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Regio- and Stereoselective Synthesis of 2-Hydroxymethyl-1,3-enynes by Rhodium-Catalyzed Decarboxylative C–C Coupling

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Abstract. A regio- and stereoselective protocol for rhodium(I)-catalyzed decarboxylative C–C coupling between propiolic acids and propargyl alcohols has been achieved. This efficient catalytic approach could facilitate the preparation of a diversity of synthetically valuable 2-hydroxymethyl-1,3-enynes with high *Z*-stereoselectivity. Notably, non-terminal alkynes were smoothly transformed into the target products that show intriguing synthetic utility.

Keywords: Wilkinson's catalyst; Decarboxylative C–C coupling; 2-Hydroxymethyl-1,3-enyne; Regioselective synthesis; *Z*-stereoselectivity

The 1,3-Enynes of which versatile functionalized molecules are composed can be ubiquitously found in naturally occurring products[1] and medicinally relevant compounds,[2] and they are also important precursors in materials science.[3] Consequently, extensive efforts have been dedicated to transition-metal-catalyzed coupling reactions of terminal alkynes to control the regio- and stereoselectivity and provide head-to-tail and *Z*- and *E*-head-to-head conjugated enynes.[4] Among abundant enyne compounds, 2-hydroxymethyl-1,3-enynes have recently received considerable attention due to their potential application in the preparation of dihydrofuran derivatives with fluorescent properties.[5] Besides conventional multistep synthesis of 2-hydroxymethyl-1,3-enynes involving the Sonogashira cross-coupling reaction as the key procedure,[6] the groups of Sato[7] and Trost[8] independently developed regioselective synthesis of 2-hydroxymethyl-1,3-enynes relying on nickel and palladium catalysis, respectively. Subsequently, Miura and co-workers reported an interesting homocoupling of 1,1-disubstituted 3-aryl-2-propyn-1-ols in company with the cross-coupling reactions of the same components with bis(trimethylsilyl)acetylene to give rise to *E*-selective enynes.[5b,c] In 2017, Hirano, Uchiyama, and co-workers achieved the first *trans*-selective alkynylboration of propargylic alcohols with subsequent protodeboration to deliver 2-hydroxymethyl-(*E*)-enynes.[9] Very recently, a dual Ni/Cu-catalyzed protocol for the regioselective synthesis of *gem*-1,3-enynes was accomplished by Xia, Lee, and co-workers.[4d] However, the substrates were limited to terminal alkynes as well as aryl-substituted propiolic acids. To the best of our knowledge, regio- and stereoselective synthesis of 2-hydroxymethyl-(*Z*)-enynes from two different non-terminal alkynes by transition metal catalysis remains elusive.

The evolution of transition-metal-catalyzed decarboxylative transformations has always been a fascinating research topic in the field of organometallic chemistry because of its step-economy and regioselective reaction sequence.[10] Propiolic acids, which are simple and sufficiently available feedstocks, can achieve a rapid elaboration of structural complexity through decarboxylative C–C coupling reactions.[11] Typically, the initially formed metal propiolate undergoes decarboxylation to produce the alkynylmetal species, which usually participates in a subsequent coupling reaction. In terms

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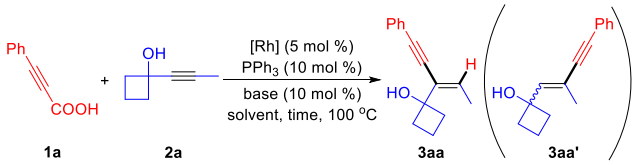
of availability of the starting materials and a wide range of applications in organic synthesis, it would be highly desirable and still challenging to use the decarboxylative coupling reactions of propiolic acids in achieving regio- and stereocontrol.

On the basis of our experience with the rhodium-catalyzed functionalization of benzylic alcohols and allylic alcohols,[12] we envisioned that the combination of elaborated designed non-terminal alkynes bearing a chelation-assisting group with alkynoic acids under rhodium catalysis may address the regioselective synthesis of 2-hydroxymethyl-1,3-enynes, and control the stereoselectivity to obtain one isomer predominantly. This method described herein also aims to use alkynoic acids with diverse substitution patterns which would broaden the scope of decarboxylative C–C coupling reactions substantially.

Table 1. Evaluation of the Reaction Conditions for the Synthesis of 2-Hydroxymethyl-1,3-enynes.[a]



entry	Rh	base	solvent	time (h)	yield (%)[b]	rr[c]
1	$[Rh(COD)Cl]_2$	K_2CO_3	toluene	12	45	7.8:1
2	$[Rh(COD)OH]_2$	K_2CO_3	toluene	12	36	6.9:1
3	$RhCl(PPh_3)_3$	K_2CO_3	toluene	12	58	10.4:1
4	$RhCl(PPh_3)_3$	K_2CO_3	toluene	6	62	10.1:1
5	$RhCl(PPh_3)_3$	K_2CO_3	toluene	4	69	10.9:1
6[d]	$RhCl(PPh_3)_3$	K_2CO_3	toluene	4	44	12.2:1
7	$RhCl(PPh_3)_3$	Na_2CO_3	toluene	4	56	9.8:1
8	$RhCl(PPh_3)_3$	Cs_2CO_3	toluene	4	53	7.6:1
9	$RhCl(PPh_3)_3$	*t*-BuOK	toluene	4	68	8.3:1
10[e]	$RhCl(PPh_3)_3$	K_2CO_3	toluene	4	24	10.6:1
11	$RhCl(PPh_3)_3$	K_2CO_3	DCE	4	42	5.4:1
12	$RhCl(PPh_3)_3$	K_2CO_3	THF	4	51	9.5:1
13	$RhCl(PPh_3)_3$	K_2CO_3	*p*-xylene	4	40	8.7:1
14[f]	**$RhCl(PPh_3)_3$**	**K_2CO_3**	**toluene**	**4**	**74**	**11.3:1**
15[g]	\	K_2CO_3	toluene	4	0	-
16[f,g]	$RhCl(PPh_3)_3$	K_2CO_3	toluene	4	47	11.1:1
17	$RhCl(PPh_3)_3$	\	toluene	4	41	10.3:1

[a] Unless noted otherwise, all reactions were performed using **1a** (0.3 mmol, 1 equiv.), **2a** (1.5 equiv.), [Rh] catalyst (5 mol %), PPh_3 (10 mol %), and base (10 mol %) in 1.5 mL of solvent at 100 °C.
[b] Yield denotes isolated (*Z*)-isomer.
[c] Regioisomeric ratio (rr) of combined (*Z*)- and (*E*)-**3aa** to **3aa′** was determined by ^1H NMR analysis of the crude mixture.
[d] 80 °C.
[e] 1.0 equiv. of KF was added.
[f] 20 mol % of K_2CO_3 was used.
[g] Without PPh_3.

This chemistry was initiated by choosing phenylpropiolic acid (**1a**) and 1-(prop-1-yn-1-yl)cyclobutan-1-ol (**2a**) as model substrates to evaluate the reaction conditions (Table 1). When the coupling reaction was conducted with the $[Rh(COD)Cl]_2/PPh_3/K_2CO_3$ catalytic system in dry toluene at 100 °C for 12 h, (*Z*)-1-(1-phenylpent-3-en-1-yn-3-yl)cyclobutan-1-ol (**3aa**) was provided in 45% yield in a regioisomeric ratio of 7.8:1 (Table 1, entry 1). Further screening of the other two rhodium(I) catalysts demonstrated that Wilkinson's catalyst was the best choice (Table 1, entry 2–3). The yield was increased gradually by decreasing the reaction time, indicating that the product may be unstable to prolonged heating (Table 1, entry 4–5). Lowering the temperature to 80 °C resulted in an inferior yield and slightly improved regioselectivity (Table 1, entry 6). Among the bases tested (Table 1, entry 7–9), potassium *tert*-butoxide delivered a yield comparable to that achieved with K_2CO_3. Using KF (1.0 equiv.) as an additive decreased the yield considerably (Table 1, entry 10). Furthermore, switching toluene to other dry solvents such as DCE, THF, and *p*-xylene proved to be inefficient to promote the reaction and decreased the regioselectivity (Table 1, entry 11–13). To our delight, an enhancement in base loading had a positive effect on the reaction turnover, and 2-hydroxymethyl-(*Z*)-enyne **3aa** was produced with the highest yield (Table 1, entry 14). Under the optimal conditions, the ratio of (*Z*)-isomer to (*E*)-isomer was 88:12, as determined by ^1H NMR integration of the crude mixture. Control experiments demonstrated that the $RhCl(PPh_3)_3/PPh_3$ catalytic couple was essential for the reaction (Table 1, entry 15), and the absence of the ligand or the base led to lower yields of the product (Table 1, entry 16–17).

After identifying the optimized reaction conditions, we evaluated the decarboxylative C–C coupling reactions of a series of propiolic acids with alkynyl cycloalkanol **2a** (Scheme 1). Propiolic acids bearing electron-donating groups on the benzene ring, such as alkyl (**3ba**–**3ca**) and alkoxy (**3da**–**3fa**) groups, underwent the coupling reactions smoothly to provide the 2-hydroxymethyl-(*Z*)-enynes in satisfactory yields and regioselectivities. The reactions of aryl-substituted propiolic acids with **2a** gave the corresponding enynes (**3ga**–**3ha**) in 61% and 58% yield, respectively. It was found that the substrates with fluoro (**3ia**), chloro (**3ja**), trifluoromethyl (**3ka**), and ester (**3la**) groups were also compatible with the catalytic system. To our delight, 3-(benzo[*b*]thiophen-2-yl)propiolic acid successfully engaged in the decarboxylative addition to furnish the desired compound **3ma**, albeit with low regioselectivity. However, pyridyl-substituted alkynoic acid did not react. Furthermore, exposure of the substrates bearing methyl and trimethylsilyl groups to the reaction conditions produced the corresponding 1,3-enynes (**3na**–**3oa**) in moderate yields, thus

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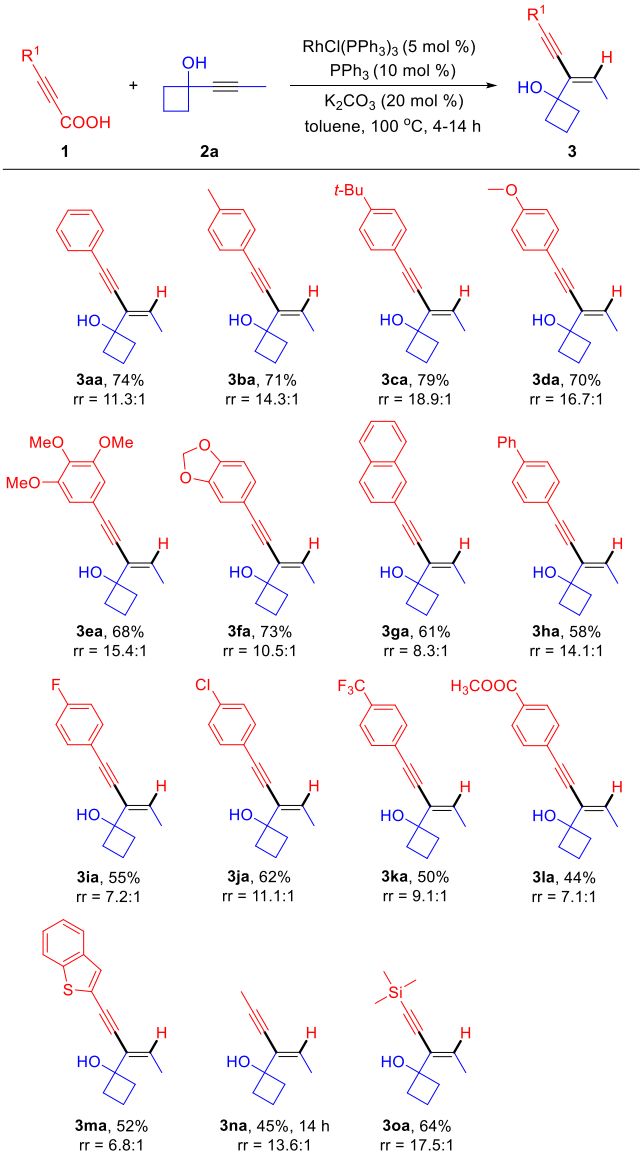
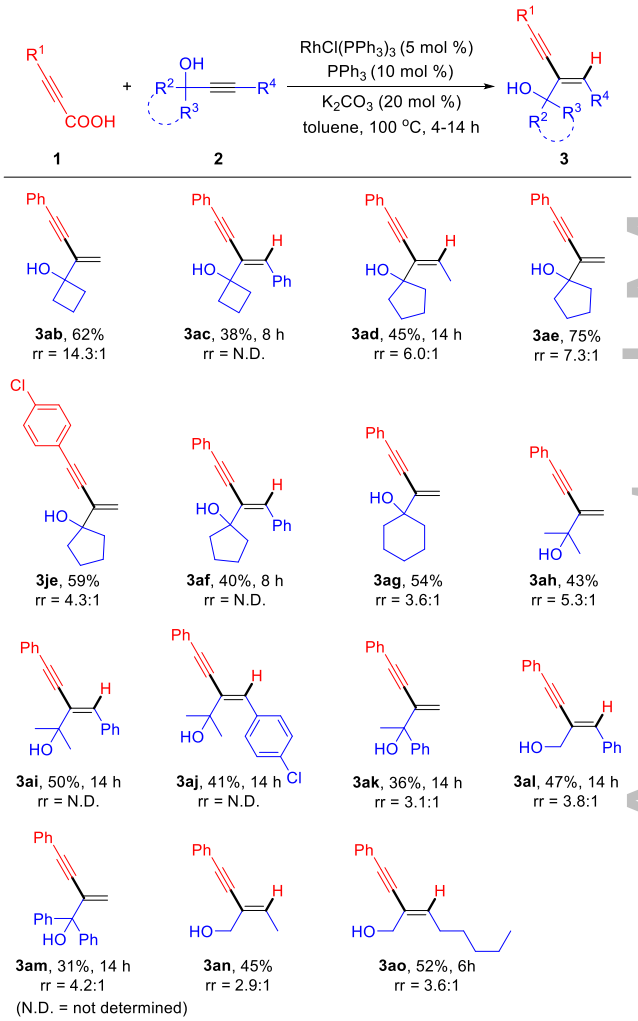
expanding the scope of the decarboxylative C–C coupling reactions compared with the recently developed method with only aryl-substituted alkynoic acids as the coupling partner.[4d] It needs to be pointed out that only the (*Z*)-isomer was isolated as the major product from these reactions.



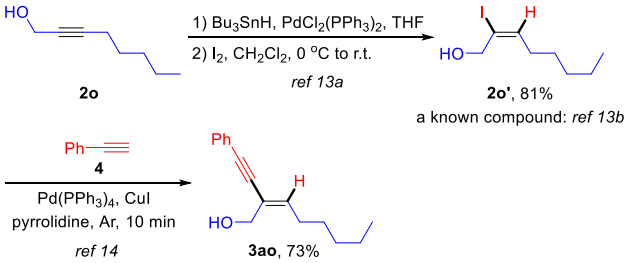
Scheme 1. Scope of Propiolic Acids for the Synthesis of 2-Hydroxymethyl-(*Z*)-enynes.

As shown in Scheme 2, a myriad of terminal and non-terminal alkynes were then examined for the decarboxylative C–C coupling reactions with propiolic acids. For example, the conversion of terminal alkynes bearing different kinds of carbocycles regioselectively delivered *gem*-1,3-enynes (**3ab**, **3ae**, **3je**, **3ag**) with the yield varying from 54% to 75%. In addition to *γ*-methylated propargyl alcohol **2d**, the alkynes bearing a phenyl group at the *γ*-position were suitable substrates to produce the anticipated molecules (**3ac**, **3af**). However, 2-methylbut-3-yn-2-ol (**2h**) exhibited lower reactivity toward phenylpropiolic acid (**1a**). This unique protocol could be utilized to the preparation of the 2-hydroxymethyl-(*Z*)-enynes (**3ai**–**3aj**) bearing an aromatic ring at the *γ*-position of the hydroxyl group, complementing the reported methods for constructing the corresponding (*E*)-isomers.[5b,9] Moreover, the present catalytic system was observed to be effective for the coupling reactions of 2-phenylbut-3-yn-2-ol (**2k**) and 3-phenylprop-2-yn-1-ol (**2l**) with **1a** to provide the regiospecific products (**3ak**–**3al**). 1,1-Diphenyl-substituted substrate participated in the decarboxylative C–C coupling reaction sluggishly (**3am**) because of the steric hindrance. Finally, when 3-alkyl-substituted propargyl alcohols were treated with **1a** in the presence of the rhodium catalyst, the desired 2-hydroxymethyl-(*Z*)-enynes (**3an**–**3ao**) were afforded in yields of 45% and 52%, respectively.

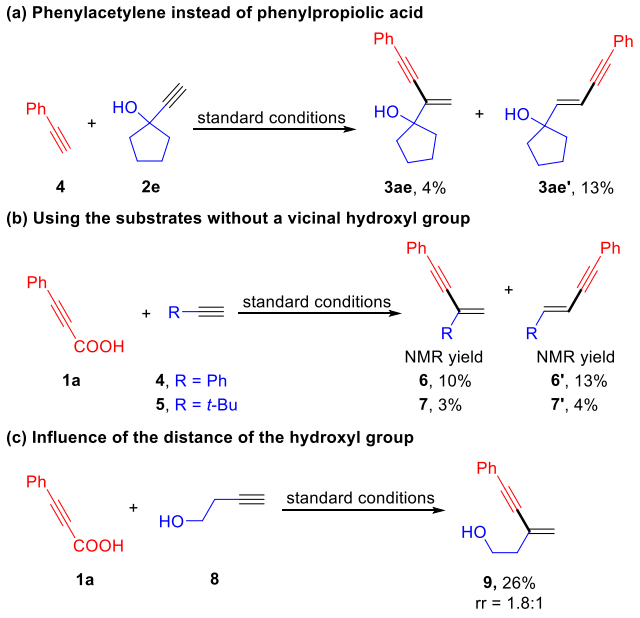


Scheme 2. Scope of Alkynes for the Synthesis of 2-Hydroxymethyl-1,3-enynes.

To confirm the regio- and stereoselectivity of this protocol, we turned to use an unambiguous route to prepare the representative compound (Scheme 3). Initially, palladium-catalyzed stereospecific hydrostannation of 2-octyn-1-ol (**2o**) followed by treatment with iodine[13a] produced the (*E*)-vinyl iodide **2o′** (81% overall yield), which is a known compound.[13b] The Sonogashira cross-coupling reaction was successfully achieved by treating the intermediate with phenylacetylene (**4**),[14] leading to the corresponding product in 73% yield. ^{1}H NMR, ^{13}C NMR, and NOESY analyses of the product were in agreement with those of **3ao**, which was synthesized by rhodium-catalyzed decarboxylative C–C coupling.

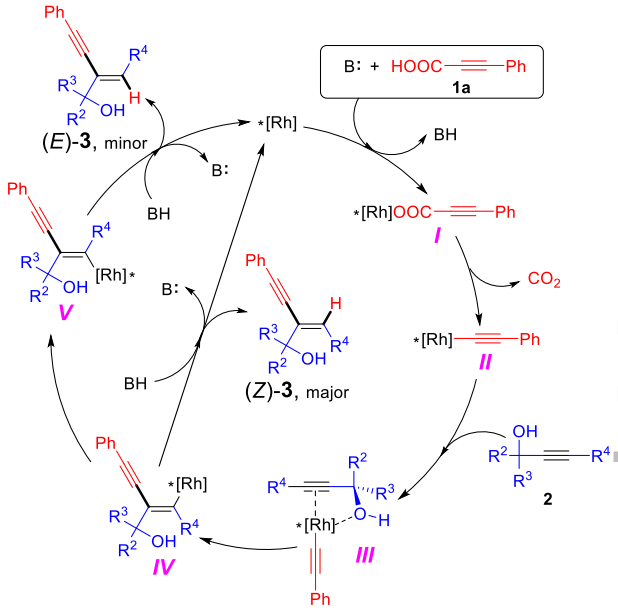


Scheme 3. An Unambiguous Route to Confirm the Structure.



Scheme 4. Mechanistic Investigations.

To probe the mechanism of this rhodium-catalyzed decarboxylative C–C coupling reaction, several control experiments were carried out (Scheme 4). To form as few isomers as possible, the incorporation of ethynyl cyclopentanol (**2e**) to phenylacetylene (**4**) instead of phenylpropiolic acid (**1a**) was investigated, resulting in **3ae** in 4% isolated yield along with (*E*)-isomer **3ae′** in 13% isolated yield (Scheme 4a). The low yield and regioselectivity indicated that phenylacetylene exhibited poor reactivity toward **2e** under the standard conditions and that oxidative addition of the acetylene C–H bond to the metal with subsequent hydroalkynylation is unlikely to occur in our catalytic system.[4c,15] While performing the coupling reactions of phenylpropiolic acid (**1a**) with terminal alkynes bearing different substituents (**4**, **5**) in the absence of a vicinal hydroxymethyl group (Scheme 4b), inferior regioselectivities were detected. The result highlighted the importance of the hydroxy group in assisting chelation to the rhodium intermediates. Moreover, the coupling of the homologue of propargyl alcohol to **1a** provided *gem*-1,3-enyne **9** in 26% yield with a relatively low regioselectivity (Scheme 4c), suggesting that the chelation of the hydroxyl group and the alkyne moiety to rhodium(I) may require an appropriate steric distance.



Scheme 5. Proposed Catalytic Cycle.

Based on the depicted mechanistic evidence, we propose that the 2-hydroxymethyl-1,3-enyne might be formed by the catalytic mechanism illustrated in Scheme 5. After generation of rhodium propiolate **I**, decarboxylation proceeds readily to afford unstabilized alkynylrhodium species **II**. The alkyne moiety of propargyl alcohol **2** is activated by electrophilic rhodium(I) to form π-complex **III**[16] with the strong chelation assistance of the hydroxyl group, which upon regioselective insertion of the alkyne into the Rh–C bond provides vinylrhodium species **IV**.[5b] This unusual regioselectivity of the carbometallation step has been reported to be mainly attributed to steric factors.[5b,8a] The successive protonation preferentially produces target molecule (*Z*)-**3** and regenerates the active rhodium(I) catalyst. Note that the stereochemical isomerization of intermediate **IV** to **V**

through a zwitterionic form[17] allows the production of (*E*)-**3**, which was detected by ^{1}H NMR.

In summary, we have developed a rhodium(I)-catalyzed regio- and stereoselective synthesis of 2-hydroxymethyl-1,3-enynes from readily accessible aryl-, alkyl-, and trimethylsilyl-substituted propiolic acids and propargyl alcohols through decarboxylative C–C bond formation. This research highlights the employment of non-terminal alkynes for the coupling reactions, which predominantly deliver a diversity of (*Z*)-enynes. The subject of our ongoing studies will focus on further elucidation of the *Z*-stereochemistry and synthetic applications of this attractive approach.

Experimental Section

To an oven-dried sealed tube (20 mL) equipped with a stirrer bar was added $RhCl(PPh_3)_3$ (13.9 mg, 0.015 mmol, 5 mol %), PPh_3 (7.9 mg, 0.03 mmol, 10 mol %), K_2CO_3 (8.3 mg, 0.06 mmol, 20 mol %), phenylpropiolic acid **1a** (43.8 mg, 0.3 mmol, 1.0 equiv.), and 1-(prop-1-yn-1-yl)cyclobutan-1-ol **2a** (49.6 mg, 0.45 mmol, 1.5 equiv.) under ambient atmosphere. Dry toluene (1.5 mL, 0.2 M) was then added. After the reaction mixture was stirred at room temperature for 15 min, the resulting mixture was heated at 100 ℃ for 4 h. Upon completion, the reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography (petroleum ether/EtOAc) to obtain the desired product **3aa**.

Acknowledgements

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UPDATE

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