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Rhodium-Catalyzed Enantioselective Decarboxylative Alkynylation of Allenes with Arylpropiolic Acids

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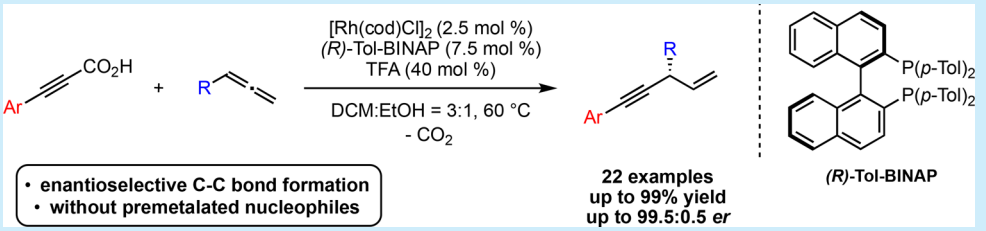
Supporting Information



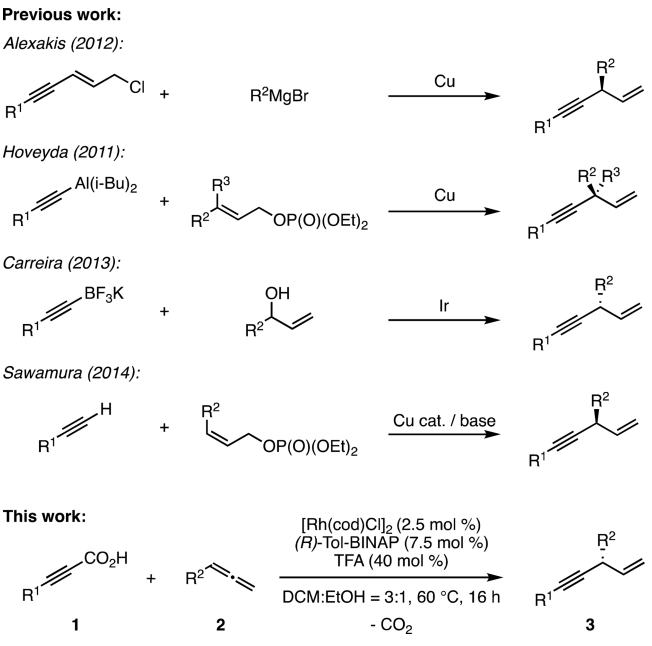
ABSTRACT: A rhodium-catalyzed chemo-, regio-, and enantioselective intermolecular decarboxylative alkynylation of terminal allenes with arylpropiolic acids is reported. Employing a Rh(I)/(*R*)-Tol-BINAP catalytic system, branched allylic 1,4-enynes were obtained under mild conditions. The overall utility of this protocol is exemplified by a broad functional group compatibility.

Properly addressing the prerequisites for the ideal organic synthesis[1] in which a selective extension of the carbon skeleton is preferably accompanied by a direct installation of desired functional groups within the molecule allowing for further functionalization still remains of tremendous interest for the development of useful synthetic methodologies.[2] Aside from significant advances during the past years, strategies allowing enantioselective couplings of terminal alkynes to carbon electrophiles still remains scarce, even though such methods would grant access to new possibilities for synthetically approaching more complex molecules like pharmaceuticals or natural products.[3] While methods for enantioselective additions of alkyne-based nucleophiles to aldehydes,[4] ketones,[4] and imines[5] have been studied extensively, catalytic methods involving additions to unactivated carbon−carbon multiple bonds are far less represented.[6]

Chiral 1,4-enynes are valuable and versatile intermediates for organic synthesis, mostly due to the fact that they bear two different handles in direct vicinity to the stereogenic center that allow for selective further functionalization.[7] Transition-metal-catalyzed synthesis thereof has predominantly been achieved by strategies involving asymmetric allylic alkylation (Scheme 1).[8] In 2012, Alexakis developed a protocol for selective displacement of enyne-chlorides with Grignard reagents.[8a] Hoveyda[8b,c] and Carreira[8c] independently reported the addition of alkynylaluminum and alkynylboron reagents to allylic electrophiles employing copper- and iridum-based cataylsts. In 2014, Sawamura[8d,e] reported the direct addition of terminal alkynes to (Z)-allylic phosphates catalyzed by a Cu−NHC complex.

However, all of these methods require rather basic reaction conditions, premetalated alkyne nucleophiles, or multistep substrate syntheses which diminishes their attractiveness and utility regarding applications for the syntheses of more complex scaffolds.

Scheme 1. Strategies for Transition-Metal-Catalyzed Asymmetric Syntheses of 1,4-Enynes



Throughout the last years, we reported on a series of transition-metal-catalyzed regio- and enantioselective coupling reactions involving allenes[9,10] and alkynes[11,12] as allylic electrophile precursors with various pronucleophiles, thus establishing a more atom-economic alternative to the classic Tsuji−Trost allylation.

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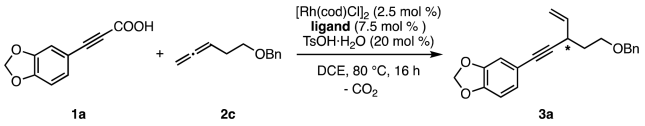
Despite extensive investigations, a strategy involving the direct addition of terminal alkynes to allenes could not be developed yet, presumably due to their inherent high reactivity regarding oxidative addition with transition metal catalysts. In this respect, we envisioned that arylpropiolic acids[13,14] could serve as terminal alkyne surrogates in a similar manner to our previously developed strategy on the decarboxylative allylation of β-ketoacids as masked ketone pronucleophiles.[10a] We assumed that introducing a carboxylic acid group may facilitate the reaction through a faster formation of the desired allylrhodium intermediate (vide infra) and eventually releases the desired C/C-coupling product after decarboxylation (Scheme 1).

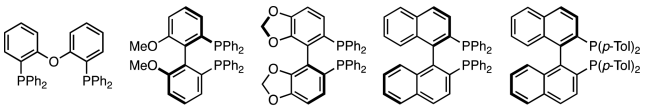
To test our hypothesis, we commenced our investigations employing 3-(benzo[*d*][1,3]dioxol-5-yl)propiolic acid (**1a**) and ((penta-3,4-dien-1-yloxy)methyl)benzene (**2c**) as model substrates (Table 1).

Table 1. Ligand Screening and Optimization of Reaction Conditions[a]



entry	ligand	yield (%)	er
1	DPEphos	29	
2	*rac*-BINAP	44	
3	(*R*)-MeO-Biphep	19	64:36
4	(*S*)-Segphos	88	89:11 (−)
5	(*S*)-BINAP	43	60:40 (−)
6	(*R*)-Tol-BINAP	54	94.5:5.5
7[b]	(*R*)-Tol-BINAP	51	97:3
8[c]	(*R*)-Tol-BINAP	70	96:4
9[d]	(*R*)-Tol-BINAP	99	95:5

[a]**1a** (0.2 mmol), **2c** (0.6 mmol), $[Rh(cod)Cl]_2$ (2.5 mol %), ligand (7.5 mol %), acid cocatalyst (20 mol %), DCE (1.0 mL), 80 °C, 16 h. All yields given as isolated yields. [b]20 mol % TFA used instead of $TsOH·H_2O$. [c]Reaction performed in DCM at 60 °C. [d]Reaction performed in DCM/EtOH = 3:1 at 60 °C with 40 mol % TFA.

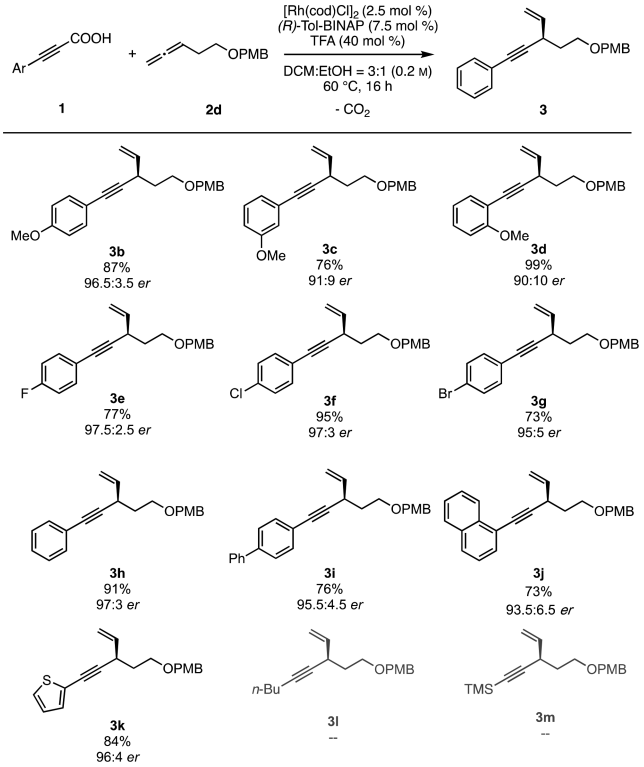


In the presence of 2.5 mol % of $[Rh(cod)Cl]_2$ and 7.5 mol % of DPEphos as phosphine ligand combined with 20 mol % of $TsOH·H_2O$ as acid cocatalyst in 1,2-dichloroethane we were able to isolate the desired 1,4-enyne coupling product in 29% yield (entry 1). By changing the ligand to *rac*-BINAP the yield could be further increased to 44% (entry 2), which—due to the possibility of easily introducing axial chirality—lay the basis for the development of an asymmetric version thereof.

In this respect, we examined a variety of bidentate phosphine ligands (entries 3−5) and were delighted to find that (*R*)-Tol-BINAP provided the most promising result with an er of 94.5:5.5 aside from a moderate yield of 54% (entry 6). Striving for further improvements, we examined different Brønsted acid cocatalysts (entries 7 and 8) and solvents[15] and were able to obtain the desired product **3a** in 70% yield when performing the reaction in DCM at 60 °C with even a slight increase in enantioselectivity. Ultimately, only by increasing the amount of TFA to 40 mol % as well as performing the reaction in DCM/EtOH = 3:1 at 60 °C we could obtain **3a** in almost quantitative yield while maintaining an excellent enantioselectivity (entry 9).

With this optimized protocol in hand, we investigated the substrate scope of this decarboxylative alkynylation of allene **2d** with various arylpropiolic acids (Table 2). Efficient as well as chemo- and enantioselective coupling reactions occur with a variety of different substitution patterns.

Table 2. Decarboxylative Alkynylation with Various Arylpropiolic Acids[a]



[a]**1** (0.2 mmol), **2d** (0.6 mmol), $[Rh(cod)Cl]_2$ (2.5 mol %), (*R*)-Tol-BINAP (7.5 mol %), TFA (40 mol %), DCM/EtOH = 3:1 (1.0 mL), 60 °C, 16 h. All yields given as isolated yields. Enantioselectivities determined by HPLC on chiral stationary phases. Absolute configuration assigned by analogy.[16]

In this respect, phenylpropiolic acids bearing electron-donating methoxy substituents at different positions reacted smoothly to give rise to the corresponding 1,4-enynes in good to excellent yields (**3b−d**) as well as enantioselectivities with a substituent in the 4-position showing the highest er with 96.5:3.5. Notably, even a sterically more congested substrate with a 2-OMe substituent reacted well even though **3d** was formed in a slightly lower enantiomeric ratio of 90:10. Substrates with electron-withdrawing substituents (e.g., F, Cl, Br) showed slightly lower reactivity (73−95% isolated yields), although **3e−g** were formed in excellent enantioselectivities. With more electron-deficient arylpropiolic acids (e.g., 4-CF_3) no reactivity is observed at all. Moreover, commercially available phenylpropiolic acid without any further functionalizations (**3h**) as well as related biphenyl (**3i**) and 1-naphthyl (**3j**) substrates reacted smoothly and provided the desired products in good to excellent yields and enantioselectivities. To our delight, even heteroaryl residues (exemplified by thiophenylpropiolic acid) could participate in the reaction (**3k**). However, when trying to expand this protocol to alkyl (**3l**) or silyl (**3m**) residues only the

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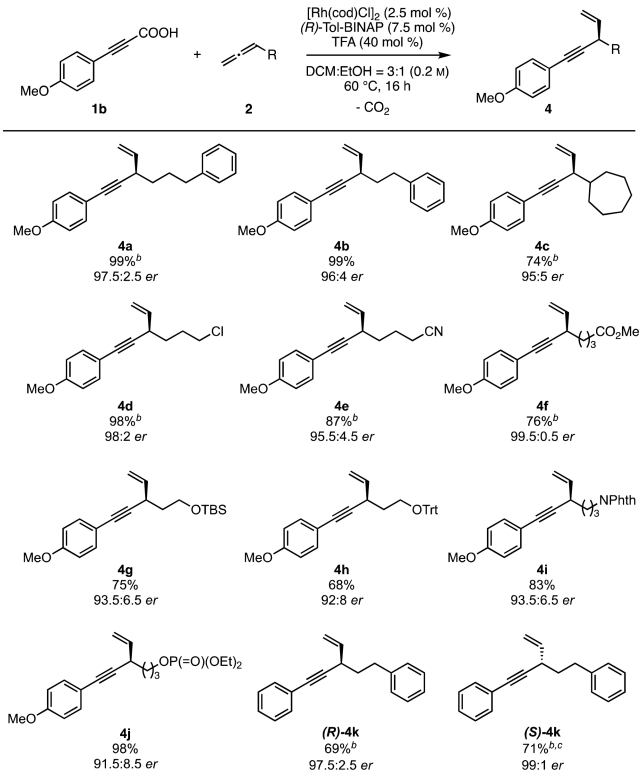
corresponding allylic esters could be isolated. This result indicates that the presence of an aryl residue in direct vicinity to the alkyne is mandatory to promote decarboxylation.

Additionally, various allenes were examined for their potential to participate in this addition of 4-(methoxyphenyl)propiolic acid (**1b**, Table 3).

Table 3. Decarboxylative Alkynylation with a Variety of Functionalized Allenes[a]

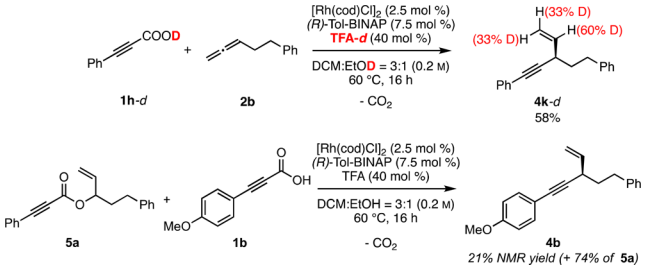


[a]**1** (0.2 mmol), **2d** (0.6 mmol), $[Rh(cod)Cl]_2$ (2.5 mol %), (*R*)-Tol-BINAP (7.5 mol %), TFA (40 mol %), DCM:EtOH = 3:1 (1.0 mL), 60 °C, 16 h. All yields given as isolated yields. Enantioselectivities determined by HPLC on chiral stationary phases. [b]Reaction performed at 80 °C. [c](*S*)-Tol-BINAP used instead.

The terminal allenic substrates utilized were easily prepared in one step from commercially available starting materials.[17] Linear aliphatic chains (**4a**,**b**) as well as branched cycloaliphatic residues (**4c**) reacted smoothly with excellent enantioselectivities. Higher functionalized allenes bearing halogenated (**4d**) residues or nitrile moieties (**4e**) also provided the coupled products in excellent yields and enantioselectivities. When a methyl ester moiety was introduced in the allene, an impressive enantiomeric ratio of 99.5:0.5 was observed for the corresponding 1,4-enyne **4f**. Moreover, different protected alcohols (**4g**,**h**) and amines (**4i**) could be introduced, even though the presence of potentially coordinating heteroatoms in the carbon chain slightly compromised enantioselectivities. Interestingly, even an acid-sensitive trialkyl phosphate (**4j**) could participate in the reaction in a comparable yield and enantioselectivity without any occurring hydrolysis. To highlight the general utility of this protocol, the synthesis of the unsubstituted enyne **4k** was performed with both (commercially available) enantiomers of the Tol-BINAP ligand, giving rise to (*R*)-**4k** and (*S*)-**4k** in comparable yields and enantiomeric ratios.

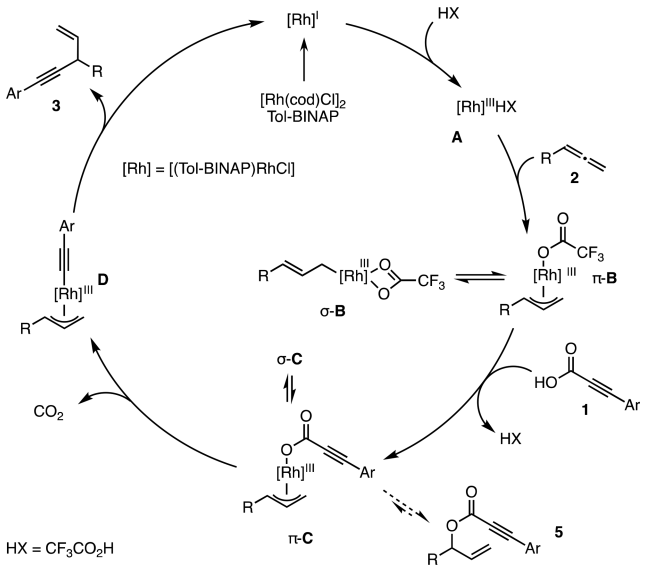
In order to further unravel the underlying mechanism of this decarboxylative reaction, deuterium-labeling studies were conducted (Scheme 2).

Scheme 2. Deuterium Labeling and Crossover Experiments



As expected for a reaction proceeding via a π-/σ-allylrhodium intermediate, deuterium incorporation was observed at all three positions of the allylic double bond indicating intermediary reversibility.[10a,12b,18] To gain deeper insight into the underlying mechanism, a crossover experiment with allylic ester **5a** was conducted, indicating that **5a** is not directly involved in the catalytic cycle but more likely a reversibly formed off-cycle side product. Moreover, it revealed that the relative rate of the decarboxylation depends on the individual electronic properties of the respective aryl substitution pattern with a higher rate for electron-rich aryl residues. Together with the outcome of further control experiments[19] as well as previous mechanistic studies, we propose the following reaction mechanism (Scheme 3).

Scheme 3. Proposed Catalytic Cycle



After initial catalyst preformation from $[Rh(cod)Cl]_2$ and (*R*)-Tol-BINAP, a rhodium(III) hydride complex **A** is generated upon reaction with TFA,[20] followed by a hydrometalation of the allene to give the allylrhodium(III) intermediate **B**. Subsequent ligand exchange with the respective arylpropiolic acid **1** gives rise to the allylrhodium complex **C** which can now undergo decarboxylation to form the alkyne complex **D**. As stated previously, this step is more likely to occur for more electron-rich aryl residues. Ultimately, **D** undergoes a reductive elimination to form the 1,4-enyne coupling product **3** while simultaneously regenerating the Rh(I) catalyst.

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In conclusion, we have accomplished a highly chemo-, regio-, and enantioselective decarboxylative alkynylation of terminal allenes with arylpropiolic acids to construct enantiomerically enriched branched 1,4-enynes under mild conditions with commercially available $[Rh(cod)Cl]_2$ and (*R*)-Tol-BINAP. This reaction releases CO_2 as the only byproduct, and neither requires strongly basic reaction conditions nor premetalated alkyne nucleophiles. Further investigations regarding an extension toward related arylpropiolic acid pronucleophiles as well as alkynes as allene surrogates are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b04035.

Experimental procedures and analytical data for the synthesized compounds, including ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784.

(2) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Ed.; Springer: Berlin, 1999. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley: New York, 2000. (c) *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley: Hoboken, 2007.

(3) (a) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995. (b) *Acetylene Chemistry: Chemistry, Biology, and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; VCH: Weinheim, 2005.

(4) For a review of enantioselective additions of alkyne pronucleophiles to carbonyl groups, see: (a) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.

(5) For selected recent examples of enantioselective additions of alkyne pronucleophiles to imines, see: (a) Orlandi, S.; Colombo, F.; Benaglia, M. *Synthesis* **2005**, 1689. (b) Liu, B.; Huang, L.; Liu, J.; Zhong, Y.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 2901. (c) Peng, F.; Shao, Z.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2010**, *21*, 465.

(6) For selected examples, see: (a) Nishimura, T.; Guo, X.-X.; Hayashi, T. *Chem. - Asian J.* **2008**, *3*, 1505. (b) Shirakura, M.; Suginome, M. *Angew. Chem.* **2010**, *122*, 3915; *Angew. Chem., Int. Ed.* **2010**, *49*, 3827. (c) Fan, B.; Yang, Q.; Hu, J.; Fan, C.; Li, S.; Yu, L.; Huang, C.; Tsang, W.; Kwong, F. *Angew. Chem.* **2012**, *124*, 7941; *Angew. Chem., Int. Ed.* **2012**, *51*, 7821. For sequential hydroalkynylation/asymmetric 1,4-reduction, see: (d) Trost, B. M.; Taft, B. R.; Masters, J. T.; Lumb, J.-P. *J. Am. Chem. Soc.* **2011**, *133*, 8502.

(7) For selected examples on transformations of 1,4-enynes, see: (a) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339. (b) Heffron, T. P.; Trenkle, J. D.; Jamison, T. F. *Tetrahedron* **2003**, *59*, 8913. (c) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (d) Bhanu Prasad, B. A.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468. (e) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614. (f) Vasu, D.; Das, A.; Liu, R.-S. *Chem. Commun.* **2010**, *46*, 4115. (g) Sato, T.; Onuma, T.; Nakamura, I.; Terada, M. *Org. Lett.* **2011**, *13*, 4992. For occurrences as intermediates in total synthesis, see: (h) Jacobson, M.; Redfern, R. E.; Jones, W. A.; Aldridge, M. H. *Science* **1970**, *170*, 542. (i) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745. (j) Iida, K.; Hirama, M. *J. Am. Chem. Soc.* **1994**, *116*, 10310. (k) Hickmann, V.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11042.

(8) For transition-metal-catalyzed enantioselective syntheses of 1,4-enynes, see: (a) Li, H.; Alexakis, A. *Angew. Chem.* **2012**, *124*, 1079; *Angew. Chem., Int. Ed.* **2012**, *51*, 1055. (b) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778. (c) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem.* **2013**, *125*, 7680; *Angew. Chem., Int. Ed.* **2013**, *52*, 7532. (d) Makida, Y.; Takayama, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem.* **2013**, *125*, 5458; *Angew. Chem., Int. Ed.* **2013**, *52*, 5350. (e) Harada, A.; Makida, Y.; Sato, T.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 13932.

(9) For a recent review, see: Koschker, P.; Breit, B. *Acc. Chem. Res.* **2016**, *49*, 1524.

(10) For examples of C−C bond formation, see: (a) Li, C.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 862. (b) Beck, T. M.; Breit, B. *Angew. Chem.* **2017**, *129*, 1929; *Angew. Chem., Int. Ed.* **2017**, *56*, 1903.

(11) For a recent review, see: Haydl, A.; Breit, B.; Liang, T.; Krische, M. J. *Angew. Chem.* **2017**, *129*, 11466; *Angew. Chem., Int. Ed.* **2017**, *56*, 11312.

(12) For examples of C−C bond formation, see: (a) Beck, T. M.; Breit, B. *Org. Lett.* **2016**, *18*, 124. (b) Cruz, F. A.; Chen, Z.; Kurtoic, S. I.; Dong, V. M. *Chem. Commun.* **2016**, *52*, 5836. (c) Li, C.; Grugel, C. P.; Breit, B. *Chem. Commun.* **2016**, *52*, 5840. (d) Beck, T. M.; Breit, B. *Eur. J. Org. Chem.* **2016**, *2016*, 5839. (e) Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 1029. (f) Cruz, F. A.; Zhu, Y.; Tercenio, Q. D.; Shen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 10641.

(13) For a review on decarboxylative coupling reactions of propiolic acids, see: Park, K.; Lee, S. *RSC Adv.* **2013**, *3*, 14165.

(14) For selected recent examples on decarboxylative reactions involving propiolic acids, see: (a) Li, X.; Yang, F.; Wu, Y.; Wu, Y. *Org. Lett.* **2014**, *16*, 992−995. (b) Sun, F.; Gu, Z. *Org. Lett.* **2015**, *17*, 2222. (c) Sun, F.; Gu, Z. *Org. Lett.* **2015**, *17*, 2222. (d) Lim, J.; Choi, J.; Kim, H.-S.; Kim, I. S.; Nam, K. C.; Kim, J.; Lee, S. *J. Org. Chem.* **2016**, *81*, 303. (e) Yang, L.; Jiang, L.; Li, Y.; Fu, X.; Zhang, R.; Jin, K.; Duan, C. *Tetrahedron* **2016**, *72*, 3858. (f) Lee, J.-H.; Raja, G. C. E.; Yu, S.; Lee, J.; Song, K. H.; Lee, S. *ACS Omega* **2017**, *2*, 6259.

(15) For details, see the Supporting Information.

(16) The absolute configuration was assigned as (*R*) by comparison with the optical rotation of known compound **4k**. For details, see the Supporting Information.

(17) For details on substrate synthesis, see the Supporting Information.

(18) Gellrich, U.; Meißner, A.; Steffani, A.; Kähny, M.; Drexler, H.-J.; Heller, D.; Plattner, D. A.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 1097.

(19) For details on further studies on elucidating the reaction mechanism, see the Supporting Information.

(20) It is likely that the formation of the Rh(III) hydride species occurs via a protonation pathway; see ref 18. However, a pathway involving oxidative addition to the O−H bond of TFA cannot be ruled out completely.

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