C–C Bond Activation

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α-Arylation of Carbonyl Compounds through Oxidative C–C Bond Activation

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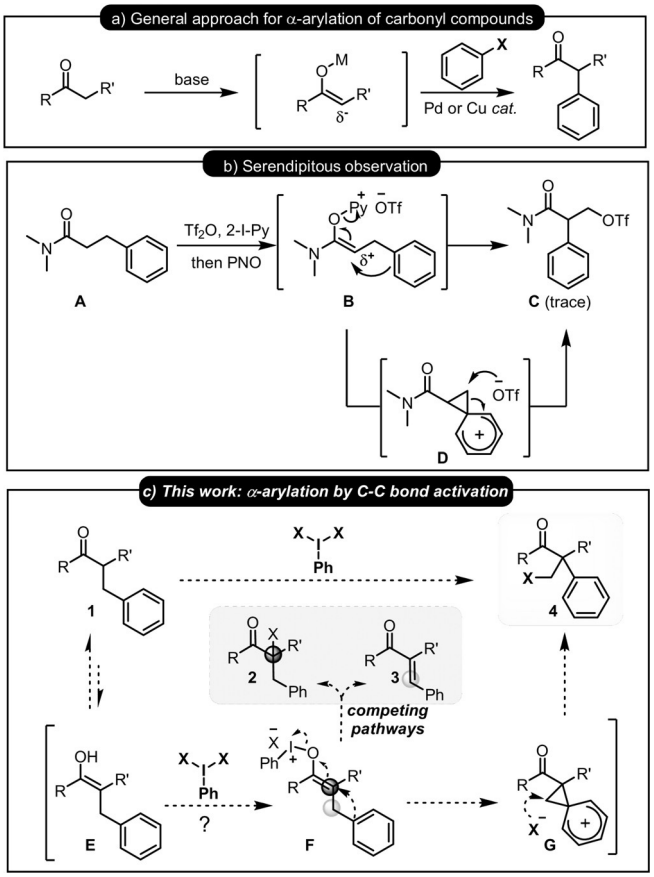
Abstract: *A synthetically useful approach for the direct α-arylation of carbonyl compounds through a novel oxidative C–C bond activation is reported. This mechanistically unusual process relies on a 1,2-aryl shift and results in all-carbon quaternary centers. The transformation displays broad functional-group tolerance and can in principle also be applied as an asymmetric variant.*

The appendage of an aryl substituent to the α-position of a carbonyl moiety remains a transformation of central importance in synthetic organic chemistry. The advent of powerful metal-catalysed coupling processes has paved the way for the introduction of catalytic (involving mainly organometallic complexes of Pd and Cu) coupling reactions that join aryl halides (or equivalents) to carbonyl-derived enolates.[1,2] Prior to and following these advances, useful transition-metal-free α-arylation processes have been developed that involve stoichiometric reactions of enolate anions (or equivalents) with electrophilic aromatic derivatives of Bi^{V},[3] Pb^{IV},[4] I(III),[5] S(IV),[6] or benzyne.[7] Stepwise methods via initial formation of *N*-alkoxyenamines[8] or enolonium equivalents followed by nucleophilic attack have also been used for the α-arylation of ketones.[9b,d]

We have established a research program exploiting the electrophilic activation of amides by drawing on pioneering work from the groups of Ghosez,[10] and more recently Charette,[11] Movassaghi,[12] Huang, and others.[13] A current focus of interest resides in the implications of an umpolung strategy that exploits pyridine *N*-oxide-mediated formation of enolonium equivalents[9,14] under mild conditions, thereby enabling a series of novel transformations for the α-functionalization of amides.[15]

During these studies, an unexpected result caught our attention (Scheme 1b). Substrate **A**, which bears a phenyl group in the β-position of the amide, generated trace amounts of an unexpected product (**C**). Our mechanistic interpretation of this result suggested that fragmentation of the enolonium **B** was triggered by nucleophilic attack of the neighboring arene to generate phenonium intermediate **D**.[16] Ring opening by weakly nucleophilic triflate accounts for formation of the unexpected product **C**.



Scheme 1. Representative approaches for α-functionalisation of carbonyl compounds and a proposed arylation through C–C bond activation. PNO = pyridine-*N*-oxide, Tf_2O = trifluoromethanesulfonic anhydride, 2-I-Py = 2-iodo-pyridine.

Aiming to capitalize on this serendipitous observation in a more general context, we hypothesized that a metal-free α-arylation that proceeds through skeletal reorganization could be developed (Scheme 1c). Our mechanistic postulate involved the conversion of a generic α-disubstituted ketone nucleophile (**1**) to an enolonium (**F**).[9a–c] We then hoped to funnel this intermediate selectively to the phenonium intermediate **G**, ring opening of which would effectively constitute a novel approach to the α-arylation of carbonyl compounds and formation of a quaternary center. Herein we report the development of this approach into a formal metal-free α-arylation through oxidative C–C bond activation.

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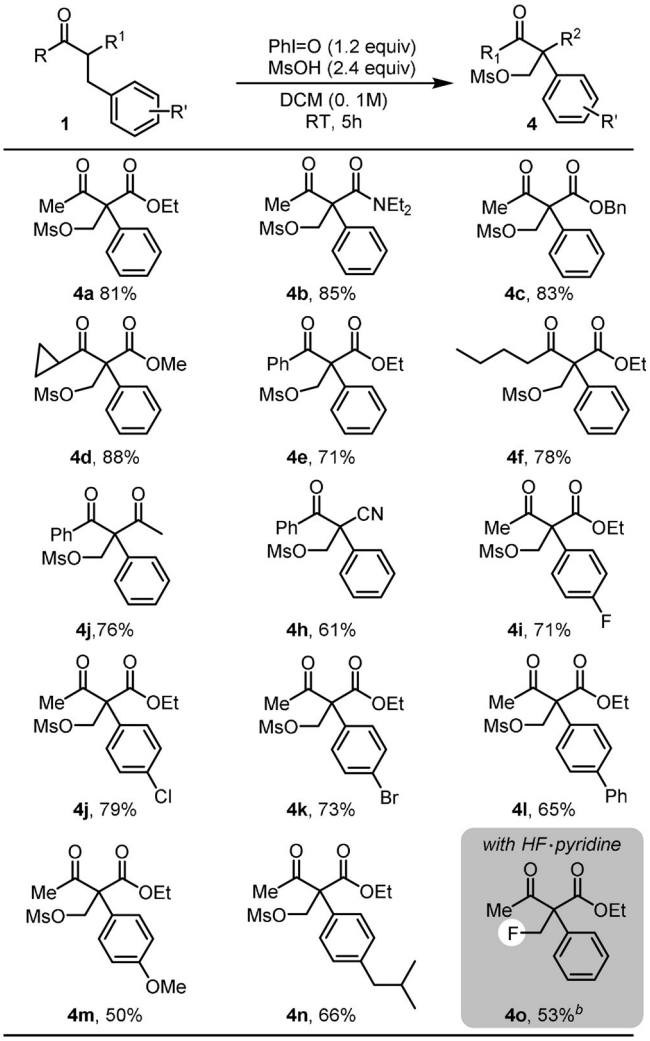
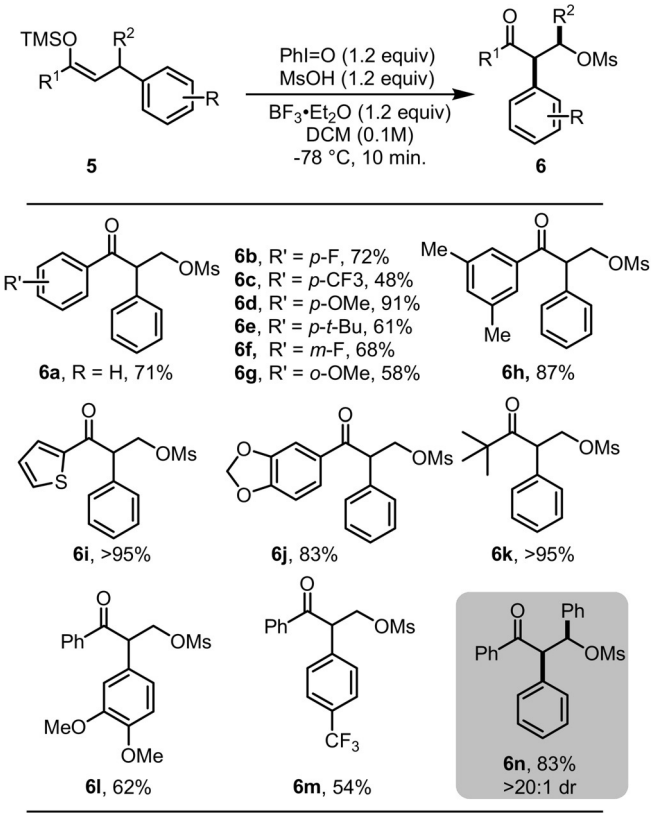
A number of potential pitfalls are readily apparent in this ambitious proposal. Most notably, 1) intermediate **F** has a readily available elimination pathway accessible to generate a particularly stable β-aryl-α,β-unsaturated carbonyl compound (**3**) and 2) even if it survives elimination, intermediate **F** can suffer direct attack by any nucleophile in solution to form (in this case) undesired α-functionalized umpolung products **2**.[9a] Bearing these possible problems in mind, we began our investigations on the proposed oxidative C–C bond activation reaction with ketoester **1a**, a compound that exists to a significant extent in the favorable enol form. Aiming to develop an operationally simple method, we explored the use of commercially available ethyl 2-benzylacetoacetate **1a** and different oxidants to mediate the proposed process (see the Supporting Information for a detailed optimization). After considerable experimentation, we found that iodosobenzene (1.2 equiv) and MsOH (2.4 equiv) enable the reorganization of **1a** to α-arylation product **4a** through oxidative C–C bond activation in an excellent 81% yield (Scheme 2).

With optimized conditions in hand, we then turned our attention to the scope of this transformation (Scheme 2). First, we evaluated a range of 2-benzyl-substituted 1,3-dicarbonyl compounds under our conditions, including ketoester **4a**, ketoamide **4b**, diketone **4j**, or ketonitrile **4h**. The reactions proceeded smoothly, affording the desired products in good chemical yield. Furthermore, this transformation exhibited good tolerance to diverse aromatic substitution (**4i**–**4n**). Finally, we turned our attention to nucleophiles other than methanesulfonate (MsO^-). Gratifyingly, when Pyridine·9HF was used instead of MsOH, the β-fluoride product **4o** was obtained in moderate yield.

After these promising investigations on oxidative C–C bond activation of active methylene compounds, we turned our attention to simple ketones. Our investigations showed that ketone-derived silyl enol ethers featuring an arene residue in the allylic position are also amenable to this transformation, resulting in α-arylated products (Scheme 3). As shown, electron-donating groups such as 3,4-di-OMe are well tolerated in the migrating arene (**6d**). Their electron-poor counterparts (e.g., *p*-CF_3 in **6m**)[16b] afforded lower yields, likely as a consequence of diminished migratory ability. Interestingly, this approach can be employed to convert β,β-diphenyl-substituted ketones into product **6n** in very good yield and as a single diastereoisomer.

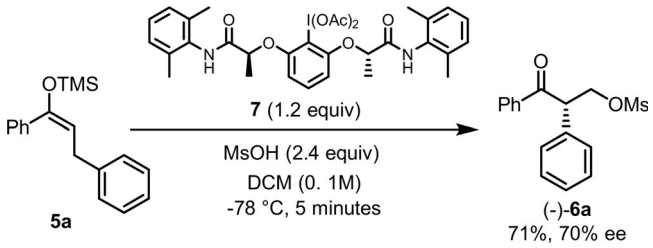


Scheme 2. Scope of oxidative C–C bond activation of 2-benzyl-substituted 1,3-dicarbonyl compounds. [a] Reaction Conditions: Reactions conducted on 0.2 mmol scale. All yields refer to pure, isolated materials (see the Supporting Information for details). [b] Pyridine·9HF (0.1 mL) used instead of MsOH. DCM = dichloromethane, MSOH = methanesulfonic acid, OMS = mesylate group.



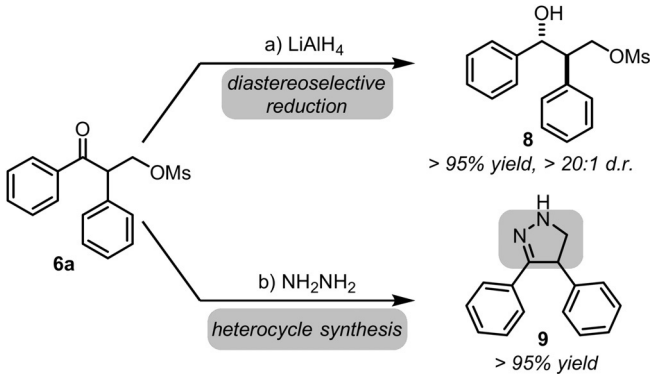
Scheme 3. Scope of the oxidative C–C bond activation of ketone-derived silyl enol ethers. [a] Reactions conducted on 0.2 mmol scale. All yields refer to pure, isolated materials (see the Supporting Information for details).

In a preliminary effort to identify asymmetric variants of this oxidative C–C bond formation, chiral hypervalent iodane **7**[17] was prepared and examined in the reaction of silyl enol ether **5a** (Scheme 4). Promisingly, the reaction proceeded in good yield and an enantioselectivity value of 70% *ee* was obtained after only 5 minutes at −78 °C. The resulting α-arylated ketones lend themselves to further functionalization.



Scheme 4. Enantioselective α-arylation of **5a** through oxidative C–C bond activation.

For instance, diastereoselective reduction of **6a** with $LiAlH_4$ proceeds in quantitative yield (Scheme 5).[18] This results in 1,3-diol **8**, a single isomeric species containing vicinal stereocenters. Alternatively, simple treatment of **6a** with NH_2NH_2 results in pyrazoline **9**[19] in very good chemical yield.



Scheme 5. Functionalization of oxidative C–C bond activation product **6a** (see the Supporting Information for details).

In conclusion, a metal-free, stereoselective α-arylation of carbonyl compounds through oxidative C–C bond activation was developed. The ability to use simple and easily available reagents under mild condition is a distinctive feature of this process, which effectively cleaves and reorganize C–C bonds in simple carbonyl-containing feedstocks.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arylation · C–C bond activation · enolonium species · ketones · umpolung

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