HHS Public Access
Author manuscript
Angew Chem Int Ed Engl. Author manuscript; available in PMC 2017 July 26.

Published in final edited form as:
Angew Chem Int Ed Engl. 2017 June 01; 56(23): 6651–6654. doi:10.1002/anie.201703089.

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

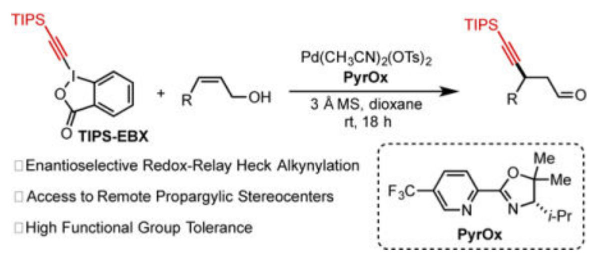
Dr. Zhi-Min Chen, **Christine S. Nervig**, **Dr. Ryan J. DeLuca**, and **Prof. Matthew S. Sigman**
Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112 (USA)

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.

Graphical abstract

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



Keywords

Heck reaction; alkenes; propargylic stereocenter; alkynylation

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

Correspondence to: Matthew S. Sigman.

Supporting information for this article can be found under: http://dx.doi.org/

Conflict of interest
The authors declare no conflict of interest.

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 1A). 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 1B). 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 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 1C), 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-oxazoline ligand (PyrOx, **ligand 1**), 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 (**ligand 1**) on the PyrOx ligand with an *i*-Pr group and adding a *gem*-dimethyl moiety on the oxazoline portion (**ligand 2**) 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. 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 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 1** 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.

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. As a result, one 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The work was supported by National Institute 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.

References

1. For selected reviews, see:a) Heck RF. Acc Chem Res. 1979; 12:146–151.b) Crisp GT. Chem Soc Rev. 1998; 27:427–436.c) Beletskaya IP, Cheprakov AV. Chem Rev. 2000; 100:3009–3066. [PubMed: 11749313] d) Shibasaki M, Vogl EM, Ohshima T. Adv Synth Catal. 2004; 346:1533–1552.e) Zeni G, Larock RC. Chem Rev. 2006; 106:4644–4680. [PubMed: 17091931] f) Le Bras J, Muzart J. Chem Rev. 2011; 111:1170–1214. [PubMed: 21391560] g) McCartney D, Guiry PJ. Chem Soc Rev. 2011; 40:5122–5150. [PubMed: 21677934] h) Seechurn CCCJ, Kitching MO, Colacot TJ, Snieckus V. Angew Chem. 2012; 124:5150–5174.Angew Chem Int Ed. 2012; 51:5062–5085.

2. For selected works, see:a) Larock RC, Leung WY, Stolz-Dunn S. Tetrahedron Lett. 1989; 30:6629–6632.b) Bouquillon S, Ganchegui B, Estrine B, Hénin F, Muzart J. J Organomet Chem. 2001; 634:153–156.c) Berthiol F, Doucet H, Santelli M. Tetrahedron. 2006; 62:4372–4383.d) Oliveira CC, Pfaltz A, Correia CRD. Angew Chem. 2015; 127:14242–14245.Angew Chem Int Ed. 2015; 54:14036–14039.e) Singh S, Bruffaerts J, Vasseur A, Marek I. Nat Commun. 2017; 8doi: 10.1038/ncomms14200

3. Werner EW, Mei TS, Burckle AJ, Sigman MS. Science. 2012; 338:1455–1458. [PubMed: 23239733]

4. a) Mei TS, Werner EW, Burckle AJ, Sigman MS. J Am Chem Soc. 2013; 135:6830–6833. [PubMed: 23607624] b) Mei TS, Patel HH, Sigman MS. Nature. 2014; 508:340–344. [PubMed: 24717439] c) Zhang C, Santiago CB, Kou L, Sigman MS. J Am Chem Soc. 2015; 137:7290–7293. [PubMed: 26030059] d) Chen ZM, Hilton MJ, Sigman MS. J Am Chem Soc. 2016; 138:11461–11464. [PubMed: 27571167]

5. a) Patel HH, Sigman MS. J Am Chem Soc. 2015; 137:3462–3465. [PubMed: 25738548] b) Patel HH, Sigman MS. J Am Chem Soc. 2016; 138:14226–14229. [PubMed: 27768842] c) Zhang C, Tutkowski B, DeLuca RJ, Joyce LA, Wiest O, Sigman MS. Chem Sci. 2017; 8:2277–2282. [PubMed: 28435657]

6. For selected works, see:a) Evans DA, Ripin DHB, Halstead DP, Campos KR. J Am Chem Soc. 1999; 121:6816–6826.b) Fürstner A, De Souza D, Parra-Rapado L, Jensen JT. Angew Chem. 2003; 115:5516–5518.Angew Chem Int Ed. 2003; 42:5358–5360.c) Yuan Y, Men H, Lee C. J Am Chem Soc. 2004; 126:14720–14721. [PubMed: 15535687] d) Nakajima R, Ogino T, Yokoshima S, Fukuyama T. J Am Chem Soc. 2010; 132:1236–1237. [PubMed: 20055392] e) Sugimoto K, Toyoshima K, Nonaka S, Kotaki K, Ueda H, Tokuyama H. Angew Chem. 2013; 125:7309–7312.Angew Chem Int Ed. 2013; 52:7168–7171.f) Trost BM, Ehmke V. Org Lett. 2014; 16:2708–2711. [PubMed: 24787546]

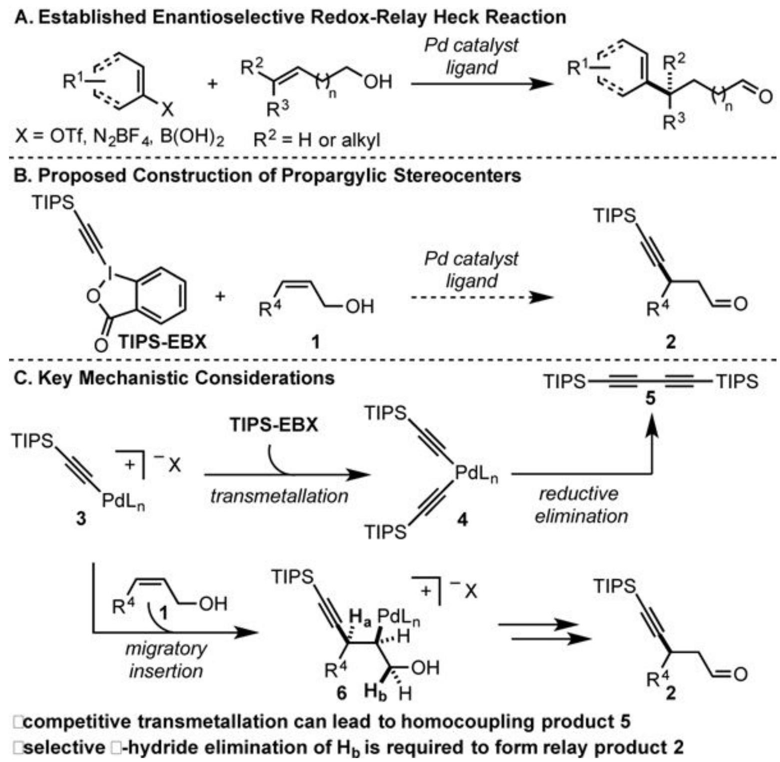
7. For selected works, see:a) Knöpfel TF, Zarotti P, Ichikawa T, Carreira EM. J Am Chem Soc. 2005; 127:9682–9683. [PubMed: 15998061] b) Fujimori S, Knöpfel TF, Zarotti P, Ichikawa T, Boyall D, Carreira EM. Bull Chem Soc Jpn. 2007; 80:1635–1657.c) Zarotti P, Knöpfel TF, Aschwanden P, Carreira EM. ACS Catal. 2012; 2:1232–1234.

8. For selected works, see:a) Nishimura T, Guo XX, Uchiyama N, Katoh T, Hayashi T. J Am Chem Soc. 2008; 130:1576–1577. [PubMed: 18197670] b) Nishimura T, Sawano T, Hayashi T. Angew Chem. 2009; 121:8201–8203.Angew Chem Int Ed. 2009; 48:8057–8059.c) Dou X, Huang Y, Hayashi T. Angew Chem. 2016; 128:1145–1149.Angew Chem Int Ed. 2016; 55:1133–1137.

9. For selected works, see:a) Fillion E, Zorzitto AK. J Am Chem Soc. 2009; 131:14608–14609. [PubMed: 19824719] b) Cui S, Walker SD, Woo JCS, Borths CJ, Mukherjee H, Chen MJ, Faul MM. J Am Chem Soc. 2010; 132:436–437. [PubMed: 20020682] c) Yazaki R, Kumagai N, Shibasaki M. J Am Chem Soc. 2010; 132:10275–10277. [PubMed: 20662511] d) Larionov OV, Corey EJ. Org Lett. 2010; 12:300–302. [PubMed: 20000753] e) Trost BM, Taft BR, Masters JT, Lumb JP. J Am Chem Soc. 2011; 133:8502–8505. [PubMed: 21557627] f) Blay G, Cardona L, Pedro JR, Sanz-Marco A. Chem Eur J. 2012; 18:12966–12969. [PubMed: 22936365] g) Sanz-

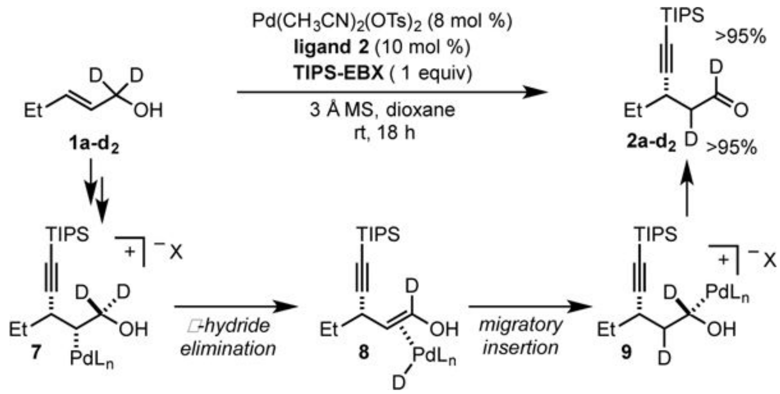
Marco A, García-Ortiz A, Blay G, Fernández I, Pedro JR. Chem Eur J. 2014; 20:668–672. [PubMed: 24339326] h) Sanz-Marco A, García-Ortiz A, Blay G, Pedro JR. Chem Commun. 2014; 50:2275–2278.

10. Sanz-Marco A, Blay G, Vila C, Pedro JR. Org Lett. 2016; 18:3538–3541. [PubMed: 27417872]
11. For selected reviews, see:a) Li Y, Hari DP, Vita MV, Waser J. Angew Chem. 2016; 128:4512–4531.Angew Chem, Int Ed. 2016; 55:4436–4454.b) Zhdankin VV, Stang PJ. Chem Rev. 2008; 108:5299–5358. [PubMed: 18986207] For selected works, see:c) Le Vaillant F, Courant T, Waser J. Angew Chem. 2015; 127:11352–11356.Angew Chem Int Ed. 2015; 54:11200–11204.d) Nicolai S, Piemontesi C, Waser J. Angew Chem. 2011; 123:4776–4779.Angew Chem, Int Ed. 2011; 50:4680–4683.
12. For selected works, see:a) Bruno NC, Tudge MT, Buchwald SL. Chem Sci. 2013; 4:916–920. [PubMed: 23667737] b) Bruno NC, Buchwald SL. Org Lett. 2013; 15:2876–2879. [PubMed: 23675976] c) Senecal TD, Shu W, Buchwald SL. Angew Chem. 2013; 125:10219–10223.Angew Chem Int Ed. 2013; 52:10035–10039.
13. Hilton MJ, Cheng B, Buckley BR, Xu L, Wiest O, Sigman MS. Tetrahedron. 2015; 71:6513–6518. [PubMed: 26392640]



Scheme 1.

Proposed redox-relay Heck alkynylation to access propargylic stereocenters.

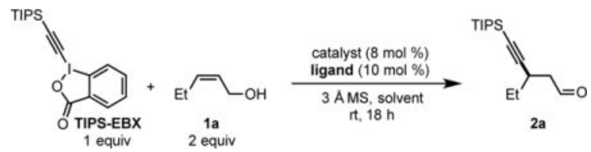


Scheme 2.

Deuterium Labeling Study.

Table 1

Reaction Optimization[a]

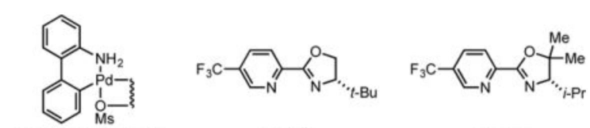


entry	catalyst	ligand	solvent	% yield	er
1	$Pd(CH_3CN)_2(OTs)_2$	ligand 1	CH_2Cl_2	40	98:2
2	$Pd(CH_3CN)_2(OTs)_2$	ligand 1	THF	48	92:8
3	$Pd(CH_3CN)_2(OTs)_2$	ligand 1	EtOAc	42	91:9
4	$Pd(CH_3CN)_2(OTs)_2$	ligand 1	dioxane	60	97:3
5	$Pd(CH_3CN)_2(OTs)_2$	ligand 2	dioxane	65	96.5:3.5
6[b]	$Pd(CH_3CN)_2(OTs)_2$	ligand 2	dioxane	63	96.5:3.5
7[c]	$Pd_2(dba)_3$	ligand 2	dioxane	<5	–
8[d]	Buchwald precatalyst	ligand 2	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.

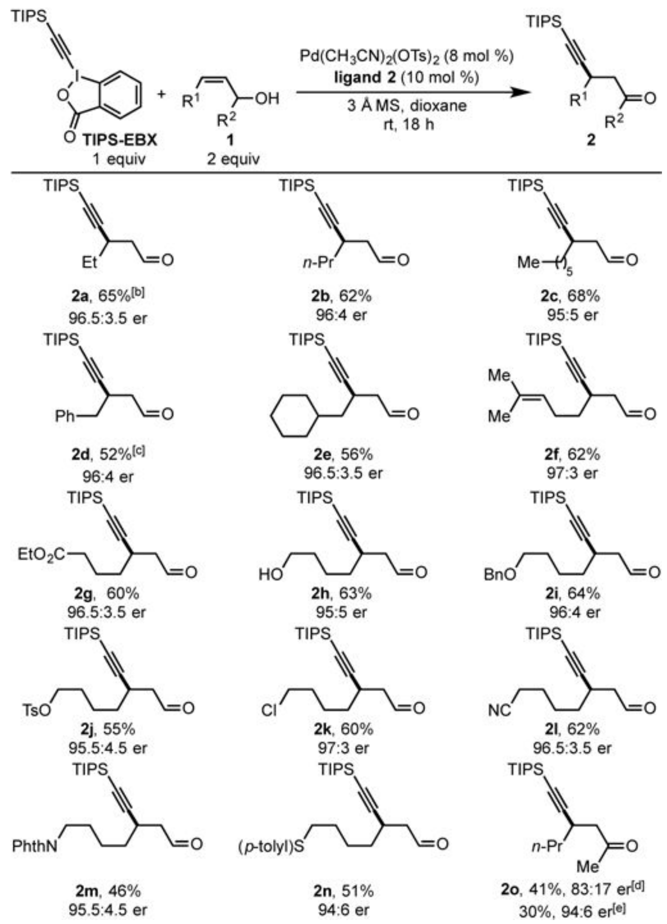
[c]4 mol % catalyst was used. The Buchwald precatalyst (4 mol %) was heated to 80 °C for 10 min prior use to generate Pd(0) and TsOH (25 mol %) was added.



Buchwald precatalyst ligand 1 ligand 2

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.

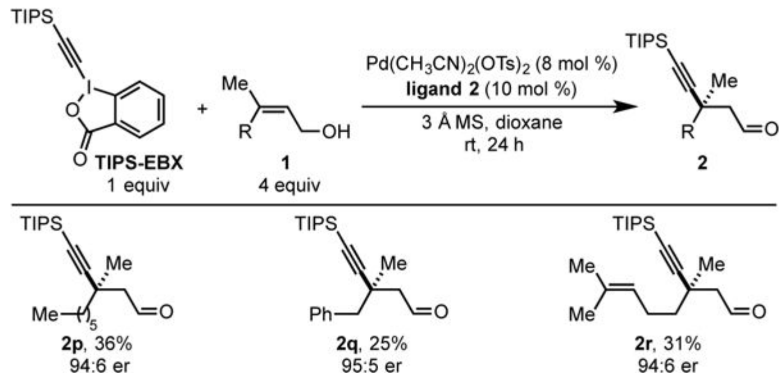
[b]64% yield and 96:4 er on 2.0 mmol scale.

[c]38% yield and 24:76 er when *trans*-**1d** was used.

[d]4.0 equiv of alkenol **1o** was used. [e] **Ligand 1** was used.

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.