C–C Coupling

International Edition: DOI: 10.1002/anie.201703089
German Edition: DOI: 10.1002/ange.201703089

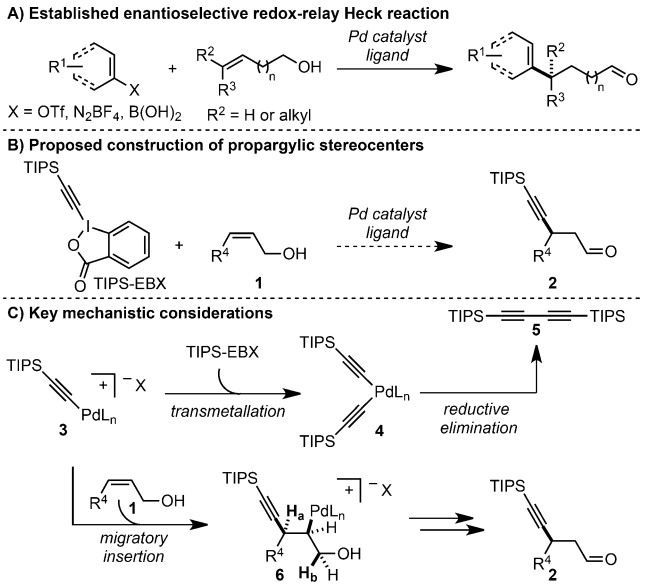
Palladium-Catalyzed Enantioselective Redox-Relay Heck Alkynylation of Alkenols to Access Propargylic Stereocenters

*Zhi-Min Chen, Christine S. Nervig, Ryan J. DeLuca, and Matthew S. Sigman**

Abstract: *An enantioselective redox-relay Heck alkynylation of di- and trisubstituted alkenols to construct propargylic stereocenters is disclosed using a new pyridine oxazoline ligand. This strategy allows direct access to chiral β-alkynyl carbonyl compounds employing allylic alcohol substrates in contrast to more traditional conjugate addition methods.*

Intermolecular Heck reactions generally feature the coupling of an sp^2-hybridized reaction partner to an alkene followed by β-hydride elimination towards the site of initial migratory insertion. This formally yields a sp^2–sp^2 carbon–carbon connection.[1] Recently, this reaction has been expanded through both substrate and catalyst design to preferentially undergo β-hydride elimination away from the site of initial migratory insertion to both set a stereocenter and allow the formation of a sp^2–sp^3 C–C bond.[2] Specifically, our group has reported a suite of such enantioselective redox-relay Heck reactions of acyclic alkenyl alcohols using aryldiazonium salts,[3] arylboronic acids,[4] and alkenyl triflates,[5] which provides direct preparation of carbonyl compounds that contain remote alkenyl/aryl stereocenters (Scheme 1 A). However, this emerging strategy has thus far been limited to sp^2-hybridized nucleophiles/electrophiles as coupling partners.

In an effort to expand the breadth of products one can access with this approach, we selected to investigate the enantioselective Heck alkynylation of alkenols to construct propargylic stereocenters and forge sp–sp^3 C–C bonds (Scheme 1 B). The successful development of an alkynyl Heck reaction would allow direct access to chiral β-alkynyl carbonyl compounds, which are versatile intermediates that have extensive applications in organic synthesis.[6] Traditionally, these types of compounds have been synthesized using enantioselective conjugate addition technologies, pioneered by Carreira,[7] Hayashi,[8] and others, through organometallic acetylide addition to α,β-unsaturated carbonyl substrates.[9] However, we envisioned that a redox-relay Heck approach that utilized allylic alcohol substrates would provide an attractive alternative to this field due to the ease of preparation, handling and improved stability of such alkenols. In addition, it was deemed possible, on the basis of our previous reports, that trisubstituted alkenols may be viable



Scheme 1. Proposed redox-relay Heck alkynylation to access propargylic stereocenters.

substrates. Using a traditional conjugate addition approach, only one report of conjugate alkynylation of β,β-disubstituted carbonyl compounds to establish propargylic quaternary stereocenters has appeared to date and is limited to β-aryl-β-trifluoromethyl enones.[10]

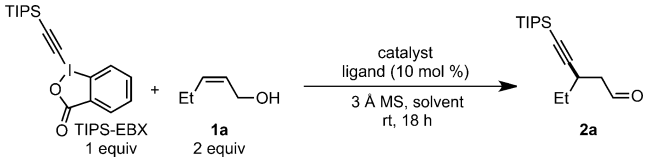
To achieve a successful alkynylative redox-relay Heck transformation three main challenges were carefully considered: 1) the identification of a suitable sp-hybridized carbon reagent (such as benziodoxole derived triisopropylsilyl variant (TIPS-EBX) initially developed by Waser), 2) avoiding competitive transmetallation with Pd-alkynyl species **3** (Scheme 1 C), which would ultimately lead to Pd-bis(alkynyl) intermediate **4** followed by reductive elimination to yield homocoupling product **5**, and 3) selective β-hydride elimination of H_b (**6**) since β-hydride elimination of H_a would produce the traditional Heck-type product (not shown) and remove the newly established propargylic stereocenter. Herein, we disclose the development of an enantioselective redox-relay Heck alkynylation of allylic alkenols as a complementary approach to access enantiomerically enriched β-alkynyl carbonyl compounds. This method utilizes easily accessible alkenol substrates, a simple chiral ligand, and a benziodoxole derived reagent as the alkyne source.

To initiate our studies, *cis*-2-penten-1-ol (**1a**, Table 1) and TIPS-EBX[11] were selected as model coupling partners with $Pd(CH_3CN)_2(OTs)_2$ as a precatalyst, a chiral pyridine-oxazo-

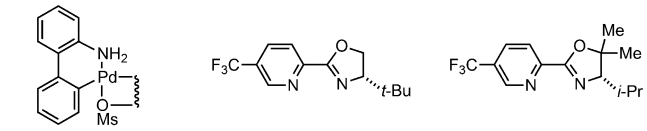
[*] Dr. Z.-M. Chen, C. S. Nervig, Dr. R. J. DeLuca, Prof. M. S. Sigman
Department of Chemistry, University of Utah
315 South 1400 East, Salt Lake City, UT 84112 (USA)
E-mail: sigman@chem.utah.edu

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201703089.

Table 1: Reaction optimization.[a]



Entry	Catalyst (mol%)	Ligand	Solvent	Yield [%]	er
1	$Pd(CH_3CN)_2(OTs)_2$ (8)	**L1**	CH_2Cl_2	40	98:2
2	$Pd(CH_3CN)_2(OTs)_2$ (8)	**L1**	THF	48	92:8
3	$Pd(CH_3CN)_2(OTs)_2$ (8)	**L1**	EtOAc	42	91:9
4	$Pd(CH_3CN)_2(OTs)_2$ (8)	**L1**	dioxane	60	97:3
5	$Pd(CH_3CN)_2(OTs)_2$ (8)	**L2**	dioxane	65	96.5:3.5
6[b]	$Pd(CH_3CN)_2(OTs)_2$ (8)	**L2**	dioxane	63	96.5:3.5
7	$Pd_2(dba)_3$ (4)	**L2**	dioxane	<5	–
8[c]	Buchwald precatalyst (4)	**L2**	dioxane	65	96:4



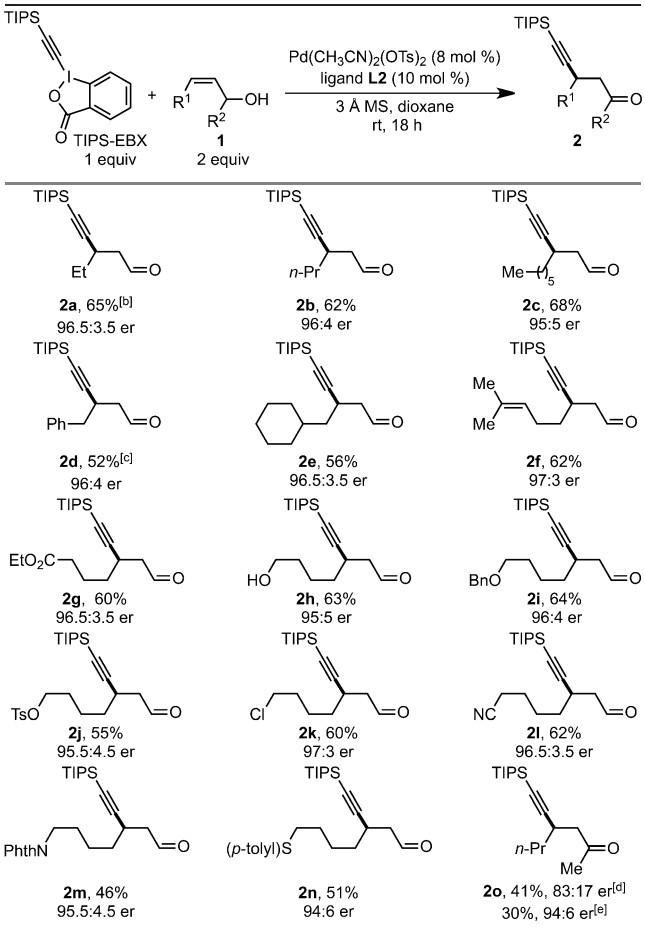
[a] Each entry represents the isolated yield on 0.20 mmol scale. er values were determined by SFC. [b] The reaction was performed at 15 °C. [c] The Buchwald precatalyst (4 mol%) was heated to 80 °C for 10 min prior use to generate Pd^0 and TsOH (25 mol%) was added.

line ligand (PyrOx, **L1**), and CH_2Cl_2 as solvent (see SI for additional ligands and alkyne sources explored). Promisingly, the desired product (**2a**) was produced in 40% yield and 98:2 er (entry 1). To improve the reaction yield, a solvent screen was performed (entries 2–4). As a result, dioxane was found to increase the product yield to 60%. Replacing the *t*-Bu group (**L1**) on the PyrOx ligand with an *i*-Pr group and adding a *gem*-dimethyl moiety on the oxazoline portion (**L2**) gave a slight boost in yield to 65% while maintaining high enantioselectivity (entry 5). The CF_3 group on the pyridine moiety of the ligand produces a more electrophilic catalyst, which has been reported to deliver higher product yields and enantioselectivities.[3] In addition, no significant change was observed when the reaction temperature was decreased to 15 °C (entry 6). Surprisingly, switching to a Pd^0 precatalyst ($Pd_2(dba)_3$) resulted in <5% product formation (entry 7). In contrast, Buchwald's precatalyst, known to form Pd^0 in situ upon heating or adding base,[12] furnished the desired product (**2a**) in 65% yield and 96:4 er (entry 8). These results suggest that the alkyne source (TIPS-EBX) can react with both Pd^0 and Pd^{II}, presumably through oxidative addition and transmetallation mechanisms, respectively. It remains unclear why $Pd_2(dba)_3$ is unable to catalyze this transformation.

In should be noted that in addition to the TIPS protecting group, a range of other groups were also investigated on the benziodoxole derived alkyne reagent. The *tert*-butyldiphenylsilyl variant (TBDPS-EBX) resulted in 61% yield and 95:5 er using the conditions shown in entry 5. Unfortunately, smaller groups such as TBS and phenyl gave significantly lower yields and enantioselectivites presumably due to other competitive processes including homocoupling (see SI for complete details). While this is a limitation, the TIPS protecting group can be easily removed and the resulting terminal alkyne is amenable to many well vetted transforms.

Under the optimized conditions (entry 5), the scope of allylic alkenols was explored (Table 2). In general, the desired alkynyl carbonyl compounds were obtained with moderate to good yields and excellent enantiomeric ratios. The mass

Table 2: Evaluation of disubstituted alkenol substrates.[a]



[a] Each entry represents the isolated yield on 0.20 mmol scale. er values were determined by SFC. [b] 64% yield and 96:4 er on 2.0 mmol scale. [c] 38% yield and 24:76 er when *trans*-**1d** was used. [d] 4.0 equiv of alkenol **1o** were used. [e] Ligand **L1** was used.

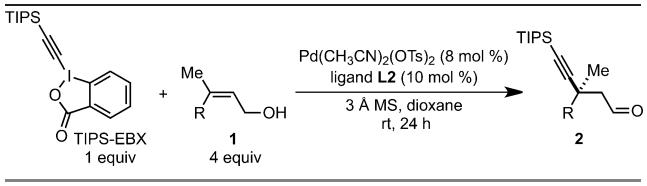
balance in all examples was overall excellent with mainly consumption of the TIPS-EBX reagent to the homocoupling byproduct (**5**, Scheme 1C). Compared with alkenol **1a**, increasing the alkyl chain length at R^1 did not have a significant effect (**2b**, **2c**). Enhancing the size of the substituent at R^1 to a benzyl or cyclohexylmethyl group led to slightly decreased yields (**2d**, **2e**). It should be noted that when *trans*-**1d** was used instead of *cis*-**1d** the yield decreased to 38% with 24:76 er (*ent*-**2d**). Alkenol **1f**, a substrate containing both di- and trisubstituted alkenes, reacted selectively at the less-hindered disubstituted alkene to afford the desired product (**2f**) in 62% yield and 97:3 er. The reaction also tolerates an ester (**1g**), an alcohol (**1h**) and a benzyl ether (**1i**) delivering the corresponding products in good yields and high enantioselectivites. Substrates containing a primary

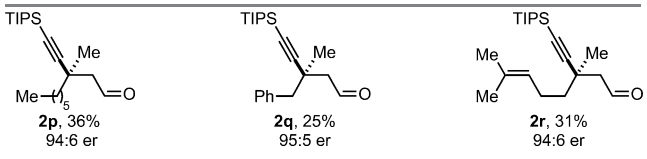
tosylate (**1j**) or primary chloride (**1k**) could also be subjected to the reaction conditions to yield products **2j** and **2k** in 55% yield and 95.5:4.5 er and 60% yield and 97:3 er, respectively. A nitrile group was also well suited under the reaction conditions providing product **2l** in 62% yield and 96.5:3.5 er. Alkenols containing a phthalimide (**1m**) or a sulfide (**1n**) were also viable substrates resulting in a modest reduction in yield of products **2m** and **2n**. Finally, a substrate containing a secondary alcohol (**1o**) furnished ketone product **2o** in 41% yield and 83:17 er. The er of product **2o** could be improved to 94:6 when ligand **L1** was employed. The absolute configuration for product **2d** was determined to be (*R*) through $[\alpha]_D$ comparison with the previously reported (*S*)-compound. All other compounds were assigned by analogy to product **2d**.[8b]

As homoallylic substrates (and longer chain alkenols) have previously been excellent substrates in sp^2 coupling processes, we evaluated these substrates under the reaction conditions. Unfortunately, the reactions delivered low amounts of the desired redox-relay product (< 20% yield). In these cases, the major byproduct was the traditional Heck product. This indicates that β-hydride elimination is not selective when an additional methylene unit is added between the alkene and the alcohol moiety suggestive that the biasing of β-hydride elimination is significantly reduced with the sp-center installed. Likely, a substantial redesign of the system will be required to overcome this limitation.

Given the difficulty associated with the enantioselective formation of propargylic quaternary stereocenters using metal-catalyzed conjugate addition approaches, we sought to extend this methodology to trisubstituted alkenol substrates. Due to the sluggish migratory insertion associated with trisubstituted alkenes,[13] we were cognizant that competitive transmetallation with Pd-alkynyl species **3** (Scheme 1c) would lead to homocoupling byproduct **5**. To increase the relative rate of migratory insertion, four equivalents of alkenol were used. As a result, when a simple alkyl group was positioned at R (**1p**, Table 3), the desired product containing a proparygylic quaternary stereocenter was obtained in 36% yield and 94:6 er (**2p**). The incorporation of a benzyl group at R delivered product **2q** in 25% yield and 95:5 er. Lastly, the presence of an additional trisubstituted alkene was also tolerated furnishing product **2r** in 31% yield and 94:6 er. The lower yields for trisubstituted alkene substrates are attributed to competitive alkyne homocoupling. Efforts to improve the product yield by increasing the relative rate of migratory insertion or slowing the rate of transmetallation have been unsuccessful thus far.

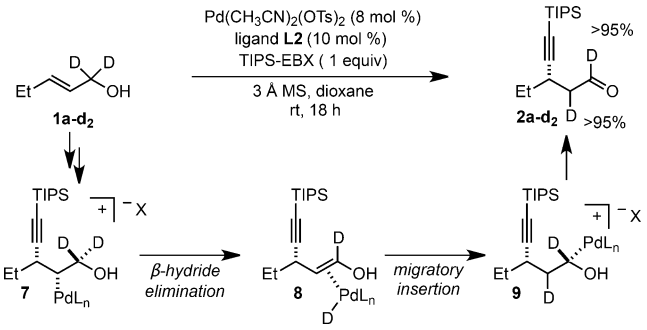
Table 3: Evaluation of trisubstituted alkenol substrates.[a]





[a] Each entry represents the isolated yield on 0.20 mmol scale. er values were determined by SFC.

In order to interrogate the reaction mechanism to determine if Pd migrates toward the alcohol functional group in a similar fashion to our previous reports, deuterated alkenol **1a-d$_2$** was subjected to the optimized Heck alkynylation reaction conditions (Scheme 2). As a result, one



Scheme 2. Deuterium labeling study.

deuterium atom was transposed to the β carbon of the newly formed aldehyde delivering **2a-d$_2$**, in accordance with our previous mechanistic reports. This implies that **1a-d$_2$** undergoes a migratory insertion with the Pd-alkynyl species resulting in Pd-alkyl intermediate **7**. Through selective β-deuteride elimination (**8**) and reinsertion, intermediate **9** is formed resulting in the transposition of one deuterium atom. Furthermore, this suggests if intermediate **9** is formed the reaction terminates through alcohol oxidation and establishment of Pd^0, presumably through β-hydride elimination or an E_2-type elimination. Moreover, since Pd^0 is formed with each catalytic turnover, TIPS-EBX (or TsO-EBX, a possible byproduct of transmetallation) must oxidize Pd^0 back to Pd^{II} in this case.

In summary, we have developed an enantioselective redox-relay Heck alkynylation of disubstituted alkenols in good yields and high enantioselectivity. The β-alkynyl carbonyl compounds obtained using this methodology contain a vast array of functionality. The ability to use allylic alcohol substrates provides a complementary approach to access such products to the more traditional conjugate addition strategies. Finally, promising results using trisubstituted allylic alkenol substrates to access propargylic quaternary stereocenters are provided. Future efforts are aimed at developing ligands and systems that prevent homocoupling of the alkyne to overcome this limitation.

Acknowledgements

The work was supported by the National Institutes of Health (NIGMS R01GM063540). C.S.N. acknowledges the NSF for a graduate research fellowship. Z.-M.C. would like to thank Shanghai Jiao Tong University for a postdoctoral fellowship.

We acknowledge Dr. Nicholas Race for preparation of the deuterated alkenol substrate.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · alkynylation · Heck reaction · propargylic stereocenter

[1] For selected reviews, see: a) R. F. Heck, *Acc. Chem. Res.* **1979**, *12*, 146 – 151; b) G. T. Crisp, *Chem. Soc. Rev.* **1998**, *27*, 427 – 436; c) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009 – 3066; d) M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.* **2004**, *346*, 1533 – 1552; e) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644 – 4680; f) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170 – 1214; g) D. McCartney, P. J. Guiry, *Chem. Soc. Rev.* **2011**, *40*, 5122 – 5150; h) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062 – 5085; *Angew. Chem.* **2012**, *124*, 5150 – 5174.

[2] For selected works, see: a) R. C. Larock, W.-Y. Leung, S. Stolz-Dunn, *Tetrahedron Lett.* **1989**, *30*, 6629 – 6632; b) S. Bouquillon, B. Ganchegui, B. Estrine, F. Hénin, J. Muzart, *J. Organomet. Chem.* **2001**, *634*, 153 – 156; c) F. Berthiol, H. Doucet, M. Santelli, *Tetrahedron* **2006**, *62*, 4372 – 4383; d) C. C. Oliveira, A. Pfaltz, C. R. D. Correia, *Angew. Chem. Int. Ed.* **2015**, *54*, 14036 – 14039; *Angew. Chem.* **2015**, *127*, 14242 – 14245; e) S. Singh, J. Bruffaerts, A. Vasseur, I. Marek, *Nat. Commun.* **2017**, *8*, https://doi.org/10.1002/ncomms14200.

[3] E. W. Werner, T.-S. Mei, A. J. Burckle, M. S. Sigman, *Science* **2012**, *338*, 1455 – 1458.

[4] a) T.-S. Mei, E. W. Werner, A. J. Burckle, M. S. Sigman, *J. Am. Chem. Soc.* **2013**, *135*, 6830 – 6833; b) T.-S. Mei, H. H. Patel, M. S. Sigman, *Nature* **2014**, *508*, 340 – 344; c) C. Zhang, C. B. Santiago, L. Kou, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 7290 – 7293; d) Z.-M. Chen, M. J. Hilton, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 11461 – 11464.

[5] a) H. H. Patel, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 3462 – 3465; b) H. H. Patel, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 14226 – 14229; c) C. Zhang, B. Tutkowski, R. J. DeLuca, L. A. Joyce, O. Wiest, M. S. Sigman, *Chem. Sci.* **2017**, *8*, 2277 – 2282.

[6] For selected works, see: a) D. A. Evans, D. H. B. Ripin, D. P. Halstead, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 6816 – 6826; b) A. Fürstner, D. De Souza, L. Parra-Rapado, J. T. Jensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 5358 – 5360; *Angew. Chem.* **2003**, *115*, 5516 – 5518; c) Y. Yuan, H. Men, C. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 14720 – 14721; d) R. Nakajima, T. Ogino, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2010**, *132*, 1236 – 1237; e) K. Sugimoto, K. Toyoshima, S. Nonaka, K. Kotaki, H. Ueda, H. Tokuyama, *Angew. Chem. Int. Ed.* **2013**, *52*, 7168 – 7171; *Angew. Chem.* **2013**, *125*, 7309 – 7312; f) B. M. Trost, V. Ehmke, *Org. Lett.* **2014**, *16*, 2708 – 2711.

[7] For selected works, see: a) T. F. Knöpfel, P. Zarotti, T. Ichikawa, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 9682 – 9683; b) S. Fujimori, T. F. Knöpfel, P. Zarotti, T. Ichikawa, D. Boyall, E. M. Carreira, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635 – 1657; c) P. Zarotti, T. F. Knöpfel, P. Aschwanden, E. M. Carreira, *ACS Catal.* **2012**, *2*, 1232 – 1234.

[8] For selected works, see: a) T. Nishimura, X.-X. Guo, N. Uchiyama, T. Katoh, T. Hayashi, *J. Am. Chem. Soc.* **2008**, *130*, 1576 – 1577; b) T. Nishimura, T. Sawano, T. Hayashi, *Angew. Chem. Int. Ed.* **2009**, *48*, 8057 – 8059; *Angew. Chem.* **2009**, *121*, 8201 – 8203; c) X. Dou, Y. Huang, T. Hayashi, *Angew. Chem. Int. Ed.* **2016**, *55*, 1133 – 1137; *Angew. Chem.* **2016**, *128*, 1145 – 1149.

[9] For selected works, see: a) E. Fillion, A. K. Zorzitto, *J. Am. Chem. Soc.* **2009**, *131*, 14608 – 14609; b) S. Cui, S. D. Walker, J. C. S. Woo, C. J. Borths, H. Mukherjee, M. J. Chen, M. M. Faul, *J. Am. Chem. Soc.* **2010**, *132*, 436 – 437; c) R. Yazaki, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 10275 – 10277; d) O. V. Larionov, E. J. Corey, *Org. Lett.* **2010**, *12*, 300 – 302; e) B. M. Trost, B. R. Taft, J. T. Masters, J.-P. Lumb, *J. Am. Chem. Soc.* **2011**, *133*, 8502 – 8505; f) G. Blay, L. Cardona, J. R. Pedro, A. Sanz-Marco, *Chem. Eur. J.* **2012**, *18*, 12966 – 12969; g) A. Sanz-Marco, A. García-Ortiz, G. Blay, I. Fernández, J. R. Pedro, *Chem. Eur. J.* **2014**, *20*, 668 – 672; h) A. Sanz-Marco, A. García-Ortiz, G. Blay, J. R. Pedro, *Chem. Commun.* **2014**, *50*, 2275 – 2278.

[10] A. Sanz-Marco, G. Blay, C. Vila, J. R. Pedro, *Org. Lett.* **2016**, *18*, 3538 – 3541.

[11] For selected reviews, see: a) Y. Li, D. P. Hari, M. V. Vita, J. Waser, *Angew. Chem. Int. Ed.* **2016**, *55*, 4436 – 4454; *Angew. Chem.* **2016**, *128*, 4512 – 4531; b) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299 – 5358; For selected works, see: c) F. Le Vaillant, T. Courant, J. Waser, *Angew. Chem. Int. Ed.* **2015**, *54*, 11200 – 11204; *Angew. Chem.* **2015**, *127*, 11352 – 11356; d) S. Nicolai, C. Piemontesi, J. Waser, *Angew. Chem. Int. Ed.* **2011**, *50*, 4680 – 4683; *Angew. Chem.* **2011**, *123*, 4776 – 4779.

[12] For selected works, see: a) N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916 – 920; b) N. C. Bruno, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 2876 – 2879; c) T. D. Senecal, W. Shu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 10035 – 10039; *Angew. Chem.* **2013**, *125*, 10219 – 10223.

[13] M. J. Hilton, B. Cheng, B. R. Buckley, L. Xu, O. Wiest, M. S. Sigman, *Tetrahedron* **2015**, *71*, 6513 – 6518.

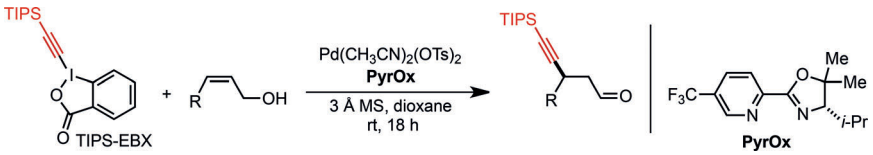
Manuscript received: March 24, 2017
Final Article published: ■■ ■■, ■■■■

Communications

C–C Coupling

Z.-M. Chen, C. S. Nervig, R. J. DeLuca, M. S. Sigman* ——— ■■■■–■■■■

Palladium-Catalyzed Enantioselective Redox-Relay Heck Alkynylation of Alkenols to Access Propargylic Stereocenters



Heck alkynylation: A convenient redox-relay Heck strategy to synthesize enantiomerically enriched β-alkynyl carbonyl compounds from allylic alcohols with high functional group tolerance is described. Trisubstituted allylic alcohols are also promising substrates allowing for the formation of propargylic quaternary stereocenters.