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Rhodium-Catalyzed Chemo- and Regioselective Cross-Dimerization of Two Terminal Alkynes

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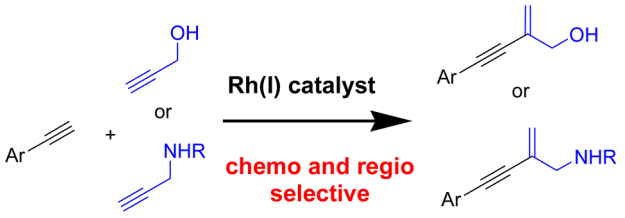
ABSTRACT



Cross-dimerization of terminal arylacetylenes and terminal propargylic alcohols/amides has been achieved in the presence of a rhodium catalyst. This method features high chemo- and regioselectivities rendering convenient and atom economical access to functionalized enynes.

Conjugated 1,3-enynes are an important class of building blocks with diverse applications in organic chemistry[1] and material science.[2] They are generally prepared from the transition metal catalyzed cross-coupling of a terminal alkyne and preactivated alkenes,[3] Wittig olefination of conjugated alkynals,[4] or dehydration of propargylic alcohols.[5] In contrast, a more atom economical method[6] for the preparation of conjugated enynes, namely direct hydroalkynylation across C−C triple bonds or dimerization of alkynes, has found fewer applications due to the challenging issues of chemo-, regio-, and stereoselectivities as illustrated in Scheme 1 for two terminal alkynes.[7] One way to overcome these obstacles is to take advantage of the

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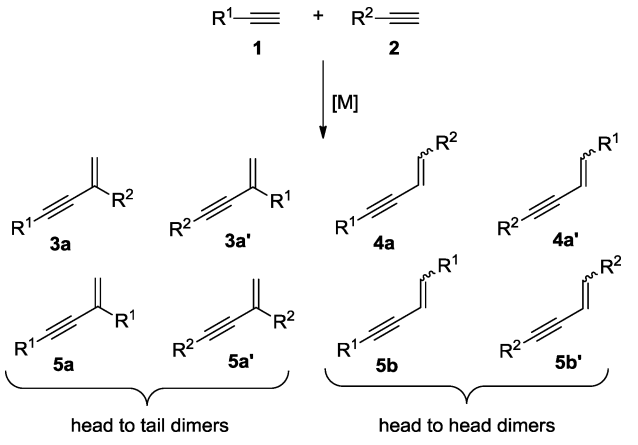
steric and/or electronic differences between the two alkynes to render chemo- and regioselectivity. Important progress has been made along this direction.[8] However, cross-dimerization of two different terminal alkynes with high chemo-, regio-, and stereoselectivity awaits further disclosure. We herein report an efficient and selective cross-dimerization of two different terminal alkynes in a head-to-tail fashion for the preparation of enynes **3a**/**3a′** (Scheme 1).

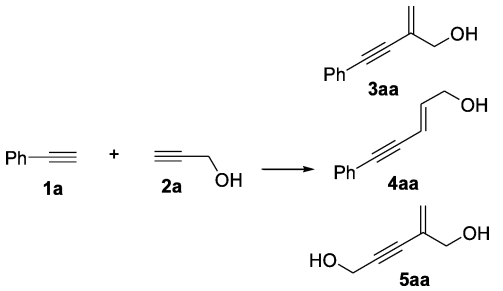
Trost's group has extensively studied the addition of terminal alkynes to various electron-deficient internal alkynes using a palladium catalyst.[8m,n] In the absence of the electron-deficient internal alkyne, the terminal alkyne underwent homodimerization in a head-to-tail fashion to form enyne **5a**/**5a′**. Interestingly, selective cross-dimerization of two terminal alkynes was found to be possible when propargylic alcohols and excess 1,3-enynes were employed.[8l] The head-to-tail products **3a**/**3a′** were obtained in synthetically useful yields. Recently, Li's group disclosed a rhodium-catalyzed homodimerization of propargyl tosylamides to give the head-to-tail product (**5a**/**5a′**) in high selectivity.[8b] Miura's group reported that the head-to-head cross-dimerization product (**4a**/**4a′**) was selectively prepared from two sterically different terminal alkynes.[8f]

Scheme 1. Possible Products from Dimerization of Two Terminal Alkynes



During our development of rhodium-catalyzed intermolecular [5 + 2] cycloaddition of 3-acyloxy-1,4-enynes and alkynes,[9] we found homodimerization of propargylic alcohols occurred in the absence of 3-acyloxy-1,4-enynes. We then explored the possibility of heterodimerizing phenylacetylene **1a** and propargylic alcohol **2a** employing a rhodium catalyst. We first examined the ligand effect using $[Rh(COD)Cl]_2$ as the rhodium precursor (Table 1). The simple Ph_3P ligand afforded the enyne products in 65% yield with good selectivity for **3a** (entry 1). Replacement of Ph_3P by $(p\text{-}CF_3C_6H_4)_3P$ or $(3,5\text{-}CF_3C_6H_4)_3P$ resulted in lower yields and selectivity (entry 4). For phosphites or more electron-deficient phosphine ligands, the catalyst showed no activity (entries 6−8). When the electron-rich cyclohexylphosphine ligand was employed, the reaction resulted in a lower yield and selectivity (entry 9). With the exception of dppf (entries 10 and 11), most other bidentate ligands appeared to be ineffective (entries 12−16). Ligand dppf actually delivered the highest regioselectivity. Yields of the desired product **3aa**, however, are moderate under these conditions. Without any ligand, the reaction did not

Table 1. Effect of Ligands[a]



entry	ligand	yield (%),[f] ratio[h]
1	PPh_3	65% (**3aa:4aa:5aa** = 9:1:2) 62%[g]
2[e]	PPh_3	54% (**3aa:4aa:5aa** = 11:1:2.6)
3[b]	PPh_3	62% (**3aa:4aa:5aa** = 10:1:1.5) 57%[g]
4	$(p\text{-}CF_3C_6H_4)_3P$	53% (**3aa:4aa:5aa** = 7:1:2)
5	$(3,5\text{-}CF_3C_6H_4)_3P$	50% (**3aa:4aa:5aa** = 6:1:1)
6	$(CF_3CH_2O)_3P$	0%
7	$(hfip)_3P$	0%
8	$(C_6F_5)_3P$	0%
9	Cy_3P	40% (**3aa:4aa** = 5:1)
10	dppf	52% (**3aa:4aa** = 20:1)
11[e]	dppf	32% (**3aa:4aa** = 20:1)
12	dppm	trace
13	dppe	trace
14	dppp	trace
15	dppb	trace
16	BINAP	33% (**3aa:4aa** = 8.5:1)
17[c]	–	0%
18[d,e]	–	65% (**3aa:4aa:5aa** = 9:1:3)
19[d]	–	55% (**3aa:4aa:5aa** = 4:1:2)

[a] General conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[Rh(COD)Cl]_2$ (5 mol %) and ligand (20 mol %), DCM (1 mL), 40 °C overnight. [b] 30 mol % $[Rh(COD)Cl]_2$ was used. [c] No ligand. [d] Wilkinson catalyst was used. [e] Room temperature. [f] NMR yield. [g] Isolated yield of **3aa** and **4aa**. [h] Determined by ^1H NMR analysis. hfip = hexafluoroisopropanol.

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proceed at all (entry 17). The Wilkinson catalyst yielded results similar to those using the $[Rh(COD)Cl]_2/Ph_3P$ combination (entries 18 and 19).

Other reaction parameters were explored using the combination of Ph_3P and $[Rh(COD)Cl]_2$ (Table 2). Since the homodimerization product **5aa** is much more polar than heterodimers **3aa** and **4aa**, it can be easily removed by column chromatography. Only the ratio of **3aa** and **4aa** was examined. A higher temperature could accelerate the reaction, and a slightly higher yield with lower selectivity was observed (entry 1 vs 2). Increasing the ratio of **1a**/**2a** from 1:2 to 2:3 was beneficial for the yield (entry 4 vs 5). When the reaction was performed in THF, the highest regioselectivity was observed. The yield, however, dropped to 55% (entry 7). While the halogenated solvents behave similarly, DCM was the best in terms of yield and selectivity (entries 8 and 9). Poor yields were obtained with lower catalyst loadings (entries 10, 11). The optimal metal/ligand ratio appeared to be 1:2 (entry 13).

Table 2. Optimization of Reaction Conditions[a]

entry	**1a:2a**	*x* mol % $[Rh(COD)Cl]_2$/ *y* mol % PPh_3	solvent/*T* (°C)	yield[b] (**3aa:4aa**)[c]
1	1:2	5/20 mol %	DCM/RT	54% (11:1)
2	1:2	5/20 mol %	DCM/40	62% (9:1)
3	1:2	5/30 mol %	DCM/40	62% (10:1)
4	1:2	5/30 mol %	DCM/RT	57% (10:1)
5	2:3	5/30 mol %	DCM/RT	65% (10:1)
6	2:3	5/30 mol %	DCM/40	70% (10:1)
7	2:3	5/30 mol %	THF/40	55% (15:1)
8	2:3	5/30 mol %	DCE/40	62% (10:1)
9	2:3	5/30 mol %	$CHCl_3$/40	65% (5:1)
10	2:3	1/6 mol %	DCM/40	30% (–)
11	2:3	2/12 mol %	DCM/40	39% (10:1)
12	2:3	5/10 mol %	DCM/40	25% (–)
13	**2:3**	**5/20 mol %**	**DCM/40**	**73% (10:1)**
14	2:3	5/60 mol %	DCM/40	61% (5:1)

[a] Reaction conditions are enssentially the same as those for Table 1, and changes are made according to each entry. [b] Isolated yield. [c] Determined by ^1H NMR of a partially purified mixture of **3aa** and **4aa** after a short column.

With the optimized conditions in hand, the scope of terminal alkynes was then explored (Figure 1). Various substituents on the phenyl ring of the donor alkyne could be accommodated. Arylacetylenes with para, meta, and ortho substituents gave comparable results. Aldehyde, bromide, amide, and even free amino groups could be tolerated. The 4-nitro group impaired the ratio of regioisomers **3ca/4ca** to 4:1 in favor of the head-to-tail dimer **3ca**. Interestingly, 3-indole acetylene furnished enyne **3ja** in 42% yield without the observation of the head-to-head dimer. The free hydroxyl group is not required, as substrate **2c** also participates in the cross-dimerization. In contrast, the steric effect on the regioselectivity is pronounced, as only head-to-head cross-dimerization product **4ab** was detected by NMR, while secondary propargylic alcohols gave a mixture of homo- and heterodimers with low selectivity.

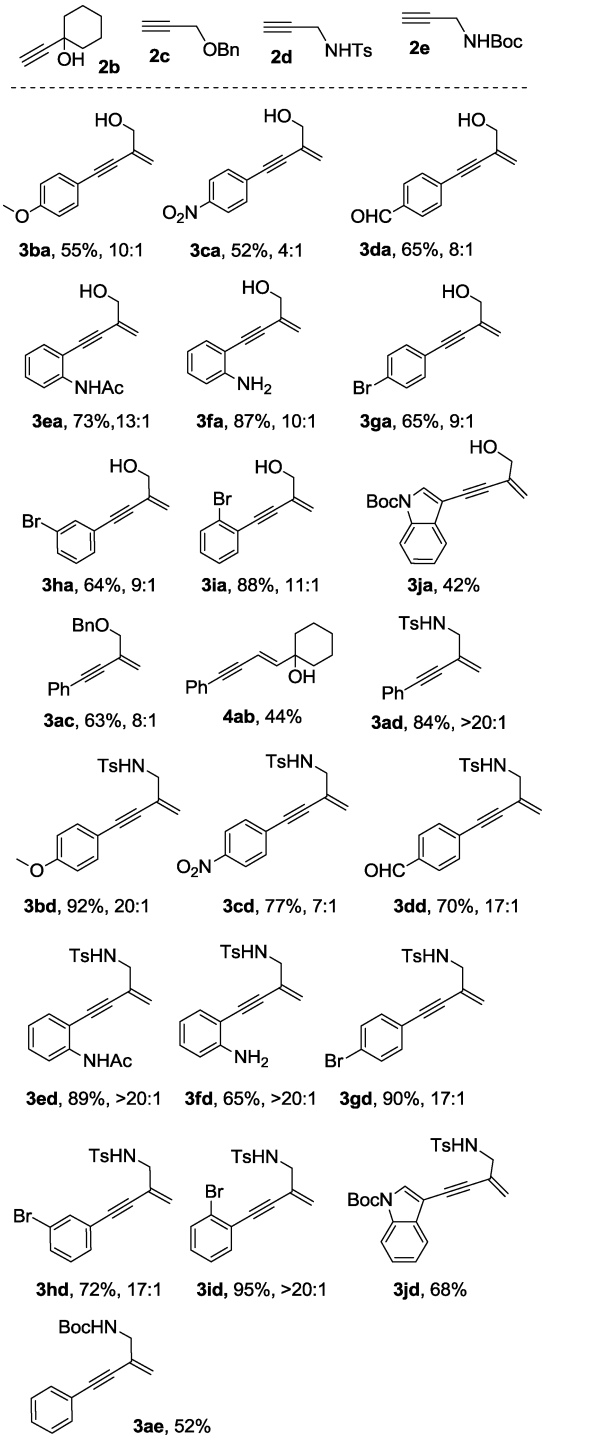

Figure 1. Rhodium-catalyzed cross-dimerization of arylacetylenes and propargylic alcohols, ethers, or amides. Reaction conditions: arylacetylene **1** (0.5 mmol), propargylic alcohol/ether/amide **2** (0.75 mmol), $[Rh(COD)Cl]_2$ (5 mol %), Ph_3P (20 mol %), DCM (1 mL), 40 °C, overnight. The ratio of two hetereodimers was determined by ^1H NMR of the purified mixtures of isomers after column chromatography, and the yields were the isolated yield of two isomers.

It should be noted that a complex mixture was observed when propargylic alcohol **2a** was reacted with terminal alkyl

substituted acetylenes such as 1-heptyne. Similarly, when phenylacetylene **1a** was reacted with homopropargylic alcohols, no significant selectivity was observed, implying that the chelating effect might not play an important role in this reaction and the inductive effect may operate (see Scheme SI 2 for details). Yet, we were pleased to find that propargylic sulfonamide **2d** afforded head-to-tail heterodimers **3ad**−**3jd** with generally higher yields and higher selectivity than their corresponding propargylic alcohols. A moderate yield of product **3ae** was obtained from propargylic carbamate **2e**.

The mechanism of this chemoselective cross-dimerization of terminal alkynes involves oxidative addition of rhodium to the arylacetylene C−H bond followed by hydroalkynylation of propargylic alcohols, ethers, or amides.[10] Further study is required to elucidate the details of this reaction, especially the chemo- and regioselectivities.

(10) For oxidative addition of various transition metals including Rh(I) to the acetylene C−H bonds and followed by hydroalkynylation, please see: (a) Villarino, L.; García-Fandiño, R.; López, F.; Mascareñas, J. L. *Org. Lett.* **2012**, *14*, 2996. (b) Sawano, T.; Ashouri, A.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 18936 and references cited therein.

In summary we have discovered a facile method for the cross-dimerization of arylacetylenes and propargylic alcohols, ethers, or amides via the atom economical direct hydroalkynylation reaction promoted by a rhodium catalyst. We found that the chemo- and regioselectivities were dependent on the steric and electronic nature of both terminal alkynes.

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Supporting Information Available. Experimental procedures along with characterizing data and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.