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Ni/Cu-Catalyzed Decarboxylative Addition of Alkynoic Acids to Terminal Alkynes for the Synthesis of *gem*-1,3-Enynes

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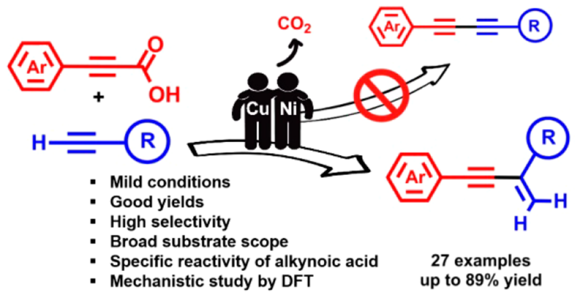
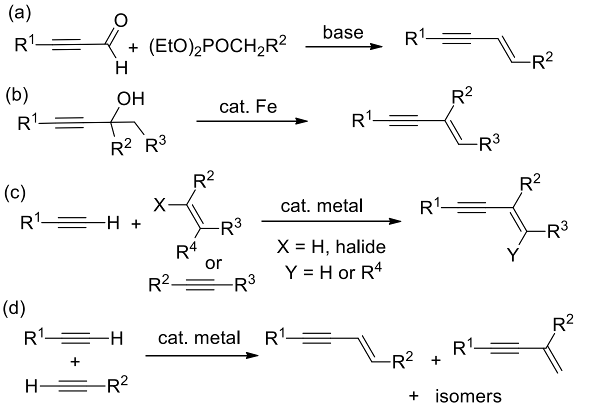
Supporting Information

ABSTRACT: The synthesis of *gem*-1,3-enynes via Ni/Cu-catalyzed decarboxylative addition of alkynoic acids to terminal alkynes has been developed. It was found that the decarboxylation of an alkynoic acid led predominantly to *gem*-1,3-enynes instead of 1,3-diynes, which have been known to be formed through the coupling of terminal alkynes. A variety of *gem*-1,3-enynes were obtained in good yields. This catalytic system exhibited excellent regioselectivity and high functional group tolerance.



Conjugated 1,3-enynes are important structural units in synthetic chemistry, materials science, and bioactive product synthesis.[1] A number of synthetic methods for the preparation of 1,3-enynes have been reported,[2] including the Wittig reaction with propargyl aldehydes[3] and dehydration of propargyl alcohols[4] (Scheme 1a,b). In terms of atom economy and availability of starting materials, direct catalytic coupling is very attractive. In this context, transition metal-catalyzed reactions of alkenes with terminal alkynes and hydroalkynation of alkynes have been developed (Scheme 1c).[5] The cross-dimerization of two different terminal alkynes has been challenging because a number of isomers can be formed and because it is difficult to control (Scheme 1d). To achieve different chemo-, regio-, and stereoselectivities, Ir,[6] Rh,[7] Ru,[8] Co,[9] Fe,[10] Pd,[11] and Ni[12] catalysts have been used. However, *gem*-selective cross-dimerization of alkynes, which occurs through head-to-tail cross-coupling, has been performed successfully only using Rh,[13] Ti,[14] and Pd[15] catalysts. Moreover, all of these methods have been limited to terminal alkynes.

Scheme 1. Synthesis of 1,3-Enynes



We have been developing a number of synthetic methods that use alkynoic acids, including transition metal-catalyzed decarboxylative coupling reactions.[16] Since simple preparation methods for aryl alkynoic acid derivatives were reported, decarboxylative reactions involving them have received much attention and have been widely applied in organic synthesis.[17] There are very few examples of metal-catalyzed coupling reactions between alkynoic acids and terminal alkynes in which they show different reactivity. Recently, we reported metal-free synthesis of propargyl amines and selective synthesis of (*Z*)-allyl nitriles and showed that only alkynoic acid derivatives afforded the desired products under our optimal conditions.[18] These results and the advantages of aryl alkynoic acids stimulated our interest in developing new synthetic methods using these compounds.

In the course of our studies of novel reactions using alkynoic acid derivatives, we found that alkynoic acids provide *gem*-1,3-enynes when they are allowed to react with terminal alkynes in the presence of Ni/Cu dual catalysts. Decarboxylative addition was preferred, and this preference is not in agreement with findings from other groups. Lei demonstrated that two different terminal alkynes afforded 1,3-diynes in the presence of Ni and Cu catalysts. In 2016, Zhou, Yin, and co-workers reported the selective heterocoupling of terminal alkynes in the presence of a copper catalyst (Scheme 2a).[19] However, 1,3-enynes were not found in either report. Hence, our finding is very interesting and represents the first synthesis of *gem*-1,3-enynes through a decarboxylative coupling reaction and the

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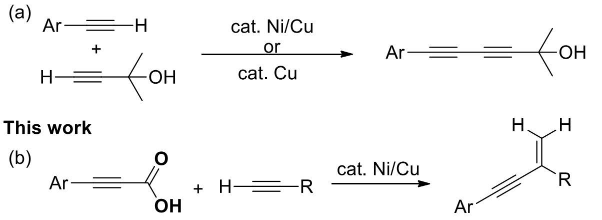
Scheme 2. Synthesis of 1,3-Diyne and *gem*-1,3-Enyne

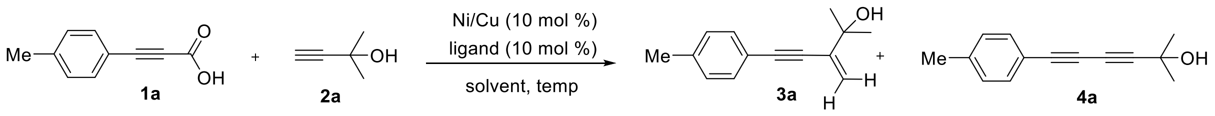


first example of nickel/copper-catalyzed synthesis of *gem*-1,3-enynes. We envisioned that these intricate transformations could be controlled at certain stages by tuning the reaction parameters to furnish the desired products. Herein, we report the selective synthesis of *gem*-1,3-enynes from alkynoic acids and terminal alkynes using a nickel/copper catalyst (Scheme 2b).

To find the optimal conditions for the formation of *gem*-1,3-enynes, *p*-tolylpropiolic acid (**1a**) and 2-methylbut-3-yn-2-ol (**2a**) were chosen as standard substrates and evaluated with varied parameters. The results are summarized in Table 1.

When 10 mol % $NiCl_2{\cdot}6H_2O$ and CuI were used as catalysts with 10 mol % tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) at 50 °C, enyne **3a** was produced in 45% yield. However, hetero-cross-coupling product **4a** was also found in 15% yield (entry 1). All tested ligands and solvents provided unsatisfactory results (entries 2–9). When TMEDA was employed as the solvent, the reaction improved dramatically to give **3a** in 69% yield (entry 10). Keeping TMEDA as the solvent, we tested other copper sources, namely, CuBr and CuCl, and other nickel sources, namely, NiF_2, $NiBr_2$, NiI_2, $Ni(acac)_2$, and $Ni(OAc)_2$. However, each reaction gave poorer results (entries 11–17, respectively). Keeping $NiCl_2{\cdot}6H_2O$ and CuI as the catalysts, we tested different reaction temperatures. No products were found when the reaction was conducted at 25 °C (entry 18). When the reaction temperature was increased to 80 °C, **3a** was afforded in 85% yield and with less **4a** (entry 19). Increasing the reaction temperature to 100 °C decreased the yield of **3a** and resulted in a significant amount of byproduct **4a**; however, other isomers were not found (entry 20). In the absence of CuI, only **3a** was produced; however, its yield was low (entry 21). The reaction without $NiCl_2{\cdot}6H_2O$ provided **3a** in only 9% yield (entry 22). When the amount of Ni/Cu was decreased to 5 mol %, the yield decreased to 59% (entry 23). Characterization of decarboxylative addition product **3a** was accomplished using $^{1}H-^{13}C$ heteronuclear multiple-bond correlation (HMBC) experimental data. In addition, isomer **3a′** was not found in any case (Figure 1). Finally, the optimal conditions are as follows: 1.0 equiv of alkynoic acid, 3.0 equiv of terminal alkyne, 10 mol % $NiCl_2{\cdot}6H_2O$, and 10 mol % CuI in TMEDA at 80 °C for 3 h.

Table 1. Optimal Conditions for the Synthesis of *gem*-1,3-Enyne[a]



						yield (%)[b]	
entry	Ni	Cu	ligand	additive	temp (°C)	3a	4a
1	$NiCl_2{\cdot}6H_2O$	CuI	TMEDA	THF	50	45	15
2	$NiCl_2{\cdot}6H_2O$	CuI	bipyridine	THF	50	4	2
3	$NiCl_2{\cdot}6H_2O$	CuI	1,10-Phen	THF	50	3	–
4	$NiCl_2{\cdot}6H_2O$	CuI	PPh_3	THF	50	6	2
5	$NiCl_2{\cdot}6H_2O$	CuI	Xantphos	THF	50	2	–
6	$NiCl_2{\cdot}6H_2O$	CuI	TMEDA	toluene	50	10	8
7	$NiCl_2{\cdot}6H_2O$	CuI	TMEDA	CH_3CN	50	5	2
8	$NiCl_2{\cdot}6H_2O$	CuI	TMEDA	dioxane	50	1	9
9	$NiCl_2{\cdot}6H_2O$	CuI	TMEDA	DMSO	50	2	7
10	$NiCl_2{\cdot}6H_2O$	CuI	–	TMEDA	50	69	4
11	$NiCl_2{\cdot}6H_2O$	CuBr	–	TMEDA	50	37	7
12	$NiCl_2{\cdot}6H_2O$	CuCl	–	TMEDA	50	6	6
13	NiF_2	CuI	–	TMEDA	50	2	10
14[c]	$NiBr_2$	CuI	–	TMEDA	50	43	4
15	NiI_2	CuI	–	TMEDA	50	36	3
16	$Ni(acac)_2$	CuI	–	TMEDA	50	5	3
17	$Ni(OAc)_2$	CuI	–	TMEDA	50	2	–
18	$NiCl_2{\cdot}6H_2O$	CuI	–	TMEDA	25	–	–
19	$NiCl_2{\cdot}6H_2O$	CuI	–	TMEDA	80	85	2
20	$NiCl_2{\cdot}6H_2O$	CuI	–	TMEDA	100	65	10
21	$NiCl_2{\cdot}6H_2O$	–	–	TMEDA	80	45	–
22	–	CuI	–	TMEDA	80	9	21
23[d]	$NiCl_2{\cdot}6H_2O$	CuI	–	TMEDA	80	59	4

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), Ni (0.03 mmol), Cu (0.03 mmol), and ligand (0.06 mmol) in solvent (1.0 mL) for 3 h. [b] Determined through gas chromatography and ^{1}H nuclear magnetic resonance spectroscopy. [c] $NiBr_2{\cdot}O(CH_2CH_2OCH_3)_2$ was used. [d] Using 0.015 mmol of Ni and Cu.

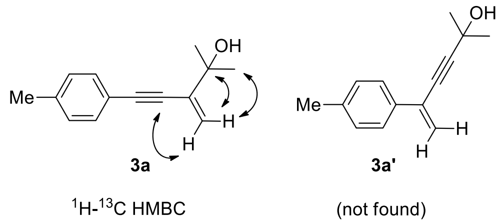
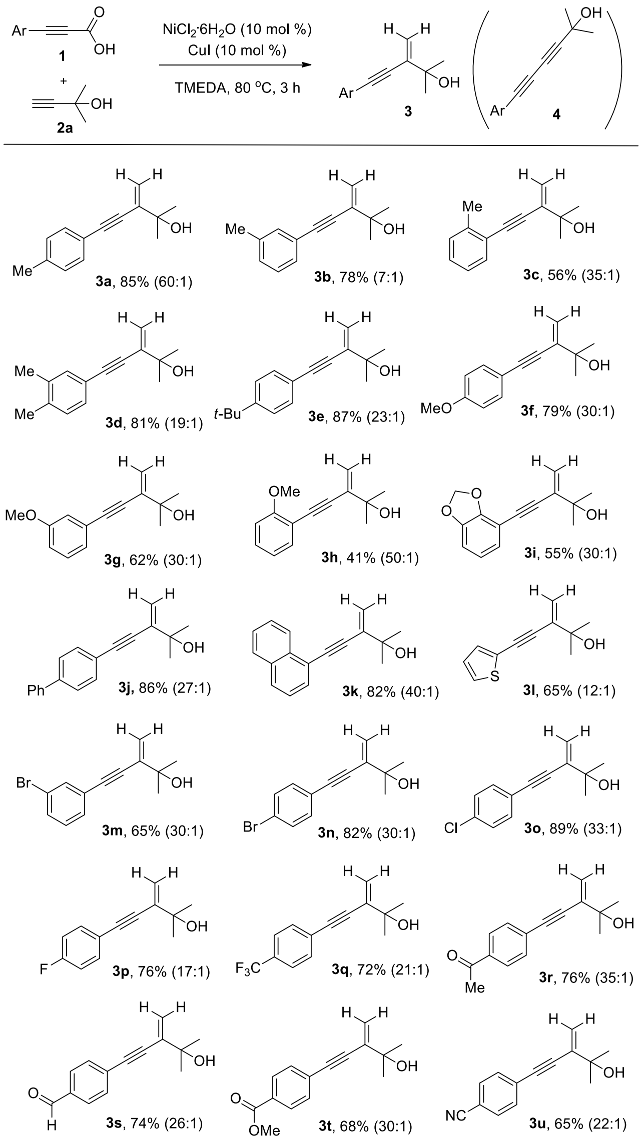


Figure 1. Isomers **3a** and **3a′**.

Using the optimal conditions, a variety of aryl propiolic acids were evaluated for the reaction with propargyl alcohol **2a** for the formation of *gem*-1,3-enynes as shown in Scheme 3.

As expected, aryl alkynoic acids featuring alkyl groups such as methyl or *tert*-butyl groups on the aryl ring reacted smoothly to generate the corresponding products, **3a**−**3e** in good yields.

Scheme 3. Synthesis of *gem*-1,3-Enynes from Aryl Propiolic Acids and 2a[a]

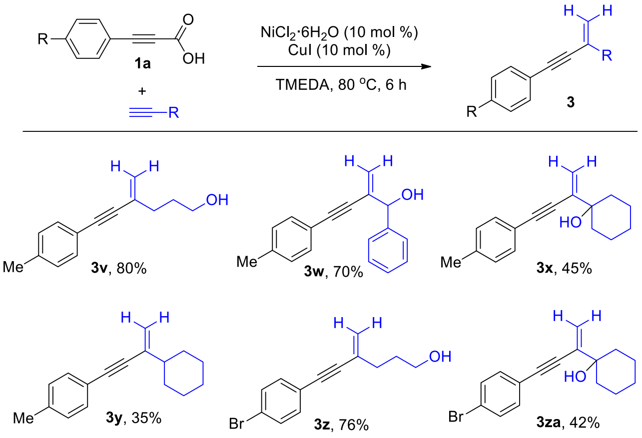


[a]Reaction conditions: **1** (2.0 mmol), **2a** (6.0 mmol), NiCl$_2$·6H$_2$O (0.2 mmol), and CuI (0.2 mmol) in TMEDA (5.0 mL) at 80 °C for 3 h. Numbers in parentheses are the ratios of **3** to **4**.

Aryl propiolic acids with a methoxy group at the *para* or *meta* position afforded *gem*-1,3-enynes **3f** and **3g** in 79% and 62% yields, respectively. However, the *o*-methoxyphenyl and benzo[*d*][1,3]dioxol-4-yl propiolic acids provided **3h** and **3i**, respectively, in slightly lower yields. Biphenyl and naphthyl propiolic acids provided corresponding *gem*-1,3-enynes **3j** and **3k** in 86% and 82% yields, respectively. 2-Thiophenyl propiolic acid gave **3l** in 65% yield. Aryl propiolic acids featuring halide groups such as bromide, chloride, and fluoride led to the formation of corresponding *gem*-1,3-enynes **3m**−**3p** in good yields. 4-Trifluoromethylphenyl propiolic acid provided **3q** in 72% yield. Aryl propiolic acids bearing electron-withdrawing groups such as a ketone, an aldehyde, an ester, and a nitrile were converted to corresponding products **3r**−**3u** in 76%, 74%, 68%, and 65% yields, respectively. It was found that all aryl propiolic acids afforded corresponding *gem*-1,3-enynes **3** as the major products, and trace amounts of the corresponding 1,3-diynes **4** were detected. Unfortunately, alkyl-substituted alkynoic acid such as 2-octynoic acid did not give the desired product.

In addition to **2a**, other terminal alkynes, namely, pent-4-yn-1-ol, 1-phenylprop-2-yn-1-ol, 1-ethynylcyclohexanol, and ethynylcyclohexane, were allowed to react with arylpropiolic acids, viz., *p*-tolylpropiolic acid and 4-bromophenylpropiolic acid. Scheme 4 shows that all terminal alkynes provided the corresponding *gem*-1,3-enynes. It was noteworthy that the heterocoupling product, the 1,3-diyne, was not found in any case. It was found that only one regioisomer formed and each product was characterized using ^{1}H−^{13}C HMBC analysis (see the Supporting Information). When phenyl acetylene and trimethylsilyl acetylene were employed as terminal alkynes, the corresponding *gem*-1,3-enynes were not detected via ^{1}H NMR analysis.

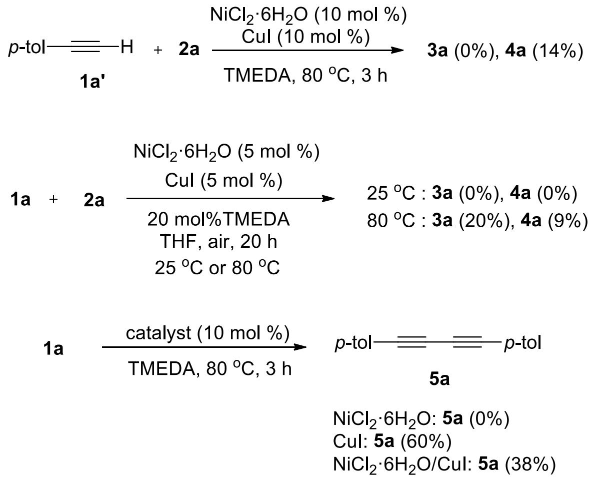
Scheme 4. Reactions with Other Terminal Alkynes[a]



[a]Reaction conditions: **1a** (2.0 mmol), terminal alkyne (6.0 mmol), NiCl$_2$·6H$_2$O (0.2 mmol), and CuI (0.2 mmol) in TMEDA (5.0 mL) at 80 °C for 3 h.

To study the different reactivities between terminal alkynes and alkynoic acids, control experiments were conducted (Scheme 5). When *p*-tolylacetylene (**1a′**) was employed instead of *p*-tolylpropiolic acid under the standard conditions, **3a** was not found; however, cross-coupling product **4a** was afforded in 14% yield. When the previously reported conditions, which provided the cross-coupling products in the reactions with terminal alkynes, were used in reactions

Scheme 5. Control Experiments



between *p*-tolylpropiolic acid and **2a**, neither **3a** nor **4a** was found at 25 °C. However, **3a** and **4a** were formed with 20% and 9% yields, respectively, when the reaction temperature increased to 80 °C. To study the roles of nickel and copper, **1a** was treated with nickel and/or copper in the absence of **2a**. No homocoupling products **5a** formed when a nickel-only catalyst system was used. The reaction with the copper catalyst afforded **5a** in 60% yield. However, its yield decreased when the nickel and copper catalysts were combined.

To better understand the experimental results, density functional theory (DFT) calculations were carried out to shed light on the exact mechanism of the transformation (Figure 2).[20]

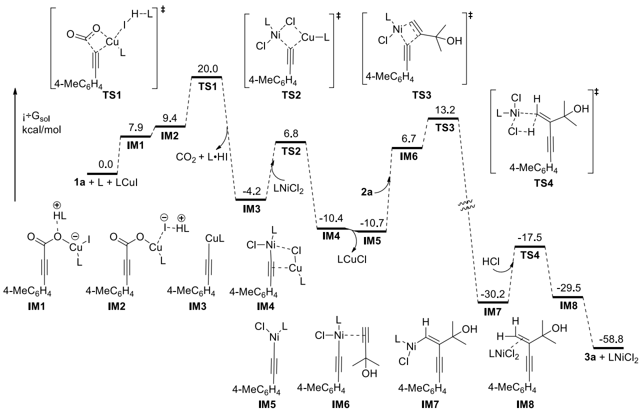


Figure 2. DFT-computed mechanism for the Ni/Cu-catalyzed enyne synthesis (L = TMEDA).

The reaction conditions suggest that stable chelation complexes LCuI and LNiCl$_2$ (L = TMEDA) should be formed favorably from the corresponding metals and TMEDA. Theoretical results indicated that Cu(I) is more effective in the decarboxylation process while Ni(II) is essential for the coupling process. To start the reaction, complex **IM1** could be formed through the deprotonation of **1a** by the basic solvent (L). This step is endergonic by 7.9 kcal/mol. Prior to the decarboxylation, **IM2** could be formed via an interaction between HL$^+$ and iodide. The decarboxylation occurs via **TS1** with an activation barrier of 20.0 kcal/mol, generating Cu(I)-acetylide **IM3** exergonically. This step is facilitated by the association of the L·HI moiety with Cu(I), as a higher barrier was predicted if L·HI was removed. The direct coupling of **IM3** with **2a** was found to be difficult; however, the incorporation of Ni(II) through transmetalation via **TS2** is quite facile and affords more stable Ni(II)-acetylide intermediates **IM4** and **IM5**. The complexation of **IM5** with **2a** produces **IM6** endergonically, and migratory insertion in the latter intermediate occurs via **TS3**. This step requires an overall activation barrier of 23.9 kcal/mol and generates alkenyl Ni(II) intermediate **IM7** highly exergonically. In the last step, the protodemetalation could occur smoothly via **TS4** if HCl is involved as the proton source. The resulting π complex, **IM8**, undergoes dissociation favorably, forming **3a** and regenerating LNiCl$_2$ with an overall exergonicity of 58.8 kcal/mol. The potential energy surface in Figure 2 suggests that the Cu(I)-catalyzed decarboxylation step is relatively easy and generates the acetylide irreversibly, while the Ni(II)-catalyzed migratory insertion is the rate-determining step of the entire reaction. Other possible pathways and isomeric TSs were thoroughly studied using DFT but were found to be higher in energy (more details are provided in the Supporting Information). All of the DFT results corroborate the beneficial combination of Ni(II) and Cu(I) for the generation of enynes **3** from **1** and **2**.

In summary, we have found that reactions between alkynoic acids and terminal alkynes in the presence of NiCl$_2$·6H$_2$O and CuI provide decarboxylative head-to-tail dimerized products, *gem*-1,3-enynes, in good yields. The employment of first-row transition metals like nickel and copper for catalysts has advantages. They are not only inexpensive because of their abundance but also stable toward catalyst poisoning as a result of heteroatom coordination. The reaction system uses mild conditions and shows good functional group tolerance. It was found that the nickel catalyst suppressed alkyne coupling, which was dominated by the copper catalyst. Our findings were different from those of reports that stated that two different terminal alkynes coupled to give 1,3-diynes in the presence of a Ni/Cu or Cu catalyst system. This was the first example of a decarboxylative addition to an alkyne to afford a *gem*-1,3-enyne. On the basis of DFT calculations, we suggested that alkynyl copper is formed through decarboxylation and this is followed by transmetalation to provide an alkynyl nickel complex; in addition, Ni(II)-catalyzed migratory insertion is the rate-determining step of the entire reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01625.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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