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Palladium-Catalyzed Alkyne Insertion/ Reduction Route to Trisubstituted Olefins

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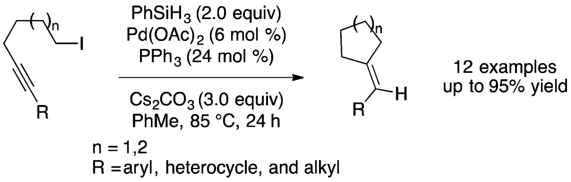
ABSTRACT



A new route to trisubstituted olefins through a palladium-catalyzed alkyne insertion/reduction reaction with unactivated alkyl iodides is reported. The reaction proceeds under mild conditions and tolerates a range of functional groups and substitution patterns. Preliminary mechanistic inquiry suggests that the transformation may proceed through a hybrid radical/organometallic pathway.

Aryl and vinyl halides account for the vast majority of electrophiles employed in palladium-catalyzed cross-coupling reactions.[1] However, the use of alkyl halides as electrophiles in these reactions is relatively rare.[2] The rarity of these reactions stems in part from the difficulty of preventing the facile β-hydride elimination inherent to alkyl palladium species.[3] The alkyl-Heck reaction, where an olefin undergoes migratory insertion into an alkyl palladium species, remains relatively underdeveloped, but the reaction offers an attractive method to functionalize alkenes.

The synthetic potential of the alkyl-Heck reaction has motivated researchers to explore the reaction in greater detail. For example, Fu et al. reported a successful alkyl-Heck reaction using alkyl bromides and chlorides as electrophiles.[2a] The reaction was made possible by controlling the rate of β-hydride elimination relative to migratory insertion of the pendant olefin. The use of the N-heterocyclic carbene ligand SIMes was critical to the success of this reaction, presumably due to the disruption of β-agostic interactions by the sterically encumbered ligand. The authors propose an S_N2 oxidative addition based on a deuterium-labeling study that revealed inversion of stereochemistry at the carbon site of oxidative addition. A later iteration of an alkyl-Heck-type reaction by Alexanian et al. demonstrated a significantly broader substrate scope for primary iodide substrates (Figure 1b).[2b]

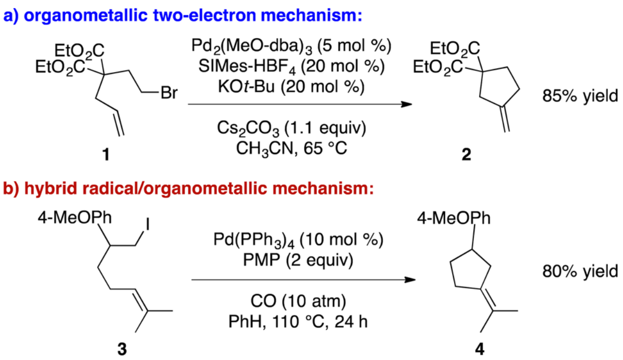


Figure 1. Palladium-catalyzed (a) alkyl-Heck reaction with unactivated alkyl bromide and (b) Heck-type reaction with unactivated alkyl iodide.

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[1] Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.

[2] For recent examples, see: (a) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340–11341. (b) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146–20148. (c) Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 15297–15300. For relevant reviews, see: (d) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656–2670. (e) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688.

[3] (a) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457. (b) Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626. (c) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333. (d) Bissember, A. C.; Levina, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 14232–14237.

10.1021/ol4018694

Interestingly, the authors provide evidence for a hybrid radical/organometallic process under tetrakis(triphenylphosphine)palladium(0) catalysis.

The relative scarcity of reactions reported for alkyl palladium species, along with our interest in discovering fundamental organometallic processes with rates comparable or faster than β-hydride elimination,[4] inspired our group to investigate the migratory insertion of alkynes. These studies led to the recently reported tandem alkyne insertion/Suzuki reaction of unactivated iodides.[2c] Initial work on the alkyne insertion/Suzuki reaction revealed the formation of trisubstituted olefin **8** in 7% yield (Figure 2).[2c] The formation of **8** offers a unique palladium-catalyzed route to trisubstituted olefins.[5] Since such exocyclic trisubstituted olefins represent important structural motifs in natural products,[6] we sought to optimize conditions favorable for its formation. Here we offer a new approach to trisubstituted olefins through a tandem alkyne insertion/reduction reaction.

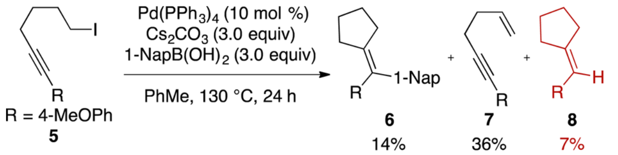
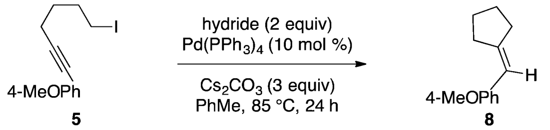


Figure 2. Unoptimized reaction conditions for an alkyne insertion/Suzuki reaction provides trisubstituted olefin **8** as a side product.

While all the pertinent reaction parameters were examined during the course of optimization (see Supporting Information (SI)), the hydride source had the most significant impact on the formation of trisubstituted olefin product **8** (Table 1). When the reaction was conducted in the presence of sodium formate, the desired trisubstituted olefin **8** was obtained in 35% yield (entry 1, Table 1). Interestingly, there was little difference in yield between a strong hydride donor ($NaBH_4$) or hydrogen atom donor n-Bu_3SnH, both providing a 29% yield (entries 3–4, Table 1). Tertiary amines also functioned as hydride donors. For example, proton sponge produced the desired product in 25% yield (entry 5, Table 1).[7] However, silanes proved the most effective in the formation of desired trisubstituted olefin **8**, with phenylsilane providing the highest yield at 77% (entry 8, Table 1). Further substitution of the silane, such as diphenylsilane and triphenylsilane, provided lower yields (entries 6–7, Table 1).

Table 1. A Sample of Hydrides Employed in the Formation of Trisubstituted Olefin **8**



entry	hydride	conv (%)	yield (%)[a]
1	NaO_2CH	100	35
2	Hantzsch ester	100	23
3	$NaBH_4$	100	29
4	n-Bu_3SnH	100	29
5	proton sponge	50	25
6	Ph_3SiH	51	8
7	Ph_2SiH_2	100	62
8	$PhSiH_3$	100	77

[a] Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

To ascertain the scope of the reaction, a variety of alkynyl iodide substrates were prepared and subjected to the optimized conditions (Table 2). When aryl alkynes were employed, both electron-rich and electron-deficient aryl substituents provided high yields (entries 1–8 and 12, Table 2). Furthermore, the reaction proceeds on > 700 mg scale (2.3 mmol) with comparable yield (84% isolated yield of **8**, 90% BORSM, see SI). While alkyl substituted alkynes generally performed well in the reaction (entries 9 and 11, Table 2), the sterically encumbered *tert*-butyl alkyne **25** only provided product **26** in 50% yield (entry 10, Table 2). Heterocycle-substituted alkynes such as thiophene **17** and quinoline **19** provided trisubstituted olefins **18** and **20** in 71% and 78% yield, respectively (entries 6 and 7, Table 2). Since the formation of six-membered rings is rare in palladium-catalyzed alkyl-Heck-type reactions,[2a,b] we were pleased when substrate **21** formed trisubstituted olefin **22** in 61% yield (entry 8, Table 2). Since migratory insertion proceeds through a *syn* addition to an alkyne,[8] the formation of product **30** in a 1:3 ratio of E/Z isomers came as a surprise (entry 12, Table 2).

The lack of stereospecificity for the presumptive migratory insertion step of the reaction raises an interesting question with regard to the mechanism of isomerization. Recent work by Lipshutz et al. demonstrates that vinyl palladium species can isomerize through a proposed palladium carbene intermediate.[9] If such an isomerization pathway is operable here (Scheme 1a), then vinyl palladium species **31** could isomerize to vinyl palladium **34**. This isomerization would occur through the formation of palladium carbene **32**, which allows for a bond rotation event

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(4) Gao, P.; Cook, S. P. *Org. Lett.* **2012**, *14*, 3340–3343.

(5) For examples of tin-based reductions of alkynes to form trisubstituted olefins, see: (a) Chatgilialoglu, C.; Ferreri, C. *Chem. Triple-Bonded Funct. Groups* **1994**, 917–944. (b) Martinez-Grau, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 5679–5698. (c) Curran, D. P. *Synthesis* **1988**, *7*, 489–513. For an example of a nickel-catalyzed reduction to form trisubstituted olefins, see: (d) Kim, H.; Lee, C. *Org. Lett.* **2011**, *13*, 2050–2053.

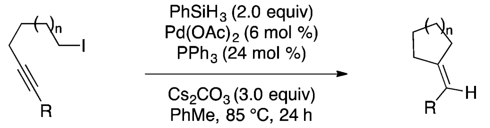
(6) Sassa, T.; Zhang, C.-S.; Sato, M.; Tajima, N.; Kato, N.; Mori, A. *Tetrahedron Lett.* **2000**, *41*, 2401–2404.

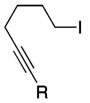
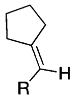
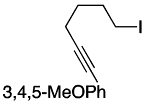
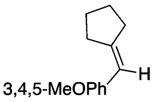
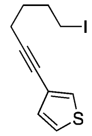
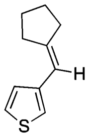
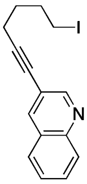
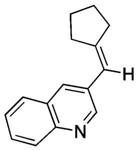
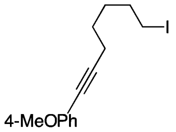
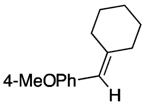
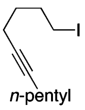
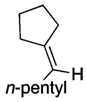
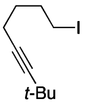
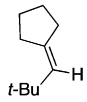
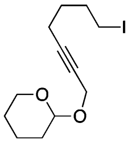
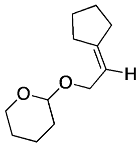
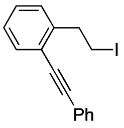
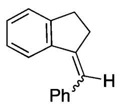
(7) Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 9253–9258.

(8) (a) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; Murdzek, J., Eds.; University Science Books: Mill Valley, CA, 2010; p 379. (b) Thorn, D. L.; Hoffman, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079–2090.

(9) (a) Krasovskiy, A.; Lipshutz, B. H. *Org. Lett.* **2011**, *13*, 3818–3821. (b) Lu, G.-P.; Voigtritter, K. R.; Cai, C.; Lipshutz, B. H. *J. Org. Chem.* **2012**, *77*, 3700–3703. (c) Lu, G.-P.; Voigtritter, K. R.; Cai, C.; Lipshutz, B. H. *Chem. Commun.* **2012**, *48*, 8661.

Table 2. Substrate Scope of Alkyl Iodides

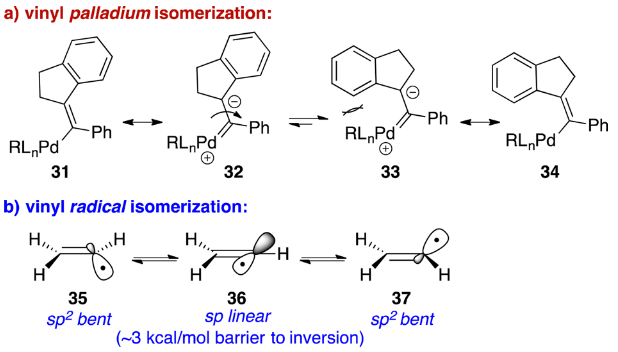


entry	substrate	product	yield (%)[a]
1	R = 4-MeOPh **5** 	 **8**	95 (89)
2	= Ph **9**	**10**	76 (70)
3	= 4-Me$_2$NPh **11**	**12**	81 (50)
4	= 4-CF$_3$Ph **13**	**14**	67 (63)
5	 **15**	 **16**	85 (79)
6	 **17**	 **18**	71 (64)
7	 **19**	 **20**	78 (71)
8	 **21**	 **22**	61 (55)
9	 **23**	 **24**	81 (ND)[b]
10	 **25**	 **26**	50 (ND)[b]
11	 **27**	 **28**	63 (53)
12	 **29**	 **30**	90 (87)[c]

[a] Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard; isolated yields in parentheses. [b] The low boiling product was isolated as a mixture with hexanes. [c] The product produced was a 1:3 *E*/*Z* mixture of stereoisomers.

to form carbene isomer **33**. Palladium carbene **33** could then isomerize to vinyl palladium **34**, which eventually forms the *E* trisubstituted olefin. According to this mechanism, both the electronic and steric properties of the phosphine ligands on palladium should have an influence on the *E*/*Z* ratio. For example, electron-deficient phosphines would likely destabilize the formally cationic palladium carbene **32**, thereby preventing isomerization and favoring formation of the *Z* isomer. Conversely, electron-rich phosphines would stabilize cationic palladium carbenes **32** and **33** and allow *Z* to *E* isomerization. If palladium carbenes **32** and **33** establish an equilibrium, the K_{eq} will depend on the relative steric repulsion between ligated palladium and the phenyl substituent.

Scheme 1. Potential Mechanisms for Olefin Isomerization: (a) Vinyl Palladium Isomerization and (b) Vinyl Radical Isomerization



To examine the role of the ligand in isomerization, several isosteric aryl phosphines with varying degrees of σ donicity were examined for their effects on *E*/*Z* product ratios (Table 3). Interestingly, both electron-rich and -deficient triaryl phosphines produced identical 1:3 *E*/*Z* ratios (entries 1–5, Table 3).

Next the steric properties of the ligand were evaluated for their effect on selectivity. Isomerization to the *E* isomer should be disfavored by phosphines with larger cone or bite angles due to steric interactions between the bulky phosphine and the aryl substituent fused to the five-membered ring **33** (Figure 2a). However, while triphenylphosphine (cone angle = 145°) provided an *E*/*Z* ratio of 1:3, the use of tri-*o*-tolylphosphine (cone angle = 194°) produced product **30** in only an *E*/*Z* ratio of 1:4 (entries 1 and 6, Table 3).[10] Furthermore, the ratio did not improve by increasing the cone angle to 212° with the use of trimesitylphosphine (entry 7, Table 3).[10] Bidentate ligands dppe and dppf, with bite angles of 78.1° and 99.1°, respectively, also provided the products in a 1:3 *E*/*Z* ratio (entries 8–9, Table 3).[11] These results indicate that either the palladium carbene isomerization pathway is inoperable under our conditions or the phosphine ligand is likely not influencing the isomerization event.

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(11) Kranenburg, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1998**, 25–27.

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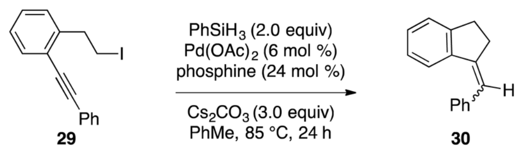
Table 3. Variation in Electronic and Steric Properties of the Phosphine

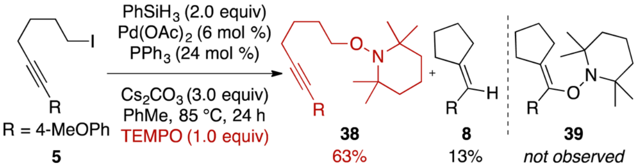


entry	phosphine	E/Z	yield (%)[a]
1	PPh_3	1:3	84
2	$(4\text{-}MeOPh)_3P$	1:3	85
3	$(4\text{-}MePh)_3P$	1:3	84
4	$(4\text{-}CF_3Ph)_3P$	1:3	86
5	$(4\text{-}FPh)_3P$	1:3	90
6	$(o\text{-}tol)_3P$	1:4	87
7	$(mes)_3P$	1:4	85
8	dppe	1:3	70
9	dppf	1:3	70

[a] Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Since vinylic radicals have a low barrier to inversion (Scheme 1b),[12] a free-radical mechanism could explain the lack of stereospecificity in the reaction. To test for the intermediacy of radicals, the radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was included with the optimized conditions (Scheme 2).[13] Interestingly, the reaction produced primary TEMPO product **38** in 63% yield along with trisubstituted olefin **8** in 13% yield (Scheme 2). A completely free-radical mechanism would predict the formation of primary TEMPO product **38** since the rate of intramolecular primary radical addition to an alkyne (10^4–10^5 M^{-1} s^{-1})[14] is slower than the rate of recombination with TEMPO (10^9 M^{-1} s^{-1}).[15] The formation of trisubstituted olefin **8** would suggest that radical recombination with phenylsilane is faster than with TEMPO. This is surprising since the rate constant for hydrogen atom abstraction from phenylsilane by a *tert*-butoxyl radical is on the order of 10^7 M^{-1} s^{-1},[16] thereby implying hydrogen atom abstraction by a vinylic radical is significantly faster than the *tert*-butoxyl radical. However, since TEMPO can react with palladium hydrides to form palladium radicals,[17] this result may not be relevant to the optimized reaction conditions. Furthermore, BHT, an efficient radical inhibitor, has no effect on the yield when included under the optimized reaction conditions. Moreover, the rate appears linear throughout the course of the reaction (i.e., no induction period indicative of radicals), and no dimeric products from radical termination were observed. Consequently, a completely free-radical mechanism appears unlikely, and the hybrid radical/organometallic mechanism (presumably via Pd(I) species)[18] remains consistent with these results.

Scheme 2. TEMPO Reacts with the Substrate under the Optimized Reaction Conditions



In summary, we have developed a palladium-catalyzed alkyne/insertion reduction reaction of alkyl iodides for the production of trisubstituted olefins. The reaction proceeds under mild conditions and tolerates a range of functional groups. While additional mechanistic studies are needed, the reaction may be operating through a hybrid radical/organometallic mechanism. Further experiments to examine these mechanistic possibilities are currently underway.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.