mediated oxidative intramolecular α-arylation of ketones with a tethered phenolic nucleophile. In the present reaction, a chroman core with a quaternary carbon center is constructed, which is an important structural motif in bioactive molecules.[10]

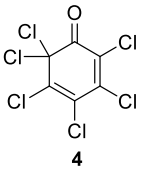
We first investigated the oxidative intramolecular α-arylation of cyclopentanone **1a** bearing a tethered phenoxy group with 2.4 equiv of oxidant in trifluoroethanol ($CF_3CH_2OH$) and dichloroethane (DCE) at 80 °C (Table 1). When halogenating agents such as $CuBr_2$, $CuCl_2$, NCS, 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (**4**) were employed as oxidant, respectively, the desired spirocyclic ketone **2a** was obtained in low to good yields (entries 1–4). In these cases, formation of enone **3a** was observed. The reaction of **1a** with $CuCl_2$ in the presence of 1N HCl gave **2a** in a slightly decreased yield (entry 5). The addition of 2,6-*t*$Bu_2$-pyridine completely shut down the reaction (entry 6). Use of DCE as solvent resulted in no reaction, and the presence of $CF_3CH_2OH$ was shown to be crucial for the present reaction (entries 7 and 8).[11] When the reaction was performed under an oxygen atmosphere with the expectation that the in-situ generated CuCl would be reoxidized, **2a** was obtained in a slightly increased yield (entry 10).[9d]

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




| Entry | Oxidant | Additive[b] | **2a** [%][c] | **3a** [%][c] |
|---|---|---|---|---|
| 1 | $CuBr_2$ | - | 45 | 16 |
| 2 | $CuCl_2$ | - | 72 | 14 |
| 3 | NCS | - | 14 | 17 |
| 4 | **4** | - | 25 | <1 |
| 5 | $CuCl_2$ | 1N HCl aq. | 62 | 7 |
| 6 | $CuCl_2$ | 2,6-*t*$Bu_2$-pyridine | 0 | 0 |
| 7[d] | $CuCl_2$ | - | 59 | 7 |
| 8[e] | $CuCl_2$ | - | 0 | 2 |
| 9[f] | $CuCl_2$ | - | 72 | 8 |
| 10[f,g] | $CuCl_2$ | - | 76 | 6 |

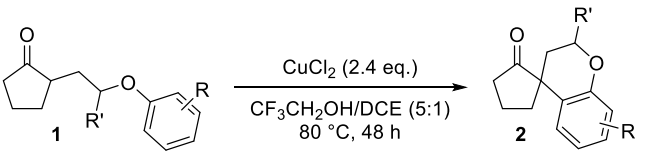
[a] All reactions were performed on a 0.1 mmol scale in 1.0 mL of solvent. [b] Use of 2.4 eq. of additive. [c] Determined by $^1$H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.[d] $CF_3CH_2OH$ as solvent. [e] DCE as solvent. [f] $CF_3CH_2OH$/DCE (5:1) as solvent. [g] Performed under 1 atm of $O_2$.

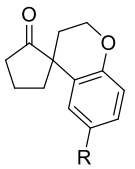


**4**

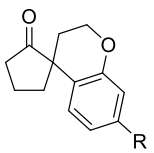
We next investigated the scope of cyclopentanones bearing a variety of phenolic nucleophiles (Table 2).[12] The reaction of ketone having an electron-rich *para*-methylphenyl group afforded **2b** in good yield. Introduction of a *para*-methoxy group led to a significant decrease in yield (33%) because of the oxidation of the product **2c**. The shorter reaction time resulted in an increase in yield (50%). When an electron withdrawing Br group was introduced to the *para*-position, **2d** was obtained in low yield (11%) due to the undesired enone formation and the remaining α-chloroketone. Interestingly, the addition of 1.2 equiv of $ZnCl_2$ was effective for increasing the yield of **2d** (44%). The present α-arylation was not applicable to a phenolic nucleophile having a cyano group, probably because of the decreased electron density of the aromatic ring and further deactivation by protonation (**2e**). The *meta*-substitution led to the formation of single regioisomers (**2f**–**2i**). The yield of **2i** was drastically improved in the presence of a catalytic amount of $FeCl_2$. Incorporation of *ortho*-methyl group proved to be slightly detrimental, giving **2j** in 48% yield. When a 2-naphthoxy group was introduced, the reaction proceeded at the sterically congested 1-position of the naphthyl group exclusively (**2k**). The substrate having a branched tether gave **2l** in low yield as a mixture of diastereomers.

**Table 2.** Substrate Scope of Phenolic Nucleophiles.[a]

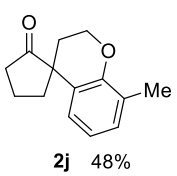


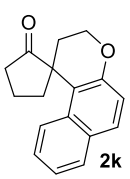
**2a** R = H 76%[b] **2d** R = Br 11%
**2b** R = Me 74% 44%[d]
**2c** R = OMe 50%[c] **2e** R = CN 0%

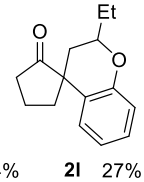


**2f** R = Me 59% **2i** R = Br 13%
**2g** R = OMe 40%[c] 54%[e]
**2h** R = F 58%
67%[e]



**2j** 48%


**2k** 74%



**2l** 27% (dr = 1.3:1)[f,g]

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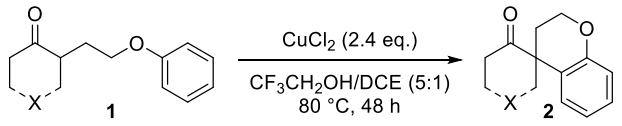
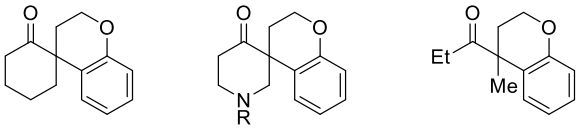
[a] All reactions were performed on a 0.1 mmol scale in 1.0 mL of solvent. [b] Performed under 1 atm of $O_2$. [c] Performed for 24 h. [d] $ZnCl_2$ (1.2 eq.) was added. [e] $FeCl_2$ (20 mol%) was added. [f] $NiCl_2$ (1.2 eq.) was added. [g] Using a diastereomer mixture (1.1:1) as starting material.

We then investigated the substrate scope of ketone moiety and the results are summarized in Table 3. A cyclic ketone having a larger ring size was well tolerated (**2m**). While the reaction of 4-piperidone derivatives did not proceed, the addition of 2.4 equiv of $FeCl_2$ led to the formation of the desired products **2n** and **2o** in modelate yields. In the presence of 20 mol% of $ZnCl_2$, an acyclic ketone also provided the arylation product **2p**, albeit in low yield.

**Table 3.** Substrate Scope of Ketones.[a]




**2m** 68% 74%[b]

**2n** R = Ts 0% 35%[c]

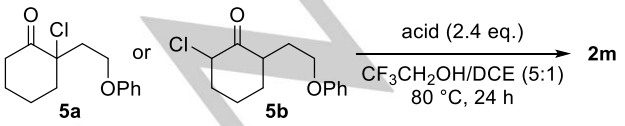
**2o** R = Ns 0% 40%[c]

**2p** 0% 17%[d]

[a] All reactions were performed on a 0.1 mmol scale in 1.0 mL of solvent. [b] $NiCl_2$ (20 mol%) was added. [c] $FeCl_2$ (2.4 eq.) was added. [d] $ZnCl_2$ (20 mol%) was added.

To gain mechanistic insight into the present α-arylation of ketones, arylation of α-chloroketones **5** was performed as shown in Table 4. Under the standard reaction conditions using $CuCl_2$, the reaction of α-chloroketone **5a** proceeded to afford the arylation product **2m** in excellent yield (entry 1). The reaction with CuCl and HCl, which can be generated in the course of the present reaction, also gave **2m** in moderate yield (entry 2). Without copper chloride, the reaction proceeded smoothly (entry 3). Use of α'-chloroketone **5b** led to the formation of **2m** under the same conditions (entries 4–6). These results imply that the identical oxy-allyl cation intermediate would be generated in-situ from **5a** and **5b** as the electrophilic species before the nucleophilic addition of the phenolic moiety and that the regioselectivity in the chlorination does not affect the present intramolecular arylation.

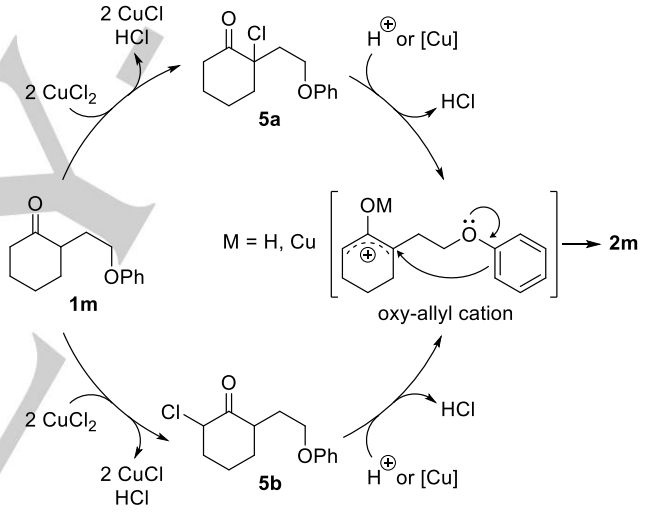
**Table 4.** α-Arylation of α-Chloroketones.[a]




| Entry | 5 | Acid | Yield [%][b] |
|---|---|---|---|
| 1 | **5a** | $CuCl_2$ | 97 |
| 2 | **5a** | CuCl, HCl | 63 |
| 3 | **5a** | HCl | 90 |
| 4 | **5b**[c] | $CuCl_2$ | 96 |
| 5 | **5b**[c] | CuCl, HCl | 94 |
| 6 | **5b**[c] | HCl | 99 |

[a] All ractions were performed on a 0.1 mmol scale in 1.0 mL of solvent. [b] Determined by $^1$H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Using a mixture of **5b**/**5a** (16:1) as starting material.

A plausible mechanism is illustrated in Scheme 2. In the presence of copper(II) chloride, ketone **1m** undergoes chlorination to generate α-chloroketones **5a** and **5b** along with two molecules of copper(I) chloride and an equivalent of HCl.[9] Formation of the enol or the copper enolate and the acid-mediated-elimiation of chloride ion generate the key oxy-allyl cation intermediate. Finally, nucleophilic addition of the phenolic moiety to the electrophilic α-carbon gives the spirocyclic ketone **2m**.




**Scheme 2.** Proposed Mechanism.

In conclusion, we have developed the $CuCl_2$-mediated oxidative intramolecular α-arylation of ketones with the tethered phenolic nucleophiles via α-chlorination and the subsequent generation of the oxy-allyl cation intermediates. This study has demonstrated that ketones having no leaving group can be employed as the oxy-allyl cation precursors, expanding the utility of the umpolung α-functionalization of ketones.

## Acknowledgements

This work was supported by JSPS KAKENHI Grant Numbers JP26220803, JP18H01975, and JP20H04815 (Hybrid Catalysis). Y.A. is grateful for Fellowships for Young Scientists from the Japan Society for the Promotion of Science (JSPS).

## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** umpolung • halogenation • arylation • quaternary stereocenters • ketones

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[12] Since *N*,*N*-dimethylaniline was smoothly consumed in the presence of $CuCl_2$, it seems to be difficult to apply the present method to the substrate having a nitrogen tether instead of the oxygen linkage.

10.1002/asia.202001032





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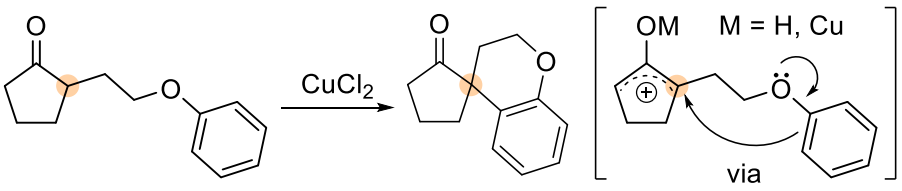


**Intramolecular α-arylation of ketones** in an umpolung fashion was achieved through the addition of tethered phenolic nucleophiles to the electrophilic oxy-allyl cation intermediates which could be formed from the in-situ generated α-chloroketones, allowing the formation of ketones bearing an all carbon quaternary center at the α-position.