Silver-Catalyzed Controlled Intermolecular Cross-Coupling of Silyl Enol Ethers: Scalable Access to 1,4-Diketones

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ABSTRACT: A protocol for silver-catalyzed controlled intermolecular cross-coupling of silyl enolates is disclosed. The protocol displays good functional group tolerance and allows efficient preparation of a series of synthetically useful 1,4-diketones. Preliminary mechanistic investigations suggest that the reaction proceeds through a one-electron process involving free radical species in which PhBr acts as the oxidant.
equivalents using a hypervalent iodine(III) compound (Koser’s reagent). However, this reaction requires extremely low temperatures and sequential addition of the coupling partners, decreasing the practicality of the disclosed protocol (Figure 1). Herein, we alleviate the drawbacks of the previously described cross-coupling manifolds of silyl enol ethers with the use of silver catalysis,15,16 providing a convenient method for the chemoselective preparation of a broad range of 1,4-dicarbonyl scaffolds under mild reaction conditions and using near-stoichiometric amounts of the two coupling partners (Figure 1).

At the beginning of our investigations, silyl enol ethers 1a and 2a were selected as model substrates to optimize the oxidative cross-coupling reaction (Table 1). To our delight, conducting the reaction in DMSO at 100 °C under air in the presence of AgF (30 mol %) and bromobenzene (2 equiv) exclusively afforded the desired 1,4-diketone 3a in 9% isolated yield after 6 h, accompanied by the generation of homocoupling product 3h in <5% yield (Table 1, entry 1). Performing the reaction under argon afforded the desired 1,4-diketone 3a in 21% yield and homocoupling product 3h in 11% yield (Table 1, entry 2). Encouraged by this result, we surveyed other silver-based precursors, including Ag₂CO₃, AgOTf, AgBF₄, and AgOAc, and found that AgF displays the best reactivity while the others proved to be less efficient (Table 1, entries 3–6, respectively). Other metal-based catalysts, including InCl₃, Cu(OTf)₂, CuI, and Pd(OAc)₂, provided a complex mixture of products and only trace amounts of product 3a (Table 1, entries 7–10, respectively). Subsequently, switching the solvent to MeCN greatly increased the yield of cross-coupling product 3a to 42% (Table 1, entry 11). In contrast, the use of aprotic or polar solvents, such as DMF, toluene, and DCE, had a negative effect on the reaction (Table 1, entries 12–14, respectively), while employing the protic solvent EtOH completely inhibited the reaction (Table 1, entry 15). Decreasing the reaction temperature from 100 °C to room temperature significantly improved the yield of the desired product 3a to 72% (Table 1, entries 16–19), while decreasing the catalyst loading from 30 to 20 mol % had a critical role in the reaction (Table 1, entry 20). A control experiment in the absence of bromobenzene provided only trace amounts of the cross-coupling product (Table 1, entry 22), thus indicating that bromobenzene plays a critical role in the reaction.7,18

With the optimized reaction conditions in hand, we explored the generality of the established protocol (Scheme 1). An array of diversely functionalized silyl enol ethers 1 engaged in the desired cross-coupling reaction with silyl enol ethers 2 to afford the corresponding products 3 in good to excellent yields (Scheme 1). For example, aryl-based silyl enol ether motifs bearing electron-donating or electron-withdrawing moieties were tolerated in the cross-coupling reaction with 1a to produce the corresponding products 3b–3h in good yields. Gratifyingly, the utilization of heteroaryl silyl ethers, including 2-furyl and 2-thienyl, afforded the corresponding adducts 3i and 3j, respectively, illustrating the compatibility of the

![Figure 1. Oxidative cross-coupling strategies for the synthesis of 1,4-diketones.](https://doi.org/10.1021/acs.orglett.2c01477)

| entry | [M] | solvent | temp (°C) | yield (%) | 3a | 3s |
|-------|-----|---------|-----------|-----------|----|----|
| 1'    | AgF | DMSO    | 100       | 9         | <5 |
| 2     | AgF | DMSO    | 100       | 21        | 11 |
| 3     | Ag₂CO₃ | DMSO | 100       | 13        | 8  |
| 4     | AgOTf | DMSO | 100       | 0         | 0  |
| 5     | AgBF₄ | DMSO | 100       | 0         | 0  |
| 6     | AgOAc | DMSO | 100       | 15        | 9  |
| 7     | InCl₃ | DMSO | 100       | 0         | 0  |
| 8     | Cu(OOTf)₂ | DMSO | 100       | 0         | 0  |
| 9     | CuI  | DMSO    | 100       | 0         | 0  |
| 10    | Pd(OAc)₂ | DMSO | 100       | 42        | 29 |
| 11    | AgF  | MeCN    | 100       | 28        | 21 |
| 12    | AgF  | DMF     | 100       | 35        | 26 |
| 13    | AgF  | toluene | 100       | 35        | 26 |
| 14    | AgF  | DCE     | 100       | 27        | 13 |
| 15    | AgF  | EtOH    | 100       | 0         | 0  |
| 16    | AgF  | MeCN    | 80        | 47        | 31 |
| 17    | AgF  | MeCN    | 60        | 53        | 27 |
| 18    | AgF  | MeCN    | 40        | 64        | 25 |
| 19    | AgF  | MeCN    | rt        | 72        | 19 |
| 20    | AgF  | MeCN    | rt        | 69        | 23 |
| 21    | AgF  | MeCN    | rt        | 43        | 28 |
| 22    | AgF  | MeCN    | rt        | 0         | 0  |
| 23    | AgBr | MeCN    | rt        | 23        | 12 |

*Reactions were carried out with 1a (0.65 mmol), 2a (0.5 mmol), catalyst (30 mol %), and PhBr (1.0 mmol) under argon for 6 h. †Isolated yields of 3a after purification by column chromatography. ‡Reactions carried out under air. §With 20 mol % catalyst. ¶With 10 mol % catalyst. ††Reaction carried out in the absence of PhBr.
developed protocol. Subjecting alkyl-based silyl enol ethers to aryl-based silyl enol ethers generated the desired products 3q and 3r in good to excellent yields. Furthermore, the homocoupling reaction with aryl-based silyl enol ethers proceeds efficiently and yields the target compounds in ≤93% yield (Scheme 1). Finally, the structure of products 3 was supported through X-ray analysis of product 3ab [CCDC 2143818 (see Scheme 1)]. To further explore the synthetic utility of the developed protocol, the applicability of the silver-catalyzed method was highlighted through a gram-scale reaction of 1a and 2a (Scheme 1). The reaction was performed on a 5 mmol scale and proceeded smoothly to give product 3a (0.86 g, 64%). The highly functionalized 1,4-diketones developed by this protocol provide opportunities for a range...
of further synthetic manipulations, especially for heterocycle synthesis. For instance, synthetic conversion of diketone 3a into functionalized pyrrole 4 and furan 5 was achieved in high yields by subjecting the diketone to ammonium acetate and triflic acid, respectively. Additional experiments were performed to gain insight into the mechanism of the developed transformation (Scheme 2).

The silver-catalyzed homocoupling reaction of silyl enol ethers 1a was completely suppressed by the addition of radical inhibitor TEMPO, indicating that the reaction proceeds through a free radical pathway. Additionally, we isolated TEMPO-based adduct 6 in 50% yield. To gain additional support for the proposed mechanism, ESI-MS experiments were performed, allowing detection of the phenyltrimethylsilane (PhTMS) byproduct (see Scheme 2 and Figure S1). Furthermore, when the reaction was conducted under the optimized conditions using AgBr as the silver precursor (Table 1, entry 23), only a small amount of the coupling product was produced, highlighting the essential role of fluoride for effective catalytic turnover. Also, we surmise that the developed reaction likely requires a nucleophilic counterion to mediate the desilylation of one of the silyl enol ethers upon conversion of Ag(II) intermediate A into AgF. Accordingly, while carbonate and acetate have sufficient nucleophilic character, OTf and BF₃ cannot facilitate such a process (cf. Table 1, entries 3–6). Finally, considering the possible involvement of Ag(0) in the reaction, such processes would likely (although not necessarily) produce a silver mirror, as has been observed in our previous reports featuring catalytic amounts of Ag(I) catalysts. However, the formation of a silver mirror was not observed for the developed silyl enol ether cross-coupling reaction.

On the basis of the experimental results and literature precedents, a plausible mechanism for the cross-coupling reaction between 1 and 2 was proposed (Scheme 2). Initially, AgF abstracts a bromine atom from PhBr to generate Ag(II) intermediate A and a phenyl radical. Then, the transiently formed phenyl radical reacts with silyl enol ether 1 to furnish α-carbonyl radical B along with PhTMS. Finally, α-carbonyl radical B undergoes radical addition to silyl enol ether 2 to form carbon-centered radical C, which undergoes one-electron oxidation by Ag(II) species A to form cross-coupling product 3 along with regeneration of Ag(I), thereby closing the catalytic cycle. Preliminary mechanistic studies support the events mentioned above; however, further studies are required to elucidate the mechanism of this intriguing reaction. It is also possible that a radical–radical coupling mechanism could be operating under the disclosed reaction conditions, competing with the proposed mechanism. However, given the observed high selectivity, such a mechanism is not likely to play the key role.

In conclusion, we have developed a silver-catalyzed procedure for controlled intermolecular cross-coupling of silyl enol ethers. The protocol exhibits good functional group tolerance, allowing access to a range of synthetically valuable 1,4-diketones. A plausible free radical-based pathway is proposed in which PhBr acts as the oxidant. The disclosed method presents a versatile framework for oxidative carbon–carbon bond formation from unpretentious starting materials. It is anticipated that this reaction manifold will stimulate several new synthetic strategies. Further investigations of the reaction are ongoing in our laboratories.

### ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01477.

Experimental procedures and characterization data for all of the compounds (PDF)

### Accession Codes

CCDC 2143818 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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