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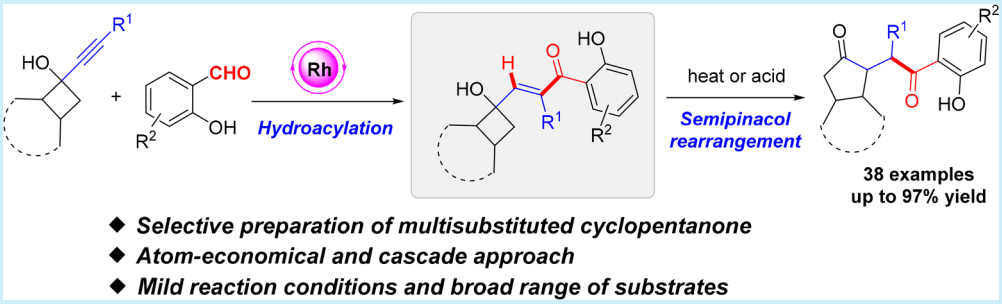
Synthesis of 2-(2-Oxo-2-phenylethyl)cyclopentanone by Rhodium-Catalyzed Tandem Alkynyl Cyclobutanols Hydroacylation and Semipinacol Rearrangement

Rui Guo, Xueling Mo, and Guozhu Zhang*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Center for Excellence in Molecular Synthesis, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China

Supporting Information



ABSTRACT: A rhodium-catalyzed tandem reaction of alkynyl cyclobutanols with salicylaldehydes has been developed. The reaction offers a new and atom-economical approach for the selective preparation of multisubstituted 2-(2-oxo-2-phenylethyl)cyclopentanone in high yields under mild reaction conditions with tolerance of a broad range of substituted alkynyl cyclobutanols and salicylaldehyes. The isolation of intermediate suggests that the reaction proceeds through a sequential process of intermolecular hydroacylation and semipinacol rearrangement.

The hydroacylation of alkynes with aldehydes is an efficient and atom-economic approach for the synthesis of α,β-unsaturated ketones.[1] Of those, rhodium-catalyzed intermolecular hydroacylation of alkynes with chelating aldehydes is one of the well-established strategies due to the compatibility of readily available aldehyde and alkyne as well as its availability to rapidly generate complicated molecular skeletons through tandem reactions.[2] These cascade processes also have been exploited in the efficient synthesis of a variety of heterocyclic ketones and medicinally relevant natural products.[3]

In 2011, the Willis group achieved the synthesis of highly substituted furans through a cascade process of intermolecular hydroacylation and acid-catalyzed dehydrative cyclization.[4] Subsequently, they reported a stepwise method to synthesize dihydroquinolones through tandem rhodium-catalyzed hydroacylation of alkynes with 2-aminobenzaldehydes and Lewis acid catalyzed aza-Michael addition.[5] Inspired by the pioneering work of Miura,[6] the Stanley group and Yoshikai group respectively developed a one-pot tandem process including alkyne hydroacylation with salicylaldehydes and oxo-Michael addition to generate chroman-4-ones by using a rhodium or cobalt catalyst[7] (Scheme 1A). Given the capability of rhodium-catalyzed hydroacylation, development of a novel cascade process leading to complex molecular skeletons with synthetic and medicinal potential is still highly desired.

As a kind of privileged building blocks, cyclobutanols are frequently studied in the field of transition-metal-catalyzed carbon−carbon bond selective cleavage and reconstruction.[8] However, to our knowledge, there are few examples of combining the unique reactivity of hydroacylation and C−C bond cleavage of strained rings through ring opening.[9] We recently reported the intermolecular hydroacylation of alkenyl cyclobutanols with nonchelating aldehydes to afford different 1,5-diketones[10] (Scheme 1B). Along with our continuing interests in this area, we envisioned the possibility of hydroacylation and transformation of alkynyl cyclobutanols. Herein, we report a new method for the synthesis of multisubstituted 2-(2-oxo-2-phenylethyl)cyclopentanone through hydroacylation of alkynyl cyclobutanols with salicylaldehydes followed by semipinacol rearrangement which represents a useful transformation and has been widely used in the total synthesis of natural products.[11] The resulting 1,4-diketone motifs have been found widely in natural products and pharmaceuticals.[12] In addition, as a kind of highly useful synthetic building blocks, 1,4-diketones are frequently being used to synthesize various heterocyclic and carbocyclic compounds.[13]

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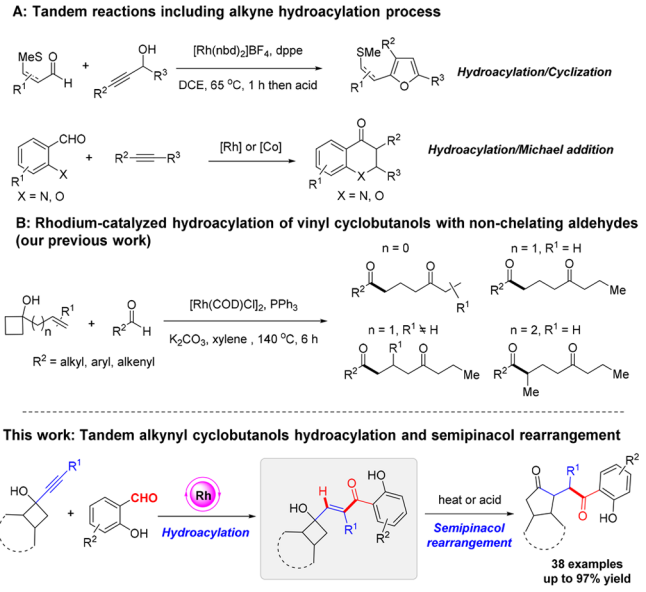
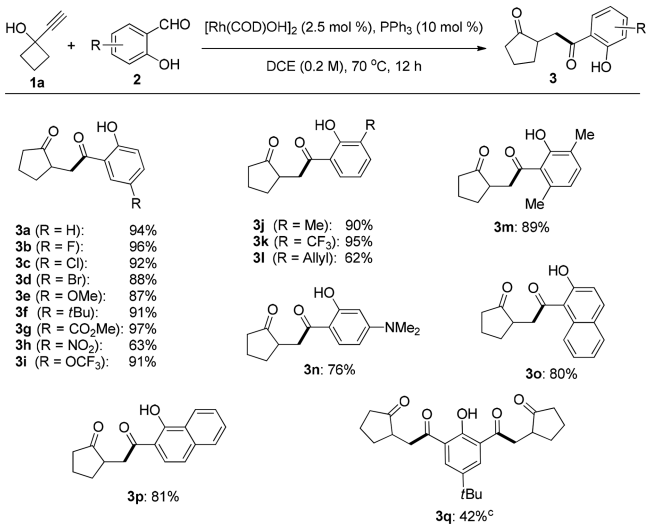
Scheme 1. Rhodium-Catalyzed Intermolecular Hydroacylation Reactions



At the outset of our investigation, we drew on the experience of our previous optimal conditions.[10] As shown in Table 1, salicylaldehyde was reacted with 1-ethynyl cyclobutanol in xylene at 140 °C in the presence of a 2.5 mol % of $[Rh(COD)Cl]_2$, 5 mol % of K_2CO_3, and 10 mol % of PPh_3 ligand. A low yield (20%) of 1,4-diketons product **3a**, which contains a cyclopentane substructure, is isolated (entry 1). After preliminary temperature screening, the yield of product **3a** could increase to 79% at 70 °C in toluene by extending the reaction time (entries 2, 3). We also isolated the hydroacylation product **4** when the reaction was carried out at room temperature for 48 hours (entries 4, 5). As was expected, compound **4** could be converted to 1,4-diketone product **3a** through rearrangement under heating conditions confirming the cascade hydroacylation and semipinacol rearrangement occurred. After different combinations of solvent and base were screened, it was determined the yield could be further increased to 91% by using 1,2-dichloroethane (DCE) as the solvent and K_2CO_3 as the base (entries 6–9). Further catalyst optimization revealed that an excellent yield (94%) of **3a** could be obtained when removing the base and using $[Rh(COD)OH]_2$ instead of $[Rh(COD)Cl]_2$ as the catalyst (entries 11). Several other Rh catalysts were surveyed with no positive effects for this chemistry (entries 10, 12).

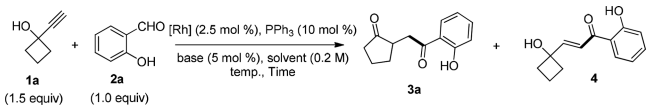
With the optimal reaction conditions in hand, we evaluated the substrate scope of salicylaldehyde **2** with various electronic and steric properties of substituents. The results are summarized in Scheme 2. For 3-, 4-, or 5-position substituted salicylaldehydes, a variety of electron-poor (**3b**–**3d**, **3g**–**3i**, **3k**), electron-rich (**3e**, **3j**, **3n**), and sterically demanding (**3f**, **3m**) substituents were tolerated to afford the corresponding

Scheme 2. Substrate Scope with Respect to Salicylaldehydes[a,b]



[a]Reaction conditions: salicylaldehyde **2** (0.2 mmol), **1a** (0.3 mmol), $[Rh(COD)OH]_2$ (2.5 mol %), PPh_3 (10 mol %), DCE (0.2 M) at 70 °C for 12 h, unless noted otherwise. [b]Isolated yield. [c]3.0 equiv of **1a** were used.

Table 1. Evaluation of Reaction Parameters



entry[a]	catalyst	base	solvent	temp (°C)	time (h)	yield **3a** (%)[b]	yield **4** (%)[b]
1	$[Rh(COD)Cl]_2$	K_2CO_3	xylene	140	6	20	n.d.
2	$[Rh(COD)Cl]_2$	K_2CO_3	toluene	110	12	47	n.d.
3	$[Rh(COD)Cl]_2$	K_2CO_3	toluene	70	12	79	n.d.
4	$[Rh(COD)Cl]_2$	K_2CO_3	toluene	rt	48	22	47
5	$[Rh(COD)Cl]_2$	K_2CO_3	DCE	rt	48	35	39
6	$[Rh(COD)Cl]_2$	K_2CO_3	DCE	70	12	91	n.d.
7	$[Rh(COD)Cl]_2$	K_2CO_3	THF	70	12	65	n.d.
8	$[Rh(COD)Cl]_2$	K_3PO_4	DCE	70	12	86	n.d.
9	$[Rh(COD)Cl]_2$	Cs_2CO_3	DCE	70	12	80	n.d.
10	$Rh(PPh_3)_2Cl$	K_2CO_3	DCE	70	12	61	n.d.
11	**$[Rh(COD)OH]_2$**	–	**DCE**	**70**	**12**	**94**	n.d.
12	$[Rh(COD)OH]_2$	–	toluene	70	12	88	n.d.

[a]Reaction conditions: salicylaldehyde **2a** (0.2 mmol), 1-ethynyl cyclobutanol **1a** (0.3 mmol), [Rh] catalyst (2.5 mol %), ligand (10 mol %), base (5 mol %), solvent (0.2 M), unless noted otherwise. [b]Isolated yield.

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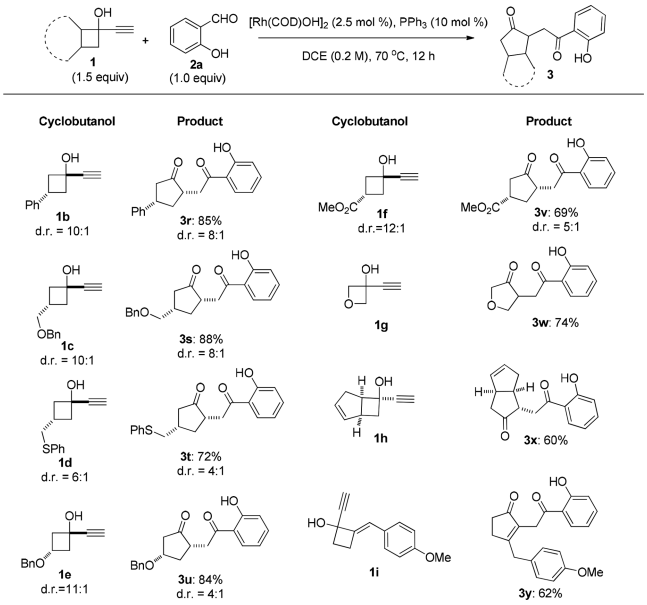
1,4-diketones in good to excellent yields. The salicylaldehyde with a strongly electron-withdrawing and polar nitro group could react smoothly to provide the product in moderate yield (**3h**). It was noteworthy that the allyl group could also be compatible with this reaction conditions to give the 1,4-diketone product **3l** with the double bond intact. In addition to phenyl, 1-hydroxyl or 2-hydroxyl substituted naphthaldehyde also demonstrated good compatibility with current reaction conditions (**30**, **3p**). Moreover, 4-*tert*-butyl-2,6-diformylphenol underwent double hydroacylation and ring expansion successfully in the presence of 3.0 equiv of **1a**, which fully showed the practicability of this method (**3q**).

Subsequently, our attention turned to the variation of ethynyl cyclobutanol with different substituents on the four-membered ring (Scheme 3). Ethynyl cyclobutanol with various

Scheme 3. Substrate Scope with Respect to Cyclobutanols[a,b]

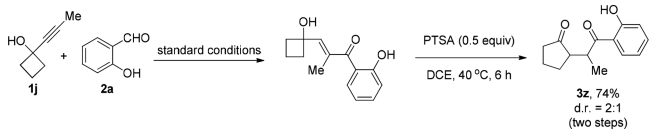


[a]Reaction conditions: salicylaldehyde **2a** (0.2 mmol), **1** (0.3 mmol), $[Rh(COD)OH]_2$ (2.5 mol %), PPh_3 (10 mol %) and DCE (0.2 M) at 70 °C for 12 h, unless noted otherwise. [b]Isolated yield.

substitutions, such as phenyl, benzyl ether, sulfur ether, and ester groups, on the 3-position underwent expected hydroacylation and rearrangement to provide the desired 1,4-diketones in moderate to good yields (**3r**−**3v**). 3-Ethynyloxetan-3-ol **1g** was a suitable substrate for this transformation to afford **3w** in 74% yield. In addition, ethynyl cyclobutanol **1h** fused with a cyclopentene ring also reacted with salicylaldehyde smoothly to provide **3x** in moderate yield. It is remarkable that **1i** [(*E*)-1-ethynyl-2-(4-methoxybenzylidene)-cyclobutan-1-ol] underwent simultaneous double bond migration to give more stable unsaturated cyclopentenone product **3y**.

We then proceeded to investigate the influence of the terminal substituent in the ethynyl group on this reaction. As shown in Scheme 4, 1-(1-propyn-1-yl)cyclobutanol could react with salicylaldehyde under the standard conditions to produce a hydroacylation intermediate smoothly. However, simple heating conditions could not initiate the rearrangement process. After screening a series of Lewis acids and Bronsted

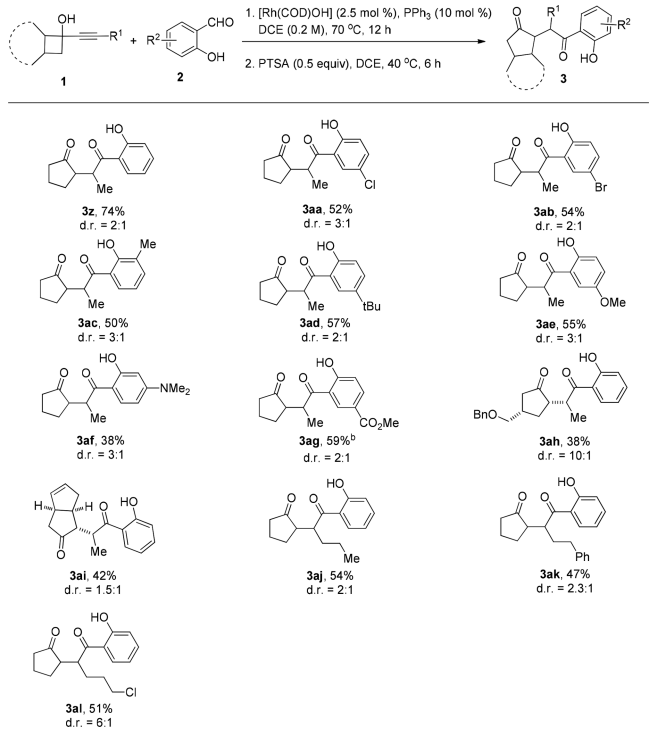
Scheme 4. Stepwise Method of Hydroacylation and Rearrangement



acids, as shown in Scheme 4, we found that *p*-toluenesulfonic acid (PTSA) could promote the rearrangement reaction efficiently to give product **3z** in 74% yield with moderate diastereoselectivity (two steps).[14]

As shown in Scheme 5, under the optimized stepwise reaction conditions, salicylaldehyde with different electronic

Scheme 5. Substrate Scope with Respect to Cyclobutanols and Salicylaldehydes[a,c]



[a]The reaction was carried out under standard conditions, unless noted otherwise. [b]Reaction conditions: methyl 3-formyl-4-hydroxybenzoate (0.2 mmol), **1j** (0.3 mmol), $[Rh(COD)OH]_2$ (2.5 mol %), PPh_3 (10 mol %) and DCE (0.2 M) at rt for 48 h. Then PTSA (0.5 equiv) and DCE (0.2 M) at 40 °C for 6 h. [c]Isolated yield.

substituents could react successfully to afford 1,4-diketone products in moderate yields (**3aa**−**3ag**). The benzyl ether or fused ring structure of cyclobutanol resulted in a slight reduction in yield (**3ah**, **3ai**). Notably, The high diastereoisomer ratio of **3ah** probably attributed to the steric effect of benzyl ether. Furthermore, propyl, phenyl ethyl, and chlorinated alkyl substituted alkynyl cyclobutanols were also appropriate substrates which reacted successfully under the same conditions to provide various 2,3- disubstituted 1,4-diketone products (**3aj**−**3al**).

Finally, we carried out several derivatization reactions of 1,4-diketones (Scheme 6). Compound **3a** could be produced at the gram scale in 82% yield and used to prepare different heterocyclic molecules. For example, treatment of **3a** with

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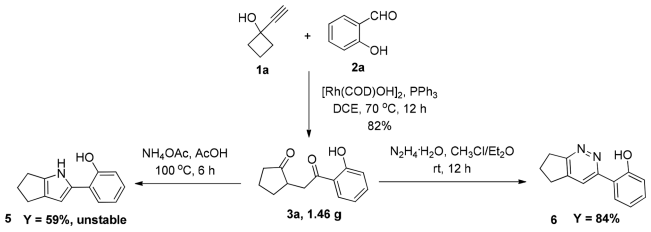
Scheme 6. Synthetic Utilities of 1,4-Diketones



NH_4OAc and AcOH at 100 °C for 6 hours resulted in the multisubstituted pyrrole compound **5**, which is not very stable in air.[15] **3a** then could undergo condensation with $N_2H_4{\cdot}H_2O$ and spontaneous air oxidation to afford pyridazine derivative **6** in 84% yield.[16]

In summary, we developed a highly efficient rhodium-catalyzed tandem reaction of alkynyl cyclobutanols and salicylaldehydes with a broad substrate scope and mild conditions. This reaction provides a new approach for the selective preparation of 2-(2-oxo-2-phenylethyl)cyclopentanone in an atom-economical fashion. The isolation and conversion of the intermediate show that the reaction proceeds through a sequential hydroacylation and semipinacol rearrangement process. As for substituted alkynyl cyclobutanols, a stepwise method could also afford multisubstituted 1,4-diketone products successfully. Our future work will focus on achieving the asymmetric transformation of this reaction through the cocatalytic strategy of a rhodium catalyst and chiral phosphoric acid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03973.

Experimental details and spectral data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: guozhuzhang@sioc.ac.cn.

ORCID

Guozhu Zhang: 0000-0002-2222-6305

Notes

The authors declare no competing financial interest.

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