Palladium-Catalyzed Decarboxylative Homodimerization of Propiolic Acids: Synthesis of 1,3-Enynes

Eunkyeong Seo, Jonghoon Oh,* and Sunwoo Lee*

Department of Chemistry, Chonnam National University, Gwangju 61186, Republic of Korea.
**E-mail: jnoh@chonnam.ac.kr; sunwoo@chonnam.ac.kr*
Received December 19, 2020, Accepted January 3, 2021, Published online January 20, 2021

The 1,3-enyne product was obtained as a result of a decarboxylative homodimerization reaction when a variety aryl propiolic acids were reacted in the presence of Pd(TFA)2/i-PrPPh2 and K_2CO_3. It was found that aryl propiolic acids bearing an electrondonating substituent provided the desired product; however, aryl propiolic acids an bearing electron-withdrawing substituent did not give the desired product.

Keywords: Homocoupling, Dimerization, Decarboxylation, Propiolic acid, Palladium

Conjugated 1,3-enynes are one of the most important building blocks in organic synthesis used for preparing biologically active molecules and conjugated functional materials.[1] Given their prominence, a variety of synthetic methods have been developed toward the synthesis of conjugated 1,3-enynes. For example, the cross-coupling reaction of terminal alkynes with vinyl halides or pseudohalides,[2] dehydration of propargyl alcohols,[3] and Wittig reaction of conjugated alkynals[4] are well established and widely used. However, they have some drawbacks, such as a high catalyst loading, harsh reaction conditions, and the requirement of a multistep process for the preparation of their corresponding starting materials.

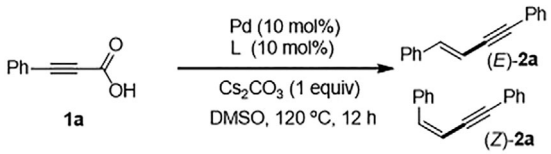
To address these issues, the transition metal-catalyzed dimerization of two terminal alkynes has received considerable attention in the organic chemistry community.[5] Not only second-row transition metals[6] but also first-row transition metals[7] have been employed in the dimerization of two terminal alkynes. These dimerization methods are straightforward and atom-economic. In addition, numerous studies have reported employing a terminal alkyne and alkene toward the formation of 1,3-enynes. However, aryl-substituted terminal alkynes are mostly prepared using a multistep reaction between an aryl halide and a protected terminal alkyne. However, this has resulted in the limited substrate scope of the reaction.

Compared to aryl-substituted terminal alkynes, aryl propiolic acid derivatives are readily prepared via a one-step coupling reaction between an aryl halide and propiolic acid without the need for column chromatography as a purification step.[8] A variety of decarboxylative coupling reactions using not only aryl propiolic acid derivatives[9] but also cinnamic acid derivatives[10] have been reported by our group and other researchers.

Recently, we reported the decarboxylative addition of propiolic acid to a terminal alkyne to synthesize *gem*-1,3-enynes. In 2019, we reported that a Ni/Cu dual catalytic system can be used to provide the desired *gem*-1,3-enyne product in a moderate to good yield. One year later, we also found that using PdI_2 as the catalyst showed a good selectivity and activity toward the formation of *gem*-1,3-enynes.[11]

While studying the Pd-catalyzed decarboxylative addition reaction of propiolic acids, we found that the decarboxylative homodimerized product, which is a 1,3-enyne, was formed

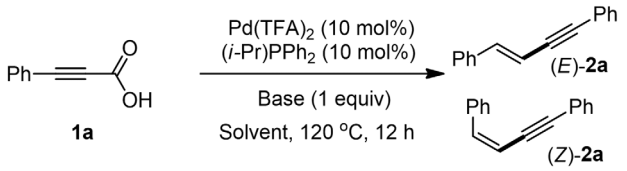
Table 1. Optimization of the palladium catalyst and ligand used in the homodimerization of phenylpropiolic acid.[a]



Entry	Pd	L	Yield (%)[b]
1	$Pd(OAc)_2$	PCy_3	Trace
2	$Pd(acac)_2$	PCy_3	Trace
3	PdI_2	PCy_3	Trace
4	$PdCl_2$	PCy_3	Trace
5	$Pd(MeCN)_2Cl_2$	PCy_3	Trace
6	$Pd(TFA)_2$	PCy_3	30 (*E*/*Z* = 10:1)
7	$Pd(TFA)_2$	dppe	Trace
8	$Pd(TFA)_2$	dppb	Trace
9	$Pd(TFA)_2$	PPh_3	12 (*E*/*Z* = 2:1)
10	$Pd(TFA)_2$	$EtPPh_2$	30 (*E*/*Z* = 8:1)
11	$Pd(TFA)_2$	$CyPPh_2$	36 (*E*/*Z* = 9:1)
12	$Pd(TFA)_2$	Cy_2PPh	39 (*E*/*Z* = 10:1)
13	$Pd(TFA)_2$	*i*-$PrPPh_2$	46 (*E*/*Z* = 12:1)

[a] Reaction conditions: **1a** (0.3 mmol), Pd (0.03 mmol), ligand (0.03 mmol), Cs_2CO_3 (0.3 mmol), DMSO (1.2 mL), 120°C, 12 h.
[b] Yields and stereoselectivity were determined by ^1H NMR.

Table 2. Optimization of the base and solvent used in the homodimerization of phenylpropiolic acid.[a]



Entry	Base	Solvent	Yield (%)[b]
1	K_2CO_3	DMSO	62 (*E*/*Z* = 20:1)
2	Na_2CO_3	DMSO	57 (*E*/*Z* = 12:1)
3	K_3PO_4	DMSO	55 (*E*/*Z* = 12:1)
4	DBU	DMSO	42 (*E*/*Z* = 9:1)
5	Et_3N	DMSO	Trace
6	Pyridine	DMSO	Trace
7	TMEDA	DMSO	Trace
8	DBN	DMSO	Trace
9	K_2CO_3	Diglyme	32 (*E*/*Z* = 5:1)
10	K_2CO_3	DMF	49 (*E*/*Z* = 14:1)
11	K_2CO_3	*o*-Xylene	Trace

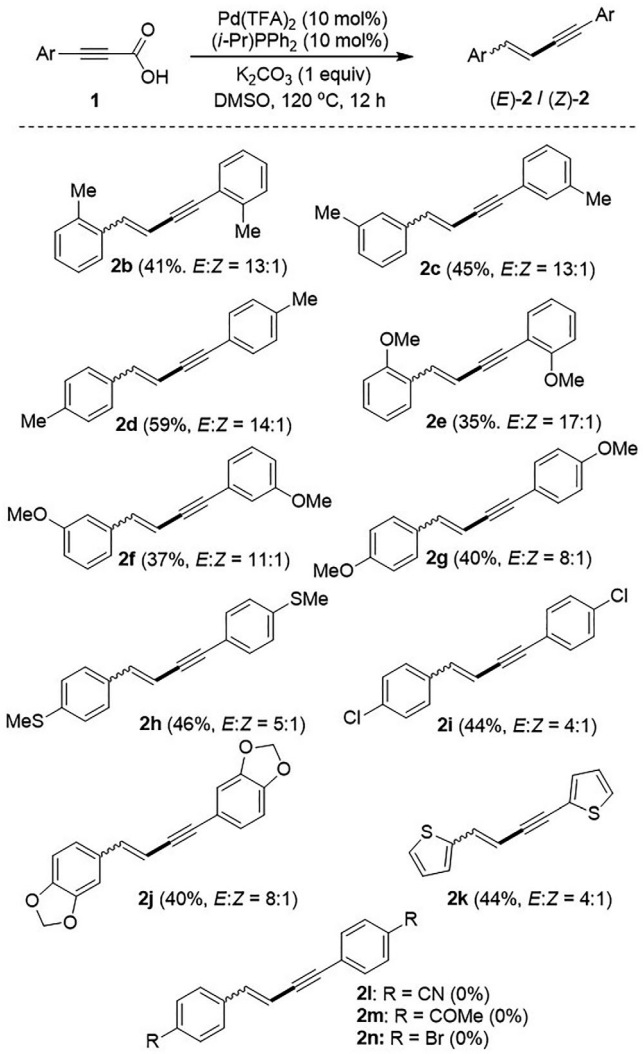
[a] Reaction condition: **1a** (0.3 mmol), $Pd(TFA)_2$ (0.03 mmol), *i*-$PrPPh_2$ (0.03 mmol), base (0.3 mmol), solvent (1.2 mL), 120°C, 12 h.
[b] Yields and stereoselectivity were determined by ^{1}H NMR.

when the aryl propiolic acid was reacted without any terminal alkyne partner in the presence of a Pd catalyst and weak base. This result motivated us to develop the selective decarboxylative homodimerization of propiolic acids using a Pd catalyst. Herein, we report the (*E*)-selective synthesis of 1,3-enynes from aryl propiolic acids.

Phenylpropiolic acid was chosen as a model substrate. Initially, the palladium source was evaluated in the presence of Cs_2CO_3 as the base and dimethyl sulfoxide (DMSO) as the solvent (Table 1).

A variety of palladium(II) complexes were investigated in the reaction; however, only $Pd(TFA)_2$ afforded the desired homodimerized enyne product with a 30% yield. The ratio of (*E*)- and (*Z*)-**2a** was 10:1. A variety of chelating phosphine ligands, such as dppe and dppb, were then investigated in the reaction using $Pd(TFA)_2$ as the palladium source. However, no product was formed. Several monophosphine ligands were studied. PPh_3 gave the desired product in 12% yield with a low stereoselectivity. The reactions using $EtPPh_2$, $CyPPh_2$, and Cy_2PPh provided the desired product in 30, 36, and 39% yield, respectively. The reaction using *i*-$PrPPh_2$ exhibited the highest yield and the best stereoselectivity.

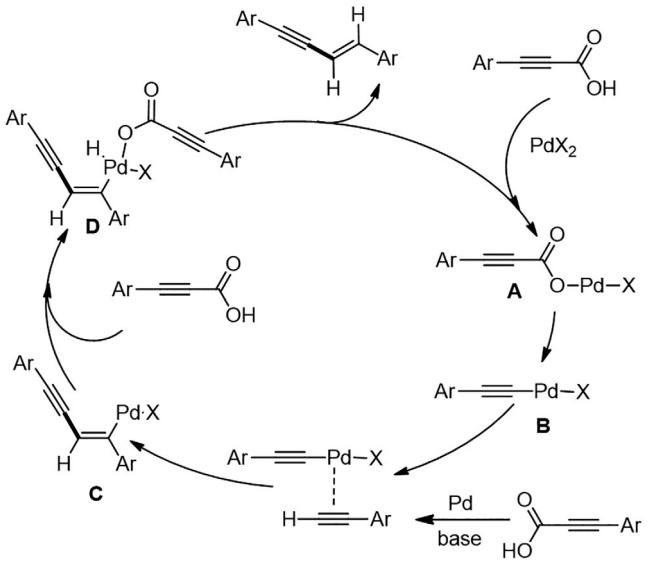
Subsequently, we investigated a variety of bases and solvents in the presence of $Pd(TFA)_2$/i-$PrPPh_2$ (Table 2). When the standard reaction was carried out using K_2CO_3,



Scheme 1. Decarboxylative homodimerization of aryl propiolic acids (reaction condition: **1** (1.0 mmol), $Pd(TFA)_2$ (0.1 mmol), *i*-$PrPPh_2$ (0.1 mmol), K_2CO_3 (1.0 mmol), DMSO (1.2 mL), 120°C, 12 h. Stereoselectivity was determined by ^{1}H NMR).

the product was formed with a 62% yield and exhibited the highest stereoselectivity. The reactions using Na_2CO_3 and K_3PO_4 did not exhibit any improvement with respect to the yield and stereoselectivity compared to that using K_2CO_3 (entries 1–3). When DBU was employed, the yield of product was not satisfactory (entry 4). The desired product was not observed when organic bases were employed in the reaction (entries 5–8). The reactions carried out in other solvents such as diglyme, DMF, and *o*-xylene showed inferior yields compared to that of DMSO (entries 9–11). Based on these results, the optimized reaction conditions were: an environment with arylpropiolic acid (1.0 equiv), $Pd(TFA)_2$ (10 mol %), *i*-$PrPPh_2$ (10 mol %), K_2CO_3 (1.0 equiv), DMSO at 120°C for 12 h.

With the optimized reaction condition known, a variety of substituted aryl propiolic acids were evaluated in the decarboxylative homodimerization reaction. When *ortho*-,



Scheme 2. Proposed reaction mechanism.

meta-, and *para*-tolyl propiolic acids were used in the reaction, products **2b**, **2c**, and **2d** were formed in 41, 45, and 59% yield, respectively. The *E*/*Z* stereoselectivity ranged between 13:1 and 14:1. The reactions using *ortho*-, *meta*-, and *para*-anisole substituted propiolic acids gave their corresponding enyne products (**2e**, **2f**, and **2g**) in 59, 35, and 37% yield, respectively. 4-Methylthio- and 4-chlorophenyl propiolic acids gave their desired products (**2h** and **2i**) in moderate yields. Benzo[d][1,3]dioxol-5-ylpropiolic acid and 2-thiophenylpropiolic acid provided **2j** and **2 k** in 40 and 44% yield, respectively. However, electron-withdrawing substituents such as cyano, acetyl, and bromo groups did not give their corresponding enyne products. Unfortunately, when octynoic acid was employed, no homodimerized product was formed (Scheme 1).

Based on previous reports, the reaction mechanism has been proposed in Scheme 2. Arylpropiolic acid reacts with $Pd(TFA)_2$ to give palladium complex **A**, followed by decarboxylation to give alkynyl palladium complex **B**. It is known that arylpropiolic acid affords the terminal alkyne in the presence of a base and palladium. Consequently, palladium complex **B** coordinates and adds to the terminal alkyne to give complex **C**. Arylpropiolic acid reacts with complex **C** to give complex **D**, followed by reductive elimination to give the final product and palladium complex **A**.

In summary, we have developed a decarboxylative homodimerization reaction of arylpropiolic acids used for the synthesis of 1,3-enynes. It was found that the use of $Pd(TFA)_2$ and *i*-$PrPPh_3$ as the palladium source and ligand, respectively, showed the best results in the presence of K_2CO_3. Arylpropiolic acids bearing electron-donating groups such as methyl, methoxy, and methylthio afforded the desired homodimerized products in moderate to good yield. In all cases, the (*E*)-isomer was the major product of the reaction. However, arylpropiolic acids bearing electron-withdrawing groups did not give the desired product.

Acknowledgments. This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (NRF-2017R1A2B2002929). The spectral data were obtained from the Gwangju center of Korea Basic Science Institute.

References

1. (a) H. Kim, H. Lee, D. Lee, S. Kim, D. Kim, *J. Am. Chem. Soc.* **2007**, *129*, 2269. (b) P. Wessig, G. Mgller, *Chem. Rev.* **2008**, *108*, 2051. (c) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 3664.
2. (a) S. Ikeda, Y. Sato, *J. Am. Chem. Soc.* **1994**, *116*, 5975. (b) E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979. (c) C. G. Bates, P. Saejueng, D. Venkataraman, *Org. Lett.* **2004**, *6*, 1441. (d) B. C. Ranu, L. Adak, K. Chattopadhyay, *J. Org. Chem.* **2008**, *73*, 5609. (e) S. Ahammed, D. Kundu, B. C. Ranu, *J. Org. Chem.* **2014**, *79*, 7391.
3. W. Yan, X. Ye, N. G. Akhmedov, J. L. Petersen, X. Shi, *Org. Lett.* **2012**, *14*, 2358.
4. H.-J. Deussen, L. Jeppesen, N. Sch-rer, F. Junager, B. Bentzen, B. Weber, V. Weil, S. J. Mozer, P. Sauerberg, *Org. Process. Res. Dev.* **2004**, *8*, 363.
5. (a) Y. Zhou, Y. Zhang, J. Wang, *Org. Biomol. Chem.* **2016**, *14*, 6638. (b) B. M. Trost, J. T. Masters, *Chem. Soc. Rev.* **2016**, *45*, 2212.
6. (a) B. M. Trost, C. Chan, G. Ruhter, *J. Am. Chem. Soc.* **1987**, *109*, 3486. (b) B. M. Trost, *Science* **1991**, *254*, 1471. (c) B. M. Trost, B. R. Taft, J. T. Masters, J.-P. Lumb, *J. Am. Chem. Soc.* **2011**, *133*, 8502. (d) B. M. Trost, J.-P. Lumb, J. M. Azzarelli, *J. Am. Chem. Soc.* **2011**, *133*, 740. (e) B. M. Trost, G. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 16403.
7. (a) S. Ogoshi, M. Ueta, M. Oka, H. Kurosawa, *Chem. Commun.* **2004**, *40*, 2732. (b) D. Xu, Q. Sun, Z. Quan, X. Wang, W. Sun, *Asian J. Org. Chem.* **2018**, *7*, 155. (c) Q. Liang, K. Sheng, A. Salmon, V. Y. Zhou, D. Song, *ACS Catal.* **2019**, *9*, 810.
8. K. Park, J.-M. You, S. Jeon, S. Lee, *Eur. J. Org. Chem.* **2013**, *2013*, 1973.
9. (a) J. Moon, M. Jeong, H. Nam, J. Ju, J. H. Moon, H. M. Jung, S. Lee, *Org. Lett.* **2008**, *10*, 954. (b) J. Moon, M. Jang, S. Lee, *J. Org. Chem.* **2009**, *74*, 1403. (c) K. Park, G. Bae, J. Moon, J. Choe, K. H. Song, S. Lee, *J. Org. Chem.* **2010**, *75*, 6244. (d) K. Park, S. Lee, *RSC Adv.* **2013**, *3*, 14165. (e) M. A. Idris, S. Lee, *Synthesis* **2020**, *52*, 2277.
10. (a) K. Park, S. Lee, *Org. Lett.* **2015**, *17*, 1300. (b) M. Jang, K. Park, J. Lim, J. Oh, S. Lee, *Bull. Kor. Chem. Soc.* **2019**, *40*, 487.
11. (a) S. Han, H.-S. Kim, M. Zhang, Y. Xia, S. Lee, *Org. Lett.* **2019**, *21*, 5426. (b) H. Jeon, S.-B. Ko, S. Lee, *Org. Chem. Front.* **2020**, *7*, 3918.

