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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Alkyne Hydroheteroarylation: Enantioselective Coupling of Indoles and Alkynes via Rh-Hydride Catalysis

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Supporting Information

ABSTRACT: We report an enantioselective coupling between alkynes and indoles. A Rh-hydride catalyst isomerizes alkynes to generate a metal-allyl species that can be trapped with both aromatic and heteroaromatic nucleophiles.

Aryl and heteroaryl rings can be used to increase nonbonding and electrostatic interactions between a small molecule and its macromolecule target.[1] Among the top selling therapeutics, more than half contain aryl structures (Figure 1A).[2] Given the relevance of chirality in medicine, inventing enantioselective tools for introducing aromatic nucleophiles warrants pursuit.[3] The hydroarylation of alkynes is a modern strategy for functionalizing aryl structures,[4] where two simple functional groups are coupled with high atom economy.[5] To date, however, this approach has been limited to generating achiral olefins (Figure 1B, eq a). Classic alkyne hydroarylations generate achiral vinylated arenes via mechanisms that involve alkyne activation with π-acids or arene activation to access aryl-metal species.[4d−n] In contrast, we imagined using metal-hydride catalysis to couple arenes with alkynes to form allylated products (Figure 1B, eq b).[6] In this communication, we disclose a regio- and enantioselective alkyne hydroheteroarylation using indoles.[7−9]

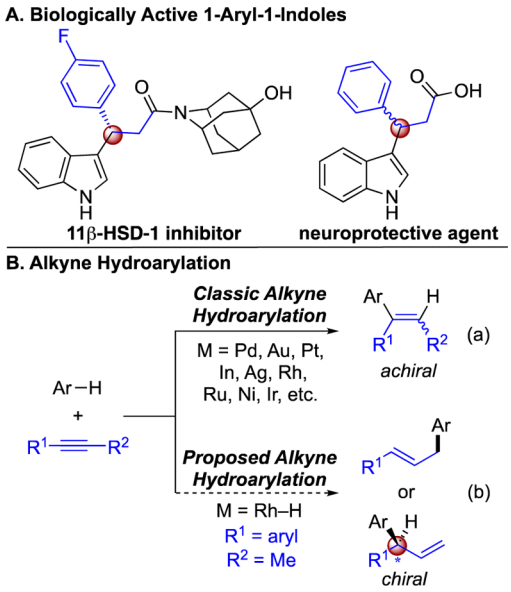


Figure 1. Inspiration for asymmetric alkyne hydroarylation.

On the basis of previous studies, Rh-hydride catalysts can isomerize alkynes (**2**) to allenes (**6**) via a Rh-vinyl species (**5**) as depicted in Figure 2.[10] Subsequent allene insertion into a Rh−H generates a Rh-π-allyl species (**7**). Various oxygen-,[11] sulfur-,[12] and nitrogen-based[13] nucleophiles have been used to trap **7** and generate carbon−heteroatom bonds with stereocontrol. However, enantioselective C−C bond formation has thus far been only achieved with aldehydes via enamine catalysis.[14e] We recognized that the key challenge to achieving alkyne hydroarylation would be trapping Rh-π-allyl **7** with an arene **1** (an inherently weaker nucleophile) to generate **3**, with high enantio- and regiocontrol. However, we were encouraged by Carreira's Ir-catalyzed polyene cyclization that demonstrates the use of arenes and heteroarenes as terminating nucleophiles.[15]

To test this hypothesis, we examined the coupling of various arenes and heteroarenes **1** and 1-phenyl-1-propyne (**2a**) (Table 1). Successful trapping of the Rh-π-allyl species affords either the branched (**3**) or the linear regioisomer (**4**). Using a combination of a Rh-bisphosphine and diphenyl phosphate,[11c,14e] we observed that arenes and heteroarenes with a wide range of nucleophilicities, based on the Mayr scale (N = 1.33−11.63), were successful coupling partners.[16,21] Initial studies using $[Rh(COD)Cl]_2$, dppf, and diphenyl phosphate showed that the structure of the nucleophile impacted which regioisomer was favored. For example, with benzofuran and 1,3-dimethoxybenzene, we observed the linear isomers as the major product, in accordance with previous studies using Brønsted acid catalysis (>20:1 *rr*, 29% and 35%, respectively).[17] In contrast, 3-ethyl-2,4-dimethyl pyrrole and indole generated the branched isomers upon addition to alkyne **2a** (>20:1 *rr*, 24% and 65%, respectively). On the basis of related studies on alkyne hydroamination, we imagine that regioselectivity can be controlled by tuning the catalyst and acid.[13a]

Indoles can be site-selectively prenylated at the *N*, 2-, 3-, 4-, or 7-position via enzymatic or synthetic processes.[18] Despite the diverse reactivity of indoles, we observed selective bond formation at the 3-position upon coupling of alkyne **2a** and indole to yield **3** as the only regioisomer.

With this promising reactivity demonstrated, we focused on developing an enantioselective coupling using indoles due to

Received: June 7, 2017

DOI: 10.1021/jacs.7b05893
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

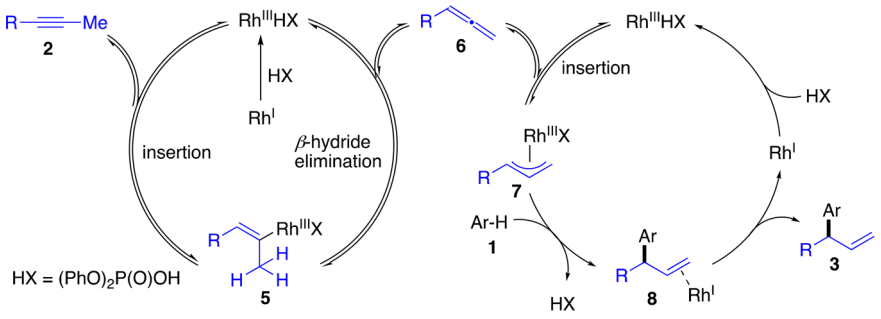
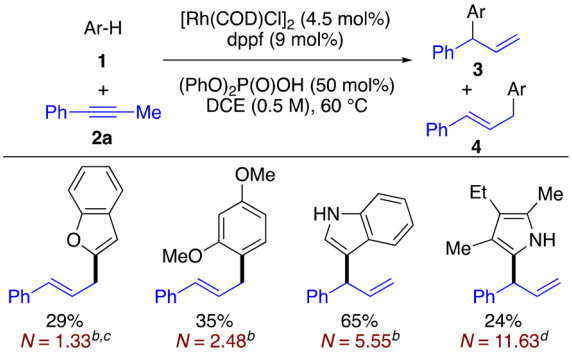


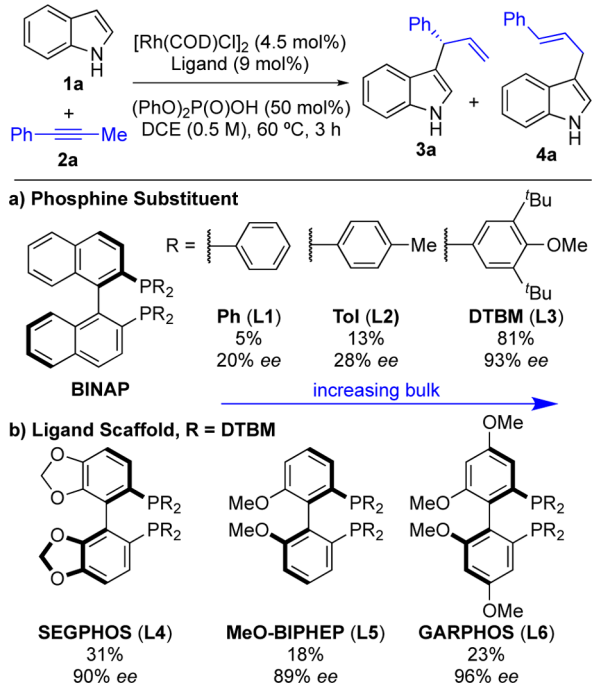
Figure 2. Proposed Rh-hydride catalyzed alkyne hydroarylation.

Table 1. Alkyne Hydroarylation using Arenes with a Range of Nucleophilicities[a]



[a]**1** (0.1 mmol), **2a** (0.12 mmol), $[Rh(COD)Cl]_2$ (4.5 mol%), dppf (9.0 mol%), $(PhO)_2P(O)OH$ (50 mol%), DCE (0.2 mL), 60 °C, [b]Nucleophilicity in DCM. [c]Nucleophilicity of furan. [d]Nucleophilicity in MeCN.

Table 2. Ligand Effects on Alkyne–Indole Coupling[a]



[a]**1a** (0.1 mmol), **2a** (0.12 mmol), $[Rh(COD)Cl]_2$ (4.5 mol%), ligand (9.0 mol%), $(PhO)_2P(O)OH$ (50 mol%), DCE (0.2 mL), 60 °C, 3 h. Yields determined by ^1H NMR with 1,2,4,5-tetramethylbenzene as internal standard. Enantioselectivities determined by chiral SFC.

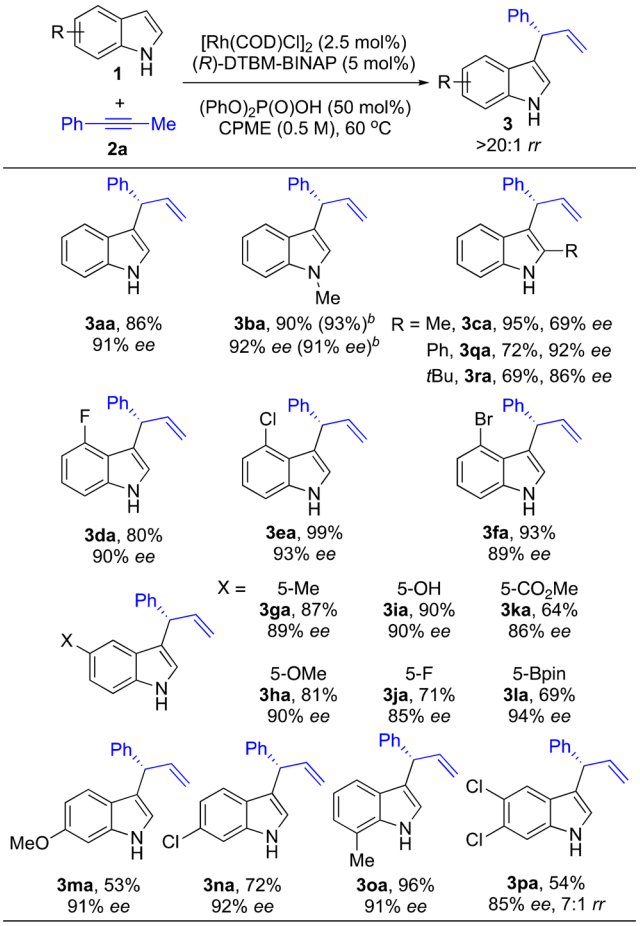
the importance of these heterocycles in natural and pharmaceutical products.[19] We found that a protocol consisting of $[Rh(COD)Cl]_2$, (*R*)-Ph-BINAP (**L1**), and diphenyl phosphate gave the desired branched product (**3a**) in 5% yield and 20% *ee* (Table 2).[20] In contrast to previous studies where carboxylic acids were used,[14a–d] more acidic acids (e.g., sulfonic and phosphoric acids) were necessary for reactivity. Increasing the steric bulk of the phosphine substituent improved enantioselectivity (**L2**, 28% *ee* and **L3**, 93% *ee*). The electron-rich DTBM-BINAP (**L3**) also dramatically improved the yield to 81% yield. Other biaryl bisphosphine ligands bearing the DTBM-phosphine substituents such as SEGPHOS (**L4**), MeO-BIPHEP (**L5**), or GARPHOS (**L6**) provided similar enantioselectivity but lower reactivity (18–31% yield). With ligand **L3**, we found that a number of solvents could be used but found that using cyclopentyl methyl ether (CPME) was optimal; **3a** was obtained in 92% yield and 91% *ee*, with lower (2.5 mol%) catalyst loadings.[21]

With this protocol in hand, we explored the hydroheteroarylation of alkyne **2a** with various indoles (Table 3). Efficient and selective indole–alkyne coupling occurs with a variety of indole substitution patterns. For example, a methyl group can be incorporated at the *N*-, 5-, and 7-positions of indole to afford the corresponding allylated indoles with up to 96% yield, > 20:1 *rr*, and 92% *ee* (**3ba**, **3ga**, **3oa**). In comparison, lower *ee* is observed with 2-methylindole (**3ca**, 69% *ee*). In general, we observe lower enantioselectivity with 2-methylindole using various aryl-substituted alkynes.[21] However, when a phenyl or *tert*-butyl group is incorporated at the 2-position, higher *ee* is observed (**3qa** and **3ra**, 92% and 86% *ee*, respectively). Halogenated indoles were successfully coupled with high selectivities (**3da**, **3ea**, **3fa**, **3ja**, **3na**, **3pa**). Chemoselective C–C bond formation was observed in the presence of a nucleophilic phenol (**3ia**) and an electrophilic methyl ester (**3ka**). A substrate bearing a pinacol borane, a convenient functional handle, was transformed smoothly (**3la**).

Next, we studied the coupling of indole **1a** with structurally diverse alkynes (Table 4). Electron-rich alkynes with alkyl or ether substitution undergo efficient and selective coupling with indole (**3ab**–**3ae**, 70–88%, >20:1 *rr*, 82–93% *ee*). Fluorinated and chlorinated alkynes act as efficient coupling partners (**3af** and **3ag**, 82–93%, >20:1 *rr*, 88–90% *ee*). In addition, electron-deficient alkynes with trifluoromethyl substitution undergo hydroarylation with indole to provide **3ai** in 97% yield and 92% *ee*. Chemoselective functionalization occurs even in the presence of electrophilic ethyl ester (**3ah**). Heteroaromatic and aromatic alkynes (3-thiophene and 1-naphthalene) also undergo hydroarylation (**3aj** and **3ak**). We found that an aromatic or heteroaromatic group on the alkyne is critical for

DOI: 10.1021/jacs.7b05893
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

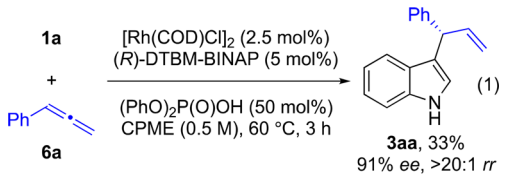
Table 3. Alkyne Hydroheteroarylation with Various Indoles[a]



[a]**1** (0.1 mmol), **2a** (0.12 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), (*R*)-DTBM-BINAP (5.0 mol%), $(PhO)_2P(O)OH$ (50 mol%), CPME (0.2 mL), 60 °C. Isolated yields. *rr*'s (**3**:**4**) determined by ^1H NMR analysis of the unpurified reaction mixture. Enantioselectivities determined by chiral SFC. [b]Values in parentheses are for the transformation performed on a 1.0 mmol scale.

reactivity. For example, an alkyl-substituted alkyne, such as 2-octyne, proved to be unreactive under these conditions (**3al**).

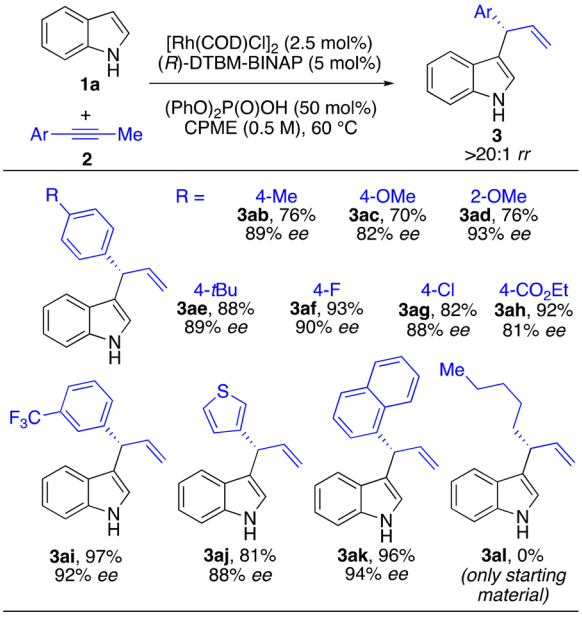
To support the intermediacy of an allene, we replaced alkyne **2a** with phenylallene **6a** (eq 1).[21] Under standard reaction



conditions, the desired coupling product **3aa** was obtained with similar enantio- and regioselectivity, although in lower yield (33% yield, 91% *ee*, and >20:1 *rr*). This result supports the possibility of an allene intermediate. But the diminished yield suggests that high concentrations of allene may be detrimental due to competing decomposition, and thus, *in situ* generation results in better efficiency.[11c,13a]

We have demonstrated a regio- and enantioselective way to hydrofunctionalize alkynes using indoles. The use of Rh-hydride catalysis to isomerize alkynes has enabled access to a complementary hydroheteroarylation motif. Moreover, our study demonstrates the potential of generating C−C bonds

Table 4. Hydroheteroarylation of Various Alkynes with Indole[a]



[a]**1a** (0.1 mmol), **2** (0.12 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), (*R*)-DTBM-BINAP (5.0 mol%), $(PhO)_2P(O)OH$ (50 mol%), CPME (0.2 mL), 60 °C. Isolated yields. *rr*'s (**3**:**4**) determined by ^1H NMR analysis of the unpurified reaction mixture. Enantioselectivities determined by chiral SFC.

under mild conditions using both aromatic and heteroaromatic motifs. Given these promising results, our future studies will focus on enantio- and regioselective coupling using other classes of aromatic nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05893.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding provided by UC Irvine and the National Institutes of Health (GM105938). We are grateful to Eli Lilly for a Grantee Award. F.A.C. is grateful for an NSF Graduate Research Fellowship.

■ REFERENCES

(1) Dalvia, D.; Sajiv, N.; Kang, P.; Loi, C.-M. Influence of Aromatic Rings on ADME Properties of Drugs. In *Metabolism, Pharmokinetics*

DOI: 10.1021/jacs.7b05893
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

and Toxicity of Functional Group; Royal Society of Chemistry: Cambridge, U.K., 2010; pp 275−327.
(2) (a) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845.
(3) For select reviews, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454. (c) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796. (d) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (e) Poulsen, T. B.; Jorgenson, K. A. *Chem. Rev.* **2008**, *108*, 2903. (f) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587. (g) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95.
(4) For select reviews, see: (a) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, *2*, 167. (b) Kitamura, T. *Eur. J. Org. Chem.* **2009**, *2009*, 1111. (c) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. For select examples of alkyne hydroarylation that generate an internal olefin, see: (d) Fallon, B. J.; Derat, E.; Amatore, M.; Aubert, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A.; Petit, M. *J. Am. Chem. Soc.* **2015**, *137*, 2448. (e) Liu, Z.; Derosa, J.; Engle, K. M. *J. Am. Chem. Soc.* **2016**, *138*, 13076. (f) Ding, D.; Mou, T.; Feng, M.; Jiang, X. *J. Am. Chem. Soc.* **2016**, *138*, 5218. (g) Kumar, N. Y. P.; Bechtoldt, A.; Raghuvanshi, K.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 6929. For select examples of alkyne hydroheteroarylation with indoles to generate vinylated products, see: (h) Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927. (i) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146. (j) Bhaskar, G.; Saikumar, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 3141. (k) Samala, S.; Mandadapu, A. K.; Saifuddin, M.; Kundu, B. *J. Org. Chem.* **2013**, *78*, 6769. (l) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (m) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4698. (n) Lu, Q.; Greßies, S.; Klauck, F. J. R.; Glorius, F. *Angew. Chem., Int. Ed.* **2017**, *56*, 6660.
(5) Trost, B. M. *Science* **1991**, *254*, 1471.
(6) For select reviews on allylic alkylation, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, *2008*, 3765. (c) Zhuo, C.-X.; Zheng, C.; You, S.-L. *Acc. Chem. Res.* **2014**, *47*, 2558. (d) Butt, N. A.; Zhang, W. *Chem. Soc. Rev.* **2015**, *44*, 7929. (e) Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. *ACS Catal.* **2016**, *6*, 6207.
(7) For select examples of Ir-catalyzed indole allylic alkylation, see: (a) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815. (b) Huang, L.; Dai, L.-X.; You, S.-L. *J. Am. Chem. Soc.* **2016**, *138*, 5793.
(8) For select examples of Ru-catalyzed indole allylic alkylation, see: (a) Zaitsev, A. B.; Gruber, S.; Plüss, P. A.; Pregosin, P. S.; Veiros, L. F.; Wörle, M. *J. Am. Chem. Soc.* **2008**, *130*, 11604. (b) Sundararaju, B.; Achard, M.; Demerseman, B.; Toupet, L.; Sharma, G. V. M; Bruneau, C. *Angew. Chem., Int. Ed.* **2010**, *49* (49), 2782.
(9) For select examples of Pd-catalyzed indole allylic alkylation, see: (a) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (b) Gao, R.-D.; Liu, C.; Dai, L.-X.; Zhang, W.; You, S.-L. *Org. Lett.* **2014**, *16*, 3919. (c) Zhang, Z.-X.; Chen, S.-C.; Jiao, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 8090. (d) Panda, S.; Ready, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 6038.
(10) For a review, see: (a) Koschker, P.; Breit, B. *Acc. Chem. Res.* **2016**, *49*, 1524. For select examples using Pd, see: (b) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262. (c) Gao, Z.; Wu, Z.; Fang, X.; Lin, A.; Yao, H. *Org. Lett.* **2016**, *18*, 3906. (d) Yang, C.; Zhang, K.; Wu, Z.; Yao, H.; Lin, A. *Org. Lett.* **2016**, *18*, 5332. For select examples of metal-catalyzed alkyne isomerization followed by trapping with electrophiles, see: (e) Obora, Y.; Hatanaka, S.; Ishii, Y. *Org. Lett.* **2009**, *11*, 3510. (f) Park, B. Y.; Nguyen, K. D.; Chaulagain, M. R.; Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 11902. (g) Liang, T.; Nguyen, K. D.; Zhang, W. D.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 3161. (h) Chen, Q.-A.; Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 3157. (i) Liang, T.; Zhang, W.; Chen, T.-Y.; Nguyen, K. D.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 13066. (j) Liang, T.; Zhang, W.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 16024.
(11) For examples of C−O bond formation, see: (a) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 2386. (b) Koschker, P.; Kähny, M.; Breit, B. *J. Am. Chem. Soc.* **2015**, *137*, 3131. (c) Liu, Z.; Breit, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 8440.
(12) For an example of C−S bond formation, see: Xu, K.; Khakyzadeh, V.; Bury, T.; Breit, B. *J. Am. Chem. Soc.* **2014**, *136*, 16124.
(13) For examples of C−N bond formation, see: (a) Chen, Q.-A.; Chen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 8392. (b) Haydl, A. M.; Hilpert, L. J.; Breit, B. *Chem. - Eur. J.* **2016**, *22*, 6547.
(14) For examples of racemic 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. For enantioselective C−C bond formation, see: (e) Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 1029.
(15) Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2012**, *134*, 20276.
(16) Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584.
(17) Le Bras, J.; Muzart, J. *Tetrahedron* **2007**, *63*, 7942.
(18) For select reviews, see: (a) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. *Top. Curr. Chem.* **2000**, *209*, 97. (b) Li, S.-M. *Nat. Prod. Rep.* **2010**, *27*, 57. (c) Lindel, T.; Marsch, N.; Adla, S. K. *Top. Curr. Chem.* **2011**, *309*, 67. For select examples, see: (d) Kranen, E.; Steffan, N.; Maas, R.; Li, S.-M.; Jose, J. *ChemCatChem* **2011**, *3*, 1200. (e) Schwarzer, D. D.; Gritsch, P. J.; Gaich, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 11514. (f) Wollinsky, B.; Ludwig, L.; Hamacher, A.; Yu, X.; Kassack, M. U.; Li, S.-M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3866. (g) Yu, X.; Liu, Y.; Xie, X.; Zheng, X.-D.; Li, S.-M. *J. Biol. Chem.* **2012**, *287*, 1371. (h) Johnson, K. F.; Van Zeeland, R.; Stanley, L. M. *Org. Lett.* **2013**, *15*, 2798. (i) Ruchti, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 16756. (j) Müller, J. M.; Stark, C. B. W. *Angew. Chem., Int. Ed.* **2016**, *55*, 4798.
(19) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, 2000. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1. (c) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532. (d) Goetz, A. E.; Silberstein, A. L.; Corsello, M. A.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 3036. (e) Moreno, J.; Picazo, E.; Morrill, L. A.; Smith, J. M.; Garg, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 1162.
(20) Absolute configuration was determined by comparison of optical rotation; see SI.
(21) See SI for further experimental details, including other substrates evaluated, solvent evaluation, and use of a deuterated alkyne.

DOI: 10.1021/jacs.7b05893
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX