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# Palladium-Catalyzed Stereospecific Decarboxylative Benzylation of Alkynes

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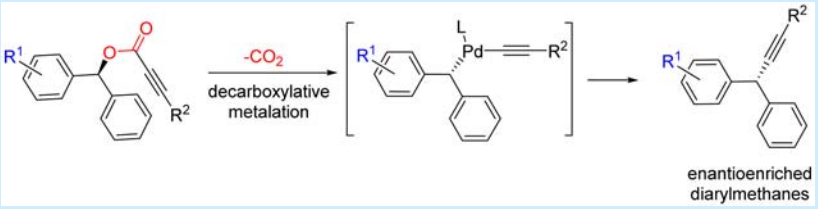
Supporting Information

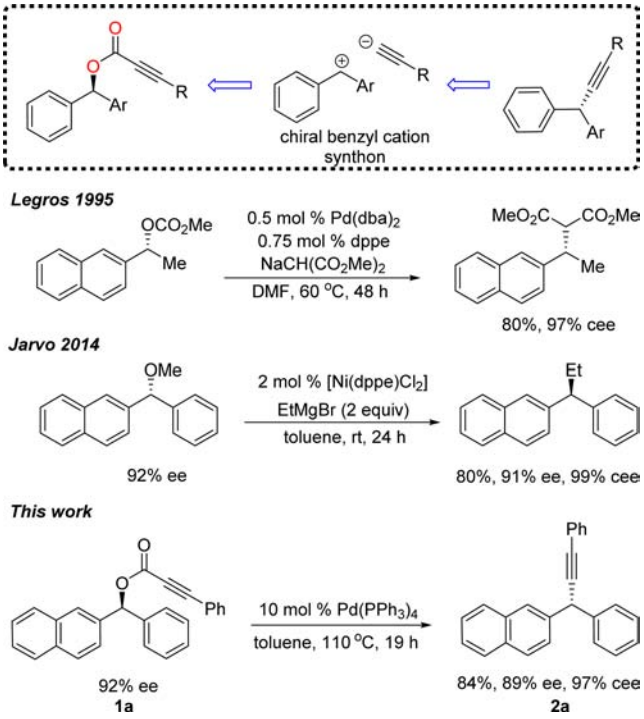



**ABSTRACT:** Enantioenriched benzyl esters of propiolic acids undergo highly stereospecific decarboxylative coupling to provide 1,1-diarylethynyl methanes. This sp–sp$^3$ coupling does not require strongly basic conditions or preformed organometallics and produces $CO_2$ as the sole byproduct. Ultimately, this method results in the successful transfer of stereochemical information from secondary benzyl alcohols to generate enantioenriched tertiary diarylmethanes.

Transition-metal-catalyzed cross-coupling reactions that generate tertiary stereogenic centers via the alkylation of secondary sp$^3$-hybridized reactants are potentially powerful tools for asymmetric synthesis.[1] Despite the significant advancements made in this area, the asymmetric alkynylation of secondary benzyl electrophiles is scarcely reported.[2] Benzyl halides are known to undergo Sonogashira coupling as well as related couplings with other organometallic acetylides.[2,3] However, these reactions rarely utilize secondary benzyl electrophiles and they suffer from the use of relatively toxic benzyl halides. Moreover, the couplings often require cocatalysts or preformed organometallics.[2,3a−c] For example, the nickel-catalyzed enantioselective benzyl-acetylide coupling requires preformed trialkyl indium complexes.[2] In addition, benzyl-acetylide cross-couplings can result in the formation of unwanted side products via isomerization of the alkyne under basic media,[3d] or further coupling of the product alkyne.[3c]

Catalytic decarboxylative coupling reactions have emerged as potentially powerful alternatives to standard cross-coupling reactions.[4] Thus, we envisioned that a wide array of tertiary diaryl methane motifs that are prevalent in biologically active compounds[5] could be accessed via decarboxylative benzyl-acetylide couplings of enantioenriched diarylmethanol derivatives (Scheme 1). Decarboxylative coupling reactions are particularly well suited for the alkynylation of benzyl electrophiles since the reactions occur under formally neutral conditions.[6] The absence of added base greatly decreases the rate of deprotonation which can lead to racemization of enantioenriched benzyl alkynes or formation of allene side products.[3d] Decarboxylative cross-coupling reactions have the further advantage that they use benzyl alcohol derivatives in lieu of more toxic benzyl halides.[2] Lastly, secondary benzyl alcohols are readily available in enantioenriched form,[7] making them ideal substrates for asymmetric cross-coupling reactions.

**Scheme 1. Catalytic Stereospecific Arylmethylation**

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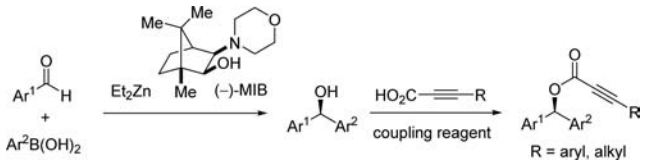
Legros and others have shown that secondary benzylic electrophiles derivatives can undergo palladium-catalyzed stereospecific cross-coupling reactions.[8] These reactions proceed via the intermediacy of Pd-$\pi$-benzyl complexes that act as chiral benzyl cation equivalents (Scheme 1).

More recently, Jarvo and Watson have made impressive progress on the development of nickel-catalyzed stereospecific cross-coupling reactions of secondary benzylic electrophiles to generate molecules with tertiary stereocenters.[9] Herein we report the synthesis of enantioenriched 1,1-diarylethynyl methanes via a highly stereospecific palladium-catalyzed decarboxylative benzylation strategy. To the best of our knowledge, this is the first report of a stereospecific decarboxylative benzylation. Moreover, we are unaware of any other cross-coupling method for the direct synthesis of enantioenriched 1,1-diarylethynyl methanes.

To begin, an array of benzylic ester derivatives were prepared via esterification of propiolic acids with enantioenriched diaryl methanols. These alcohols were obtained by a slightly modified (−)-MIB-catalyzed addition of boronic acids to aldehydes, originally reported by Braga (Scheme 2).[7b] This method

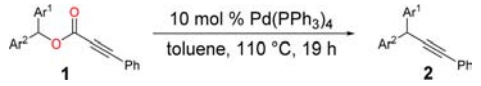
**Scheme 2. Synthesis of Enantioenriched Propiolic Esters**




produced a wide range of alcohols in high enantiomeric excess; however, several of the precursor alcohols were obtained in lower ee (e.g., **1d**, **1i**, **1o**, **1p**, Table 1). Nonetheless the Braga method provided each alcohol in large enough enantiomeric excess to accurately measure the stereospecificities of decarboxylative coupling. An additional advantage of this method for alcohol preparation is that either enantiomer of the alcohol can be obtained via the appropriate selection of the aryl boronic acid and the aromatic aldehyde reaction partners.

We then investigated the scope of the stereospecific decarboxylative benzylation reaction (Table 1). As we and others have noted,[6b,10] benzylic cross-couplings that proceed via $\pi$-benzyl intermediates are much more facile for benzylic electrophiles that have extended $\pi$-conjugation. For example phenyl propiolic ester of diphenylmethanol did not show any reactivity under standard conditions. Therefore, a variety of substituted benzyl propiolates that contain 1-naphthyl, 2-naphthyl, or indolyl groups were chosen for initial study. Since $\pi$-benzyl formation is accompanied by partial dearomatization of the coordinating arene, these aromatic groups that have relatively low resonance energies more readily form such complexes. For example, selective coordination of naphthalene instead of a phenyl group would be expected on the basis of the lower resonance energy of naphthalene (**1b**, Figure 1). Ultimately, the decarboxylative coupling of benzyl ester **1b** is facile and forms the product **2b** with a high degree of stereochemical fidelity, with a conservation of enantiomeric excess (cee) of 94% [cee = (product ee/reactant ee) × 100] (Table 1). However, oxidative addition is sterically disfavored by an ortho substituent on the naphthyl ring (**1c**, Figure 1 and Table 1), preventing the reaction. Substitution at the ortho position of the noncoordinating arene (**1d**, Figure 1) does slow the coupling; however, the reaction still proceeds with high

**Table 1. Scope of Stereospecific Decarboxylative Benzylation of Alkynes**




| entry | reactant ee(%)[a] | product | | yield (%)[b] | ee (%)[a] | cee (%) |
|---|---|---|---|---|---|---|
| **1b** | 94 | R = H | (**2b**) | 85 | 88 | 94 |
| **1c** | - | R = Me | (**2c**) | NR | - | - |
| **1d** | 69 | | (**2d**) | 31 | 64 | 93 |
| **1e** | 97 | | (**2e**) | 81 | 96 | 99 |
| **1f** | 94 | | (**2f**) | 71 | 91 | 97 |
| **1g** | 94 | R = F | (**2g**) | 83 | 92 | 98 |
| **1h** | >85 | R = Me | (**2h**) | 77 | 95 | >99 |
| **1i** | 62 | R = SMe | (**2i**) | 68 | 43 | 69 |
| **1j** | 94 | R = $^t$Bu | (**2j**) | 92 | 89 | 95 |
| **1k** | 91 | | (**2k**) | 73 | 93 | >99 |
| **1l** | 81 | | (**2l**) | 73 | 79 | 98 |
| **1m** | - | R = $NO_2$ | (**2m**) | 16[c] | ND | - |
| **1n** | - | R = CN | (**2n**) | 18[c] | ND | - |
| **1o** | 72 | X = S | (**2o**) | 69 | 64 | 89 |
| **1p** | 75 | X = O | (**2p**) | 77 | 64 | 85 |
| **1q** | 87 | | (**2q**) | 92 | 60[d] | 69 |

[a]Determined by chiral HPLC analysis. [b]Yield of isolated product All products were stored cold upon isolation to avoid decomposition or isomerization. [c]Yield reported using the racemic benzylic ester. [d]Boc group removed prior to HPLC analysis.

enantiospecificity (**1d**, Table 1). Further substitution of the benzylic esters with a variety of alkyl (**2f**, **2h**, **2j**), alkoxy (**2d**, **2e**, **2l**), or halogen (**2g**, **2k**) substituents allowed for highly



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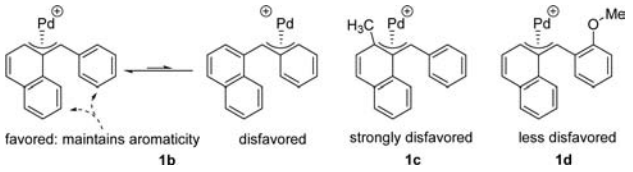
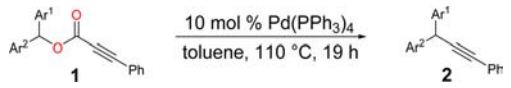



**Figure 1.** $\pi$-Benzyl formation: sterics and favorable coordination of arenes with extended $\pi$-conjugation.

enantiospecific (average cee = 97%) cross-coupling, and the products were isolated in good to excellent yield. However, a sulfur donor in the *para*-position led to partial racemization during the coupling (**2i**, Table 1). Furthermore, substitution of one of the arenes with a strongly electron-withdrawing *p*-$NO_2$ or *p*-CN substituent, which substantially acidifies the benzylic proton, drastically lowered the yield of the reaction and these products were isolated as the allene isomers (**2m**, **2n**). Interestingly, heteroaromatic phenyl propiolates (**1o**−**1q**) also underwent stereospecific decarboxylative benzylation with moderate-to-good stereochemical fidelity.

We also briefly examined the effect of the acetylide coupling partner on the yields and stereospecificity of the decarboxylative coupling (Table 2). In addition to phenyl propiolates,

**Table 2. Scope of Stereospecific Decarboxylative Benzylation: Alkynes**



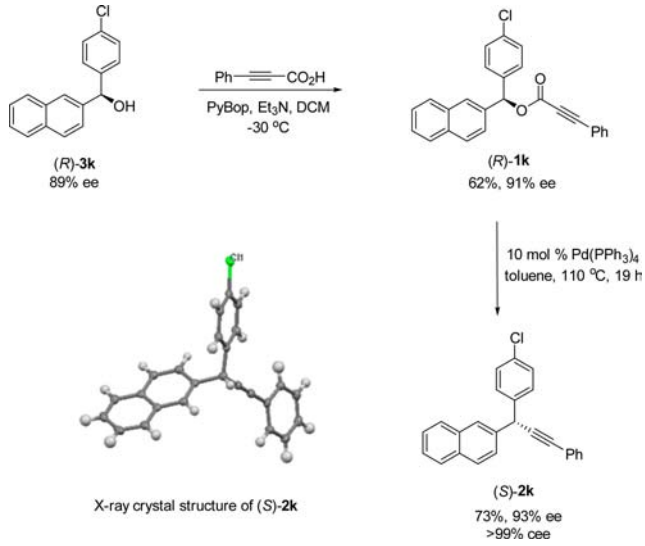

| entry | reactant ee(%)[a] | product | yield (%)[b] | ee (%)[a] | cee (%) |
|---|---|---|---|---|---|
| **1r** | 92 | (**2r**) | 43[c] | 87 | 95 |
| **1s** | 93 | (**2s**) | 53 | 81 | 87 |
| **1t** | 91 | (**2t**) | 59 | 87 | 96 |
| **1u** | 91 | (**2u**) | 62 | 85 | 93 |
| **1v** | 86 | (**2v**) | 87 | 77 | 90 |
| **1w** | ND | (**2w**) | NR | | |

[a]Determined by chiral HPLC analysis. [b]Yield of isolated product. All products were stored cold upon isolation. [c]Isolated yield after 16 h.

alkyl (**1r**, **1s**) and aryl propiolates (**1t**−**1v**) also undergo decarboxylative benzylation with high stereospecificity. However, a cyclohexenyl acetylide (**1w**) did not undergo decarboxylative benzylation under optimized reaction conditions.

While it was clear that the decarboxylative couplings of most propiolic esters occur with high stereospecificity, it was desirable to determine whether the coupling proceeded with retention or inversion of configuration. With this in mind, an alcohol [(*R*)-**3k**, Scheme 3] of known configuration was

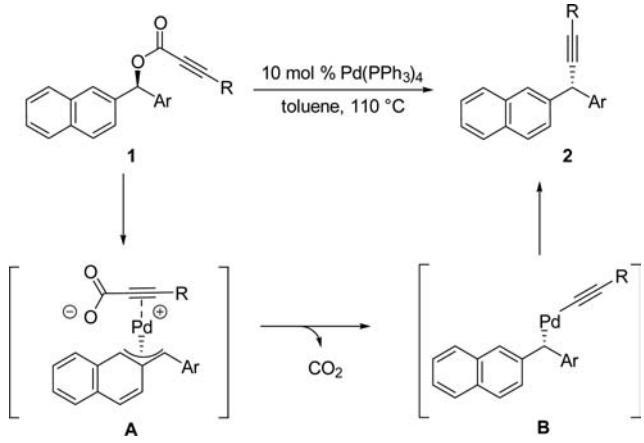
**Scheme 3. Determination of the Stereochemical Course of the Reaction**




prepared.[7c,11] The alcohol was converted to the highly enantiomerically enriched phenyl propiolate ester (*R*)-**1k** via PyBop coupling. After the decarboxylative coupling, crystals of the product were subjected to single crystal X-ray diffraction analysis which revealed the absolute configuration of **2k** to be (*S*) (Scheme 3).

The overall inversion of stereochemistry that is observed in decarboxylative coupling can be mechanistically explained as follows (Scheme 4). Substrate **1** undergoes oxidative addition

**Scheme 4. Proposed Catalytic Cycle for the Decarboxylative Coupling**




to Pd to generate an $\eta^3$-benzyl-Pd carboxylate intermediate. The oxidative addition is expected to proceed with inversion of configuration via $S_N2$-like displacement by palladium.[12]

We propose that coordination of the alkyne to Pd, as in intermediate **A**, facilitates decarboxylation resulting in the formation of a benzyl-Pd-acetylide intermediate (**B**) which undergoes reductive elimination with retention of stereochemistry to give the cross-coupled product **2** with overall inversion of stereochemistry. This is similar to Pd-catalyzed allylic alkylations, where allylation of nonstabilized or "hard" nucleophiles proceeds with inversion of configuration.[6a]



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In summary, we have shown that decarboxylative benzylation of acetylides is highly stereospecific and that the stereochemical information on a secondary alcohol is successfully transferred to generate a tertiary stereogenic center. This method provides a route for the asymmetric coupling of secondary benzylic electrophiles with alkynes that does not require preformed organometallics.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02410.

Experimental procedures, $^{1}H$, $^{13}C$ NMR data, characterization data and HPLC data of all novel products (PDF)
Crystallographic data for **2k** (CIF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) (a) Taylor, B. L. H.; Jarvo, E. R. *Synlett* **2011**, *2011*, 2761−2765. (b) Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2013**, *69*, 5799−5817. (c) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 5520−5524. (d) Xu, S.; Lee, C.-T.; Wang, G.; Negishi, E.-i. *Chem. - Asian J.* **2013**, *8*, 1829−1835.

(2) Caeiro, J.; Pérez Sestelo, J.; Sarandeses, L. A. *Chem. - Eur. J.* **2008**, *14*, 741−746.

(3) (a) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155−4160. (b) Qian, M.; Negishi, E. *Tetrahedron Lett.* **2005**, *46*, 2927−2930. (c) Pottier, L. R.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Synlett* **2004**, 1503−1508. (d) Larsen, C. H.; Anderson, K. W.; Tundel, R. E.; Buchwald, S. L. *Synlett* **2006**, *2006*, 2941−2946.

(4) (a) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846−1913. (b) Shang, R.; Huang, Z.; Xiao, X.; Lu, X.; Fu, Y.; Liu, L. *Adv. Synth. Catal.* **2012**, *354*, 2465−2472. (c) Fields, W. H.; Chruma, J. J. *Org. Lett.* **2010**, *12*, 316−319. (d) Recio, A., III; Heinzman, J. D.; Tunge, J. A. *Chem. Commun.* **2012**, *48*, 142−144. (e) O'Hair, R. A. J. *Pure Appl. Chem.* **2015**, *87*, 391−404. (f) Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030−5048.

(5) (a) Xie, W.-D.; Li, X.; Weng, C.-W.; Liu, S.-S.; Row, K. H. *Chem. Pharm. Bull.* **2011**, *59*, 511−514. (b) Ali, M. S.; Banskota, A. H.; Tezuka, Y.; Saiki, I.; Kadota, S. *Biol. Pharm. Bull.* **2001**, *24*, 525−528.

(6) (a) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510−13511. (b) Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 9280−9282. (c) Park, K.; Lee, S. *RSC Adv.* **2013**, *3*, 14165−14182.

(7) (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850−14851. (b) Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 2879−2882. (c) Salvi, L.; Kim, J. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 12483−12493.

(8) (a) Legros, J.-Y.; Boutros, A.; Fiaud, J.-C.; Toffano, M. *J. Mol. Catal. A: Chem.* **2003**, *196*, 21−25. (b) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron* **1995**, *51*, 3235−3246. (c) Assié, M.; Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 1183−1187. (d) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron: Asymmetry* **1995**, *6*, 1899−1902. (e) He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524−2525. (f) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514−55.

(9) (a) Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422−2427. (b) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083−9090. (c) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790−7793. (d) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307−3310. (e) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280−285.

(10) (a) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293−4296. (b) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104−12105.

(11) Li, K.; Hu, N.; Luo, R.; Yuan, W.; Tang, W. *J. Org. Chem.* **2013**, *78*, 6350−6355.

(12) (a) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2012**, *134*, 5778−5781. (b) Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5832−5840.




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