ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, **57**, 7386

Received 17th May 2021,
Accepted 28th June 2021

DOI: 10.1039/d1cc02576g

rsc.li/chemcomm

Ruthenium-catalyzed room-temperature coupling of α-keto sulfoxonium ylides and cyclopropanols for δ-diketone synthesis†

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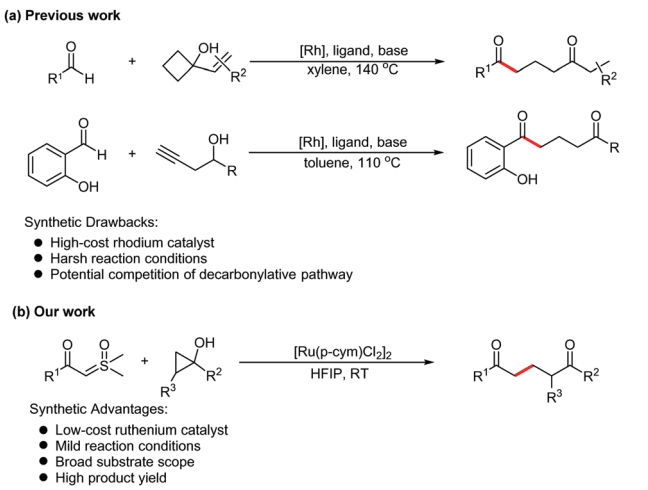
Previous transition metal-catalyzed synthesis processes of δ-diketones are plagued by the high cost of the rhodium catalyst and harsh reaction conditions. Herein a low-cost, room temperature ruthenium catalytic method is developed based on the coupling of α-keto sulfoxonium ylides with cyclopropanols. The mild protocol features a broad substrate scope (47 examples) and a high product yield (up to 99%). Mechanistic studies argue against a radical pathway and support a cyclopropanol ring opening, sulfoxonium ylide-derived carbenoid formation, migratory insertion C–C bond formation pathway.

Long-chain, acyclic δ-diketones are valuable building blocks enabling the synthesis of divergent classes of natural products, pharmaceutical compounds, and functional materials.[1–3] Therefore, tremendous efforts have been dedicated to the synthesis of these important structural motifs.[4–11] The most adopted conventional methods in this area involve the Michael addition of metal enolates to α,β-unsaturated ketones.[9–11] Despite the advances in stannyl-, silyl-, and titanium-based systems, the instability of metal enolates, narrow substrate scope, and toxicity of metals manifest significant drawbacks associated with these approaches. Indeed, large excesses of metal enolates were typically engaged to drive the reaction to completion, and post-treatment hydrolysis could produce substantial amounts of metal wastes; the reactivity of metal enolates can cause functional group compatibility issues, and organotin reagents can cause severe damage to human organs such as the liver and kidneys. Although enol acetates can be employed as metal-free surrogates, an extra organotin-catalyzed transesterification step is required for access to the authentic δ-diketone target. In view of these limitations, radical coupling has been sought as an alternative reaction modality.[12] Radical ring-opening acylation of cyclobutanols, radical addition of β-keto xanthates to vinyl carbinols, and multicomponent radical carbonylation showcase the diverse reaction manifolds that can be achieved. However, the involvement of either highly oxidative or high pressure conditions inevitably was sought as an alternative reaction modality.

Transition metal catalysis, known for its capability of mediating a rich set of transformations, has recently made inroads into this important field. Rhodium catalysis has been successfully exploited to promote two mechanistically distinct cascade processes: ring opening of vinyl cyclobutanol/transfer hydrogenation/hydroacylation and hydroacylation of homopropargyl alcohol/deconjugative isomerization (Scheme 1a). Albeit effective, the high cost of the catalyst, harsh reaction conditions (140 °C and 110 °C), and potential competition of the decarbonylative pathway are the major hurdles that need to be addressed.[4,8] To this end, herein, we wish to disclose a ruthenium-catalyzed room-temperature (RT) coupling of α-keto sulfoxonium ylides and cyclopropanols for the synthesis of δ-diketones (Scheme 1b). During the preparation of the manuscript, we noticed a patent describing a ruthenium catalytic protocol working at 80 °C.[13]



Scheme 1 Synthetic strategy for the construction of δ-diketones.

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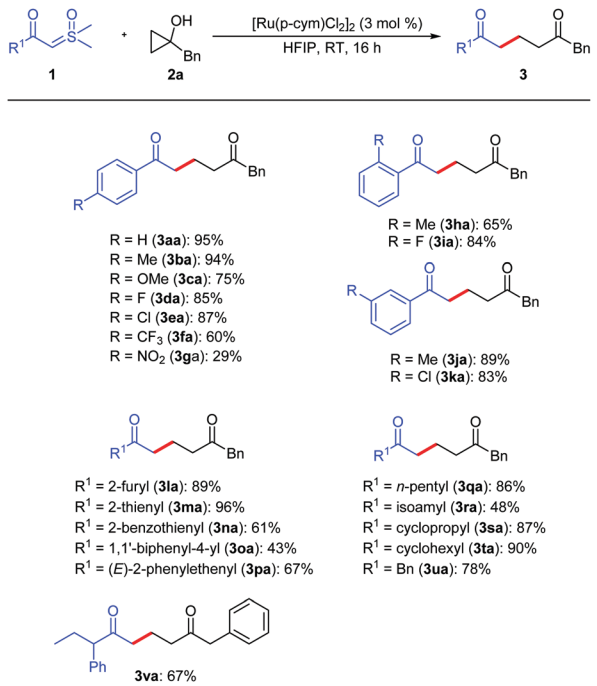
† Electronic supplementary information (ESI) available. CCDC 2087645. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc02576g

α-Keto sulfoxonium ylides are easy-to-synthesize, bench-stable reagents that have demonstrated their versatile utility, especially as precursors to carbenoids, in transition metal catalysis.[14–17] Thus far, the majority of catalytic reactions is based on rhodium and iridium systems. Cyclopropanols are also readily available compounds that can undergo facile strain-release β-carbon elimination/ring opening as a means for further elaboration.[18] The induction of this reactivity mode can be effected by a broad class of reagents, including transition metals, such as palladium, copper, rhodium, and cobalt.[19–23] We have a long-standing interest in transition metal catalysis for novel C–H functionalization and have therefore attempted to use the directing groups developed by our group for C–H coupling with either α-keto sulfoxonium ylides or cyclopropanols (see ESI† for details). For α-keto sulfoxonium ylide **1a**, no reactions were observed for coupling with 1,2,4-oxadiazol-5(4*H*)-one, *N*-chloroamide, and enaminone.[24–26] For cyclopropanol **2a**,[27,28] no coupling proceeded under enaminone; ring opening occurred for **2a** under *N*-nitroso, with the formation of a ketone product; and direct coupling of the two rings was observed, without the participation of the C–H bond, under 1,2,4-oxadiazol-5(4*H*)-one.

Inspired by the emerging use of α-keto sulfoxonium ylide as the directing group,[17,29–32] we have shifted our focus on the possibility of C–H coupling with cyclopropanol. Under all experimental conditions tested herein, no C–H coupling occurred; instead, δ-diketone was the sole product uncovered. Thus, for the reaction between **1a** (0.2 mmol, 1 equiv.) and **2a** (1.25 equiv.), under rhodium catalysis, **3aa** was afforded, albeit with the maximum attainable yield of merely 20% at 80 °C. In an attempt to seek a low-cost catalytic system and simultaneously improve the yield, we switched the metal catalyst from rhodium to palladium, copper, and ruthenium. For either palladium or copper, no **3aa** could be obtained. To our delight, extensive exploration of ruthenium complexes provided a high-yield catalytic system. Under $[Ru(\eta^6\text{-}p\text{-cym})Cl_2]_2$ (abbreviated as $[Ru(p\text{-cym})Cl_2]_2$ hereafter; 3 mol%), although no conversion could be discerned after 16 h rt reaction in THF, 1,4-dioxane, CH_3CN, and DMSO, trace amount of **3aa** was formed in CH_3OH. Alcohols have been often used as solvents for ring-opening of cyclopropanols.[23,33] In particular, hexafluoroisopropanol (HFIP) has been extensively used in organic synthesis because of its appealing properties (*e.g.*, strong hydrogen bond-donating capability, low nucleophilic reactivity, and high ionizing capacity).[34] For example, the carbon–carbon bond-forging reactions have proven to proceed well in HFIP. Satisfactorily, the use of HFIP enabled the dramatic improvement in yield. **3aa** could be obtained in 75% yield under open-air condition and in 95% yield under nitrogen protection (referred to as the optimized conditions hereafter). Elevation of the temperature is detrimental to the reaction, with the yield being reduced to 85%, 71%, and 70% respectively at 40 °C, 60 °C, and 80 °C. Replacement of $[Ru(p\text{-cym})Cl_2]_2$ with either $RuCl_3$, $Ru(acac)_3$, or $Ru_3(CO)_{12}$ led to no product formation. The effectiveness of $[Ru(p\text{-cym})Cl_2]_2$ as a catalyst is speculated to be caused by the lability of the *p*-cym ligand, which enables the facile generation of vacant coordination sites for catalysis.

Table 1 Substrate scope of sulfoxonium ylides[ab]



[a] All reactions were performed on 0.2 mmol scale (sulfoxonium ylide), 1.25 equiv. of the cyclopropanol with $[Ru(p\text{-cym})Cl_2]_2$ (3 mmol%) in the HFIP(2 mL) under nitrogen. [b] Isolated yield.

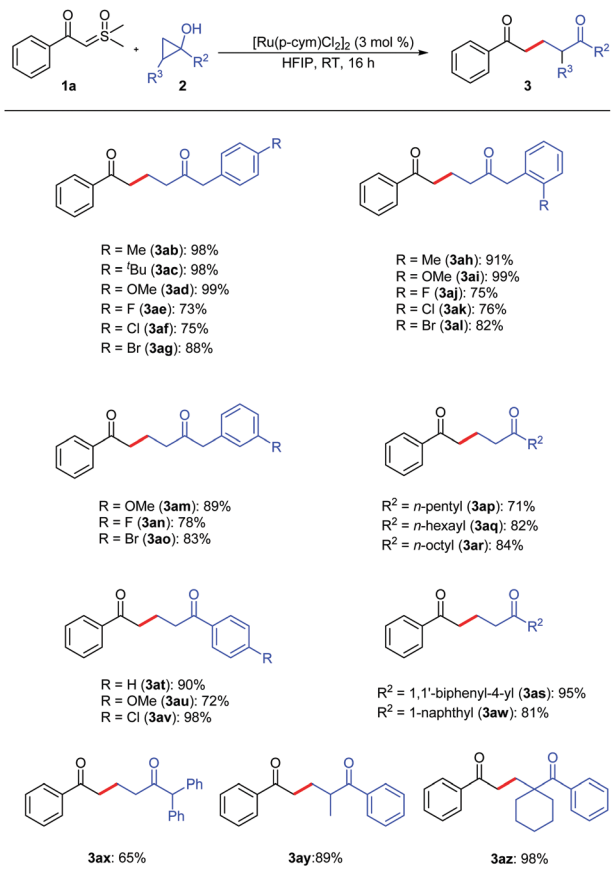
With the optimized conditions established, the substrate scope of α-keto sulfoxonium ylides was evaluated (Table 1). α-Benzoyl sulfoxonium ylides bearing both electron-donating and electron-withdrawing groups on the phenyl ring can successfully participate in the reactions with **2a**. For *para*-substituted sulfoxonium ylides, the Me variant (**1b**) gives the highest yield (94%); the OMe (**1c**) substitution lowers the yield to 75%; the F (**1d**) and Cl (**1e**) substitutions offer similar yields (85%, 87%); and the yield is decreased to 60% and 29%, respectively, for CF_3 (**1f**) and NO_2 (**1g**) variants. For *ortho*-substituted sulfoxonium ylides, sterics dictate the product yield, with the yield of Me variant (**1h**, 65%) lower than that of the F variant (**1i**, 84%). The electronic and steric effects are negligible in *meta*-substituted sulfoxonium ylides (Me, **1j**, 89%; and Cl, **1k**, 83%). The replacement of the phenyl ring with other aromatic rings provides equally viable substrates. The 2-furyl (**1l**) and 2-thienyl (**1m**) variants furnish the respective products in excellent yields (89% and 96%). By contrast, the yields for the 2-benzothienyl (**1n**), 1,1′-biphenylyl-4-yl (**1o**), and (*E*)-2-phenylethenyl (**1p**) variants are slightly lower (61%, 43%, and 67%). Significantly, α-alkylketo sulfoxonium ylides are also compatible coupling partners. The linear *n*-pentyl variant (**1q**) delivers a higher yield (86%) than the branched isoamyl variant (**1r**, 48%). The cyclopropyl (**1s**, 87%), cyclohexyl (**1t**, 90%), and benzyl (**1u**, 78%) variants, despite their relatively unfavored sterics, can react effectively. The bulkier 1-phenylpropyl variant (**1v**) gives a diminished yield (67%).

With the reactivity of α-keto sulfoxonium ylides thoroughly examined, the substrate scope of cyclopropanols was next

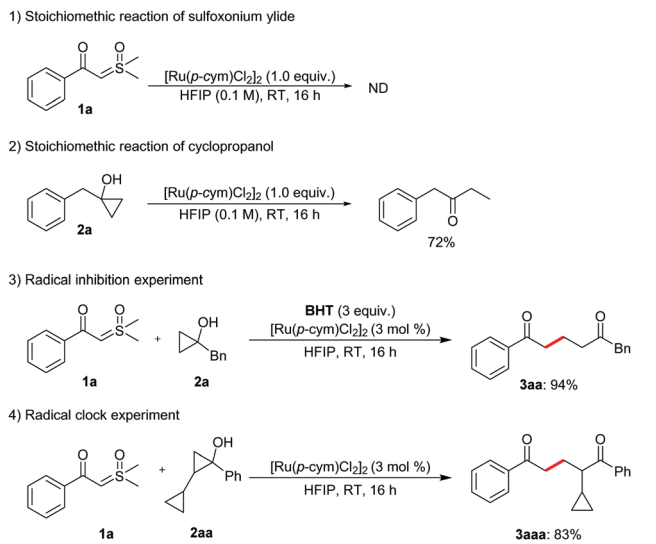
assessed (Table 2). First, the substituent on the phenyl ring of 1-benzylcyclopropanol is systematically varied to probe its impact on the reaction with **1a**. For *para* substitution, the electron-donating group exerts a positive effect on the product yield, essentially enabling a quantitative conversion (Me, **2b**, 98%; *tert*-butyl, **2c**, 98%; and OMe, **2d**, 99%). The effect of electron-withdrawing group is negative, but still good yield can be obtained (F, **2e**, 73%; Cl, **2f**, 75%; and Br, **2g**, 88%). The *ortho* substitution displays a similar reactivity pattern, with the exception of the Me variant (**2h**), which affords a slightly lower yield (91%); the performance of OMe (**2i**, 99%), F (**2j**, 75%), Cl (**2k**, 76%), and Br (**2l**, 82%) variants is virtually identical to that of their corresponding *para* analogs. This suggests that the ring opening and coupling processes are not affected by the sterics. In comparison, the *meta* substitution provides a less reactive substrate with the OMe group (**2m**, 89%), but an equally competent substrate with the F (**2n**, 78%) and Br (**2o**, 83%) groups. The reaction also proceeds in good yield with the replacement of the benzyl group by an alkyl group (*n*-pentyl, **2p**, 71%; *n*-hexyl, **2q**, 82%; and *n*-octyl, **2r**, 84%). The alteration to a diphenylmethyl group (**2x**) reduces the yield to 65%. With a phenyl group (**2t**), the yield reaches 90%, and the electronic effect is apparently reversed in the *para* substitution case (OMe, **2u**, 72%; and Cl, **2v**, 98%). With a bulkier 1-naphthyl group (**2w**), a lower yield (81%) is acquired. The yield returns to 95% with a 1,1′-biphenylyl-4-yl group (**2s**). The transformation is surprisingly highly efficient for sterically congested, even spiro-type 1,2-disubstituted cyclopropanols (1-phenyl, 2-Me, **2y**, 89%; and 1-phenyl, 2-spiro[5], **2z**, 98%). With the substrate scope completely surveyed, the utility of the protocol developed herein is demonstrated with the scale-up of the reaction to 1 mmol level (84% yield).

The mild conditions and broad substrate scope of the reaction prompted us to investigate its mechanistic basis. The stoichiometric reaction between $[Ru(p\text{-cym})Cl_2]_2$ and **1a** did not generate any new species, likely suggesting the absence of direct inner-sphere coordination (Scheme 2, eqn (1)). By contrast, a ring-opened ketone product was acquired in high yield (72%) in a reaction between $[Ru(p\text{-cym})Cl_2]_2$ and **2a**, supporting the initial occurrence of cyclopropanol coordination and β-carbon elimination (Scheme 2, eqn (2)). ^{1}H NMR monitoring of the reaction mixture between **1a** and **2a** under ruthenium catalysis revealed the formation of DMSO, a side product that is consistent with the ruthenium carbenoid pathway. Ruthenium has been previously shown to be capable of undergoing redox pathway to promote radical reactions.[35,36] To explore such a possibility, two radical-related reactions have been performed. A reaction carried out between **1a** and **2a** in the presence of a radical scavenger, butylated hydroxytoluene (BHT), gives an essentially identical yield (94%, *versus* 95% in the absence of BHT) (Scheme 2, eqn (3)). A radical clock experiment of **1a** and **2aa** witnesses no ring-opening of the 2-cyclopropyl substituent, and the expected product **3aaa** is furnished in 83% yield (Scheme 2, eqn (4)). These mechanistic studies argue against a radical reaction course. Based on these lines of experimental evidence and previous demonstration of ruthenium(II) complexes as effective catalysts,[37,38] the following mechanistic pathway is proposed (Scheme 3): cyclopropanol

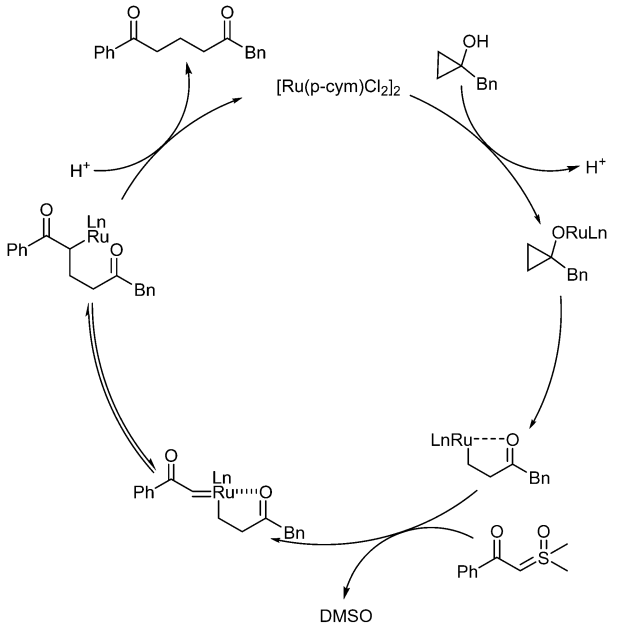
Table 2 Substrate scope of cyclopropanols[ab]



[a] All reactions were performed on 0.2 mmol scale (sulfoxonium ylide), 1.25 equiv. of the cyclopropanol with $[Ru(p\text{-cym})Cl_2]_2$ (3 mmol%) in the HFIP(2 mL) under nitrogen. [b] Isolated yield.



Scheme 2 Mechanistic studies.



Scheme 3 Proposed reaction mechanism.

coordination to ruthenium(II) with the simultaneous release of proton, β-carbon elimination generating a β-keto alkyl-metal intermediate, formation of α-keto carbenoid species, 1,1-migratory insertion/C–C bond formation, and proto-demetalation release of product and regeneration of ruthenium catalyst.

In summary, a ruthenium catalytic method has been developed for the construction of δ-diketones *via* the coupling of readily available α-keto sulfoxonium ylides and cyclopropanols. The protocol features mild reaction conditions, a broad substrate scope, and a high product yield. The ruthenium system reported herein expands the repertoire of sulfoxonium ylide-derived carbenoid chemistry and suggests the promising prospect of this under-explored, low-cost metal as a major player in this synthetically important field.

J. Z. gratefully acknowledges the support from the National Natural Science Foundation of China (21774056, 52073141).

Conflicts of interest

There are no conflicts to declare.

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