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Rhodium-Catalyzed Room Temperature C−C Activation of Cyclopropanol for One-Step Access to Diverse 1,6-Diketones

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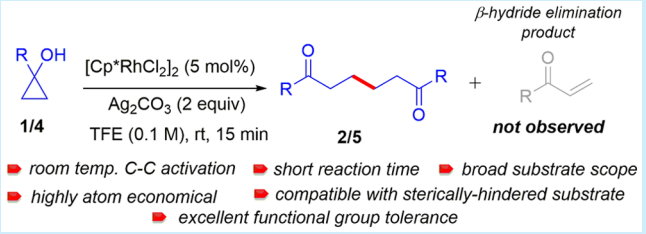
ABSTRACT: A rhodium-catalyzed room temperature C−C activation of cyclopropanol has been demonstrated for the single-step synthesis of a range of electronically and sterically distinct 1,6-diketones. This reaction proceeds efficiently in shorter reaction time following a highly atom-economical pathway. To illustrate the synthetic potential of 1,6-diketones, aldol and macrocyclization reactions have been successfully demonstrated. Preliminary mechanistic studies revealed the involvement of nonradical pathways.



Transition-metal-catalyzed C−H and C−C functionalizations have gained much attention in recent years owing to their potential applications in organic synthesis.[1,2] Although extensive studies have been carried out on C−H bond activation, strategies involving C−C bond activation remain limited. In order to resolve this issue, significant efforts have been made over the years finding new ways to activate various types of C−C bonds.[2,3] The most prominent strategies are oxidative addition,[2d] β-carbon elimination,[3a,c] and aromatization driven processes.[3d] Usually, C−C bond activation is a thermodynamically unfavorable process; in essence, it is the reverse reaction of the reductive elimination step. However, the intrinsic strain of small carbocyclic rings has been successfully exploited for C−C bond activation,[4] wherein the release of strain compensates for overcoming the thermodynamic barrier. Pioneering research groups such as the Jun, Dong, Bower, Marek, Yu, and Loh groups have demonstrated the application of this useful strategy for the synthesis of various scaffolds.[5] Recently, we have demonstrated C−C bond activation of cyclopropenone using a palladium catalyst for the synthesis of highly substituted maleimides.[6] We also recognized that cyclopropanols which are easily accessible from the Kulinkovich protocol are a useful synthon for the synthesis of valuable molecular architectures.[7] The efficacy of cyclopropanols as a source of metal homoenolate was first recognized by Kuwajima in 1985.[8] It is worth mentioning that the reactivity of transition metal homoenolates and catalyzed ring opening cross-coupling reactions have been widely exploited in numerous chemical transformations.[9−13]

In this regard, a significant contribution has been made with aryl halides, benzyl halides, and alkynes using palladium.[9] Other transition metals such as copper,[10] ruthenium,[11] cobalt,[12] and nickel[13] have been employed in different coupling reactions and rearrangements via metal homoenolates. Nevertheless, transformations using rhodium-homoenolate derived from β-carbon elimination (C−C activation) of cyclopropanol is limited,[14] possibly due to a facile β-hydride elimination pathway.[15]

Ryu and co-workers documented rhodium-catalyzed isomerization of siloxycyclopropanes to give enol- and allyl-silyl ethers (Scheme 1a-(i)).[14a] In another report, the synthesis 1,6-diketones was reported by Ryu and co-workers from siloxycyclopropanes (Scheme 1a-(ii)).[16] However, it involves the use of stoichiometric metal reagents and masked cyclopropanol to access 1,6-diketones. It is essential to note that due to the limitation of possible β-hydride elimination, and isomerization pathways, catalytic self-coupling of metal homoenolates was challenging.

Acyclic long-chain diketones, especially 1,6-diketones, are a favorable and prominent carbon synthon for the construction of pharmaceutically relevant and biologically active five- and six-membered carbo- and heterocyclic compounds.[17] Compounds bearing a 1,6-bis(3,4-dimethoxyphenyl)hexane-1,6-dione scaffold and their corresponding aldol adducts are reported to have an effective inhibition profile against cytosolic isoform hCA (Scheme 2).[17g] The aldol adducts obtained from 1,6-diketones are also the key precursor for the total synthesis of Daucane and Sphenolobane derivatives.[17i] Moreover, functionalized 1,6-diketones can also be subjected to various synthetic transformations. For example, aldol condensation,[17d,f] McMurry coupling,[17h] macro-cyclization,[17h] and reductive cyclization and pinacol coupling[17b,e] furnish an

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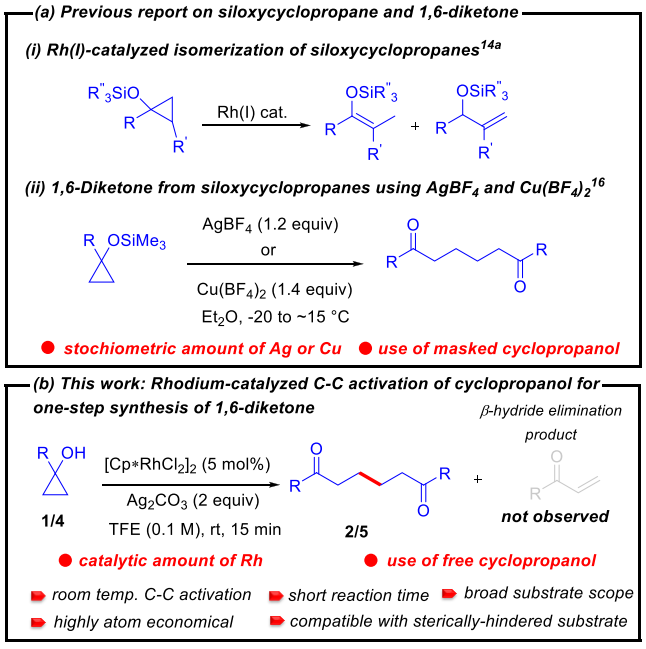
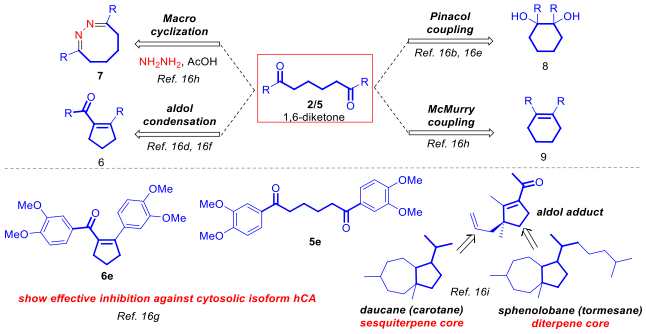
Scheme 1. Previous and Present Work



Scheme 2. Importance of 1,6-Diketone

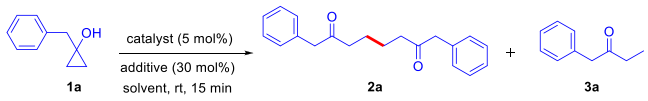


array of cyclic compounds (Scheme 2). Although several synthetic utilities have been achieved with 1,6-diketones, there has been less emphasis on their synthesis. Several methods established in the recent past include β-hydroxy hydroperoxides, oxone-promoted oxidative ring opening of cyclohexanone, magnesium-mediated reductive homocoupling of enones, and gold-catalyzed hydration of alkynes. However, the majority of them virtually involved multiple steps as well as multicomponent reactions, use of nonreadily obtainable starting materials, synthetically harsh reaction conditions, and most importantly less efficiency and selectivity.[18] Hence, a general and efficient methodology for the preparation of 1,6-diketones is highly desirable.

Perceiving the significance of rhodium-catalyzed C−C activation of cyclopropanol and the synthetic usefulness of 1,6-diketones, we envisaged that cyclopropanol-derived rhodium-homoenolate can serve as an active precursor for the preparation of 1,6-diketones. Herein, we report a rhodium-catalyzed room temperature C−C activation of readily available cyclopropanols for one-step access to diverse 1,6-diketones (Scheme 1b).

1-Benzylcyclopropan-1-ol **1a** (0.2 mmol) was used as the model substrate in the presence of the $[Cp^*RhCl_2]_2$ (5 mol %) catalyst to obtain the corresponding 1,6-diketone **2a**. Contrary to our expectations, when we screened solvents such as DCE, TFT, MeOH, and toluene, we obtained monoketone **3a** in 90%, 63%, 60%, and 76% yield instead of diketone **2a** (Table 1,

Table 1. Optimization of Reaction Conditions[a]



entry	solvent (0.1 M)	catalyst	additive	yield of **2a** (%)[b]	yield of **3a** (%)[b]
1	DCE	$[Cp^*RhCl_2]_2$	AgOAc	0	90
2	TFT	$[Cp^*RhCl_2]_2$	AgOAc	0	63
3	MeOH	$[Cp^*RhCl_2]_2$	AgOAc	0	60
4	Toluene	$[Cp^*RhCl_2]_2$	AgOAc	0	76
5	HFIP	$[Cp^*RhCl_2]_2$	AgOAc	25	72
6	TFE	$[Cp^*RhCl_2]_2$	AgOAc	30	54
7	TFE	$[Cp^*RhCl_2]_2$	$AgNTf_2$	9	82
8	TFE	$[Cp^*RhCl_2]_2$	$AgOCOCF_3$	12	51
9	TFE	$[Cp^*RhCl_2]_2$	AgOTf	15	24
10	TFE	$[Cp^*RhCl_2]_2$	$AgBF_4$	30	12
11	TFE	$[Cp^*RhCl_2]_2$	Ag_2CO_3	39	12
12	TFE	$[Cp^*RhCl_2]_2$	Cs_2CO_3	10	65
13	TFE	$[Cp^*RhCl_2]_2$	Na_2CO_3	26	60
14	TFE	$[Cp^*RhCl_2]_2$	$KHCO_3$	6	24
15	TFE	$[Cp^*RhCl_2]_2$	$NaHCO_3$	11	80
16	TFE	$[Cp^*RhCl_2]_2$	Ag_2CO_3 (0.5 equiv)	42	27
17	TFE	$[Cp^*RhCl_2]_2$	Ag_2CO_3 (1 equiv)	54	33
18	TFE	$[Cp^*RhCl_2]_2$	Ag_2CO_3 (1.5 equiv)	64	26
19	**TFE**	$[Cp^*RhCl_2]_2$	Ag_2CO_3 **(2 equiv)**	**72**	**24**
20	TFE	$[Cp^*RhCl_2]_2$	Ag_2CO_3 (2.5 equiv)	57	25
21	TFE	$[Cp^*RhCl_2]_2$	Ag_2CO_3 (3 equiv)	55	22
22	TFE	$[Cp^*RhCl_2]_2$	–	14	32
23	TFE	–	Ag_2CO_3 (2 equiv)	0	12

[a]Unless otherwise specified, all reactions were carried out using $[Cp^*RhCl_2]_2$ (5 mol %), additive (30 mol %), **1a** (0.2 mmol) in a solvent (0.1 M) for 15 min. [b]Yield by NMR with 1,3,5-trimethoxybenzene as internal reference.

entries 1−4). Formation of monoketone **3a** could be attributed to a facile protodemetalation of in situ generated rhodium-homoenolate. The protodemetalation step appears to be faster than β-hydride elimination and the perceived homocoupling of rhodium homoenolates. Interestingly we obtained a lower yield of monoketone **3a** in a protic solvent such as methanol as compared to DCE, TFT, and toluene. Therefore, we decided to screen a few other protic solvents such as HFIP and TFE. Although in lower yield, we were delighted to observe diketone **2a** (25% and 30%, respectively) product along with monoketone **3a** (72% and 54% respectively) (Table 1, entries 5 and 6). To improve the yield of diketone **2a**, we screened various silver salts such as $AgNTf_2$, AgOTf, $AgOCOCF_3$, $AgBF_4$, and Ag_2CO_3 (Table 1, entries 7−11). Interestingly in most cases monoketone **3a** was the major product. However, in the case of $AgBF_4$ and Ag_2CO_3 there is a reversal in trend leading to a significant decrease in the formation of isomerized ketone **3a** that was observed (Table 1, entries 10 and 11). Since Ag_2CO_3 afforded **2a** in 39% yield, we examined the effect

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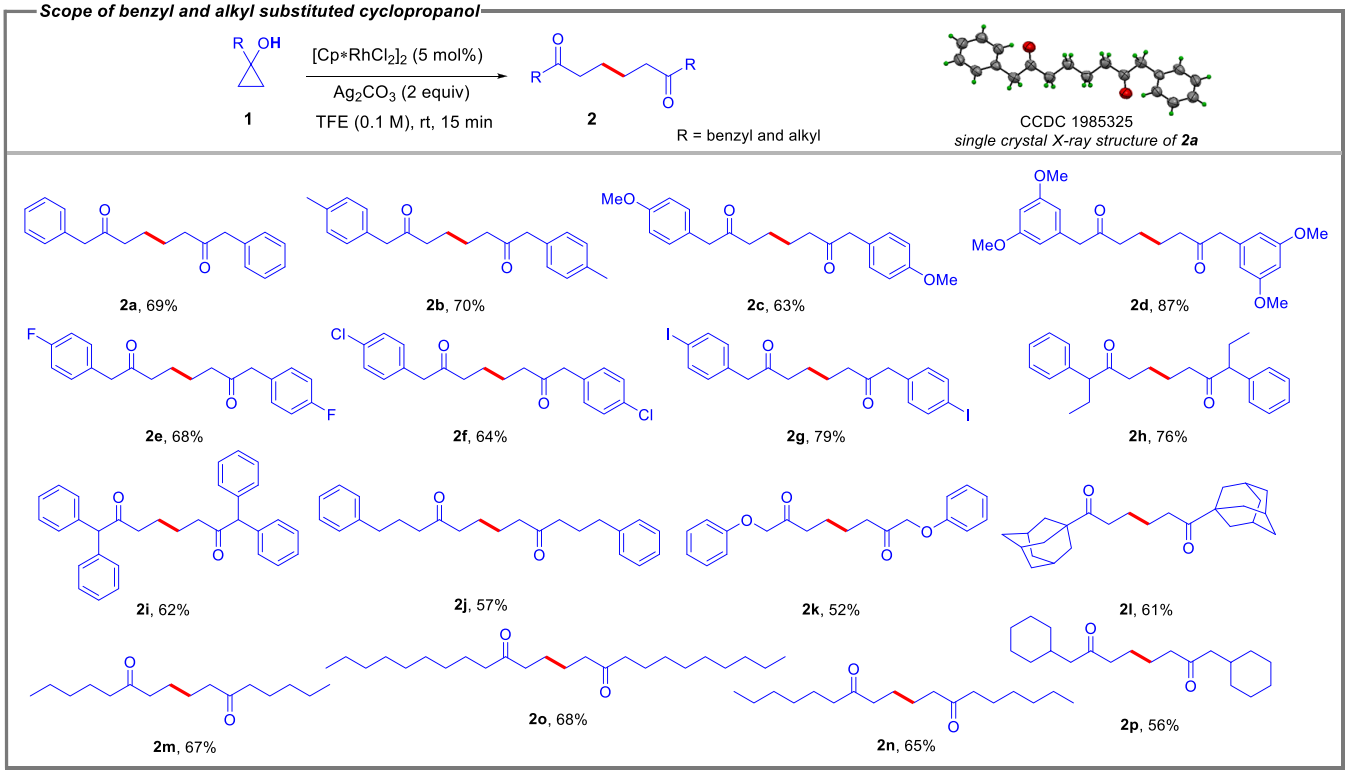
Scheme 3. Scope of Benzyl- and Alkyl-Substituted Cyclopropanol for the Synthesis of 1,6-Diketones[a]



[a]All reactions were carried out with 1 equiv of cyclopropanol **1**, 2 equiv of Ag_2CO_3, and 5 mol % of $[Cp^*RhCl_2]_2$ in the presence trifluoroethanol (0.1 M) at room temperature for 15 min. Isolated yields are mentioned.

of other carbonate additives such as Cs_2CO_3, Na_2CO_3, $KHCO_3$, and $NaHCO_3$ (Table 1, entries 12−15). Surprisingly, none of the carbonate bases were found to be effective. A careful analysis of the above results revealed that Ag_2CO_3 and trifluoroethanol facilitate the formation of the homocoupled product. Intrigued by this fact we speculated that use of higher equivalents of Ag_2CO_3 might help the reaction pathway enhancing the product yield. To our delight, a substantial increment in the yield of **2a** was noticed on increasing the equivalence of Ag_2CO_3 from 0.3 to 1.0 (Table 1, entries 11 and 16−17). For further improvement of the yield, we tested 1.5, 2.0, 2.5, and 3.0 equiv of Ag_2CO_3 (Table 1, entries 18−21). Satisfactorily, a significant rise in yield was attained on increasing the equivalents of Ag_2CO_3 up to 2.0 (Table 1, entries 17−19). However, the yield of **2a** diminished when more than 2.0 equiv of Ag_2CO_3 was used (Table 1, entries 20−21). To check the influence of the rhodium catalyst and Ag_2CO_3, two control experiments were conducted. In the absence of Ag_2CO_3, only 14% formation of **2a** was observed, while, without the rhodium catalyst, homocoupled product was not obtained (Table 1, entries 22−23). Hence, the use of 2.0 equiv of Ag_2CO_3 along with 5 mol % of $[Cp^*RhCl_2]_2$ in trifluoroethanol gave the best yield of **2a** (Table 1, entry 19).

To assess the robustness of this developed protocol an array of electronically and structurally diverse cyclopropanols **1**, **4** were subjected to the optimized reaction conditions (Scheme 3). Initially, the scope of different benzyl-substituted cyclopropanols **2a−2i** were evaluated. Cyclopropanol bearing electron-donating benzyl substituents worked efficiently affording 63−87% yields of their respective 1,6-diketones **2a−2d**. Likewise, cyclopropanols bearing electron-withdrawing *para*-substituents also produced their respective 1,6-diketones **2e−2g** in 64−79% yield. These results reveal that the reaction is facile for both electronically rich as well as electronically poor benzyl-substituted cyclopropanols. Moreover, the disubstituted benzyl cyclopropanols **1h** and **1i** worked well, producing 1,6-diketones **2h** and **2i** in good yields. Other alkyl-substituted cyclopropanols such as γ-phenyl- and α-phenoxy-substituted 1,6-diketones **2j** and **2k** were obtained in moderate to good yield from **1j** and **1k**. It is worth noting that sterically hindered cyclopropanol **1l** reacted smoothly to afford the desired 1,6-diketone **2l**. Interestingly, 1,6-diketones containing linear-chain and alicyclic substituents **2m−2p** can also be prepared in good yields.

To illustrate the generality of this protocol, various aryl- and heteroaryl-substituted cyclopropanols were subjected to the standard reaction conditions (Scheme 4). Cyclopropanols carrying both electronically rich and electronically poor aryl substituents successfully gave their respective 1,6-diketones. Aryl cyclopropanols with an electron-donating group (*o*-, *m*-, *p*-) afforded 1,6-diketones **5a−5f** in moderate to good yield. Similarly, electron-deficient cyclopropanols bearing a chloro, fluoro, and trifluoromethyl arene substituent also produced their corresponding 1,6-diketones **5g−5i** in good yield. Delightfully, excellent compatibility was observed with furan- and thiophene-containing cyclopropanols resulting in their analogous 1,6-diketones **5j** and **5k**.

Further, a 1.0 mmol scale reaction was carried out with **4a** to give **5a** in 66% yield (Scheme 5a). Again, the potential of 1,6-diketone as a synthetic precursor for different carbo- and heterocyclic scaffolds was examined.[17g,19] The aryl substituted 1,6-diketone **5e** gave corresponding aldol adduct **6e** in good

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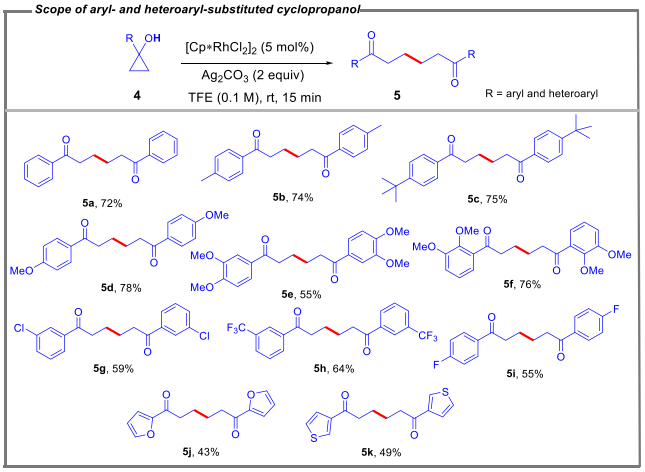
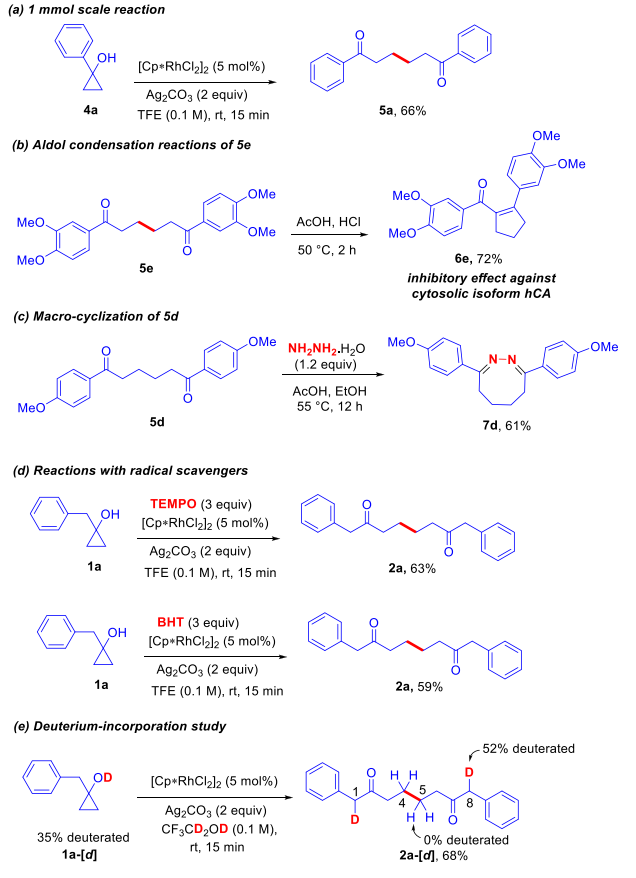
Scheme 4. Scope of Aryl- and Heteroaryl-Substituted Cyclopropanol for the Synthesis of 1,6-Diketones[a]



[a]All reactions were carried out with 1 equiv of cyclopropanol **4**, 2 equiv of Ag_2CO_3, and 5 mol % of $[Cp^*RhCl_2]_2$ in the presence of trifluoroethanol (0.1 M) at room temperature for 15 min. Isolated yields are mentioned.

Scheme 5. 1 mmol Scale Reaction, Synthetic Applications, and Mechanistic Studies

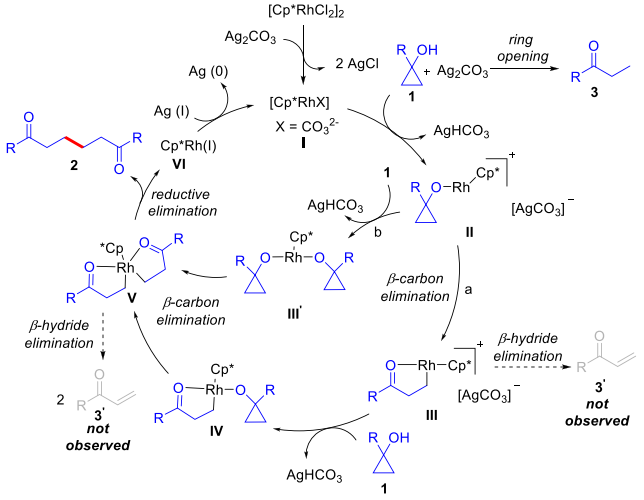


yield (Scheme 5b). Interestingly, 1, 6-diketone **5d**, when treated with hydrazine hydrate in the presence of AcOH, underwent macrocyclization affording **7d** in 61% yield (Scheme 5c).

Inspired by the scope of transformation, a series of mechanistic experiments were carried out. Initially, two reactions in the presence of radical scavengers such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methyl-phenol (BHT) showed no effect revealing a nonradical pathway (Scheme 5d). To gain further insight into the mechanism, we performed the deuterium incorporation experiment under the standard reaction conditions using deuterium-labeled cyclopropanol **1a**-[*d*] (35% deuterated) in the presence of d_3-trifluoroethanol. No deuteration was observed at the C-4 and C-5 positions of the diketone **2a**-[*d*], which again rules out the possibility of a radical pathway (Scheme 5e).

Based on the above findings and literature precedents,[9a,20] a plausible catalytic cycle is shown (Scheme 6). Initially,

Scheme 6. Proposed Catalytic Cycle



$[Cp^*RhCl_2]_2$ reacts with Ag_2CO_3 to form active rhodium species **I**. Cyclopropanol **1** undergoes ligand exchange with **I** to give alkoxide species **II** which can proceed in two different pathways to reach species **V**. In pathway a, the alkoxide species **II** follows *β*-carbon elimination to afford alkyl-rhodium homoenolate **III**. Ligand exchange of **III** with another molecule of cyclopropanol leads to the formation of species **IV** that further undergoes *β*-carbon elimination to produce dialkyl-rhodium species **V**. Alternatively, **II** can involve ligand exchange with the second molecule of cyclopropanol prior to *β*-carbon elimination to reach species **V** via the formation species **III′**. It is noteworthy that a *β*-hydride elimination pathway was not observed from homoenolate **III** or from species **V** to give the corresponding *β*-hydride eliminated product **3′**. Finally, species **V** undergoes reductive elimination to furnish product **2** along with rhodium(I)-species **VI**. Species **VI** undergoes oxidation by Ag(I) to regenerate rhodium(III)-species **I**. Formation of thin film of silver deposits on the sides of the reaction vessel further confirms this fact.

In conclusion, we have developed an efficient rhodium-catalyzed C−C activation of cyclopropanol for the quick synthesis of discrete 1,6-diketones. The developed protocol proceeds smoothly under mild conditions in short reaction time and tolerates diverse functional groups. Notably, it is facile for a wide range of substrates, including sterically hindered ones. The preliminary experiments give insight into the mechanism of the formation of 1,6-diketones via rhodium-homoenolate. Moreover, the obtained 1,6-diketones can be subjected to numerous transformations to furnish multiple

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valuable cyclic molecular architectures. This robust synthetic strategy provides a useful tool for the synthesis of numerous valuable molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00967.

Detailed experimental procedures, characterization data, and X-ray crystallographic analysis of **2a** (PDF)

FAIR data which includes the primary NMR FID files for compounds **1d**, **1e**, **1g**, **1h**, **2a−2p**, **4f**, **5a−5k**, and **7d** (ZIP)

Accession Codes

CCDC 1985325 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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Author Contributions

†B.V.P. and A.G. contributed equally.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. P. Rajakumar, Department of Organic Chemistry, University of Madras for his excellent teaching and training to scores of Organic Chemists.

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