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Palladium-Catalyzed Alkyne Insertion/Suzuki Reaction of Alkyl Iodides

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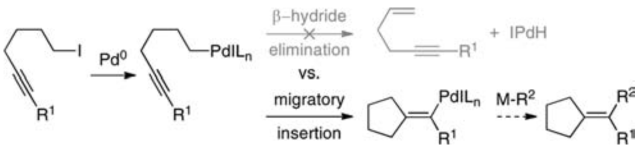
Supporting Information

ABSTRACT: A palladium-catalyzed alkyne insertion/Suzuki reaction with unactivated alkyl iodides is described. Under the reaction conditions, selective migratory insertion of alkynes avoids *β*-hydride elimination and provides a facile synthesis of stereodefined, tetrasubstituted olefins. The transformation offers broad substrate scope for both the alkyl iodide and boron nucleophile. Mechanistic studies have revealed inversion of the stereocenter for the carbon bearing the iodide.

Palladium-catalyzed Csp^2−Csp^2 cross-coupling reactions have had a transformative impact on the field of organic chemistry.[1] They have found widespread use in total synthesis[2] and represent the most important carbon−carbon bond-forming reaction in medicinal chemistry.[3] In contrast, Csp^3−Csp^2 cross-coupling reactions involving Csp^3−halide electrophiles remain rare.[4] When such electrophiles are employed, the cross-couplings suffer from slow oxidative addition and the potential for *β*-hydride elimination of intermediate alkylpalladium species.[5] Identification of fundamental organometallic processes that proceed with rates comparable to *β*-hydride elimination allows the incorporation of complexity-building transformations into Csp^3 cross-couplings. As such, our group has initiated a program aimed at intercepting alkylpalladium intermediates prior to *β*-hydride elimination.[6] Here we describe the migratory insertion of internal alkynes into Csp^3−palladium intermediates, providing straightforward access to tetrasubstituted olefins.

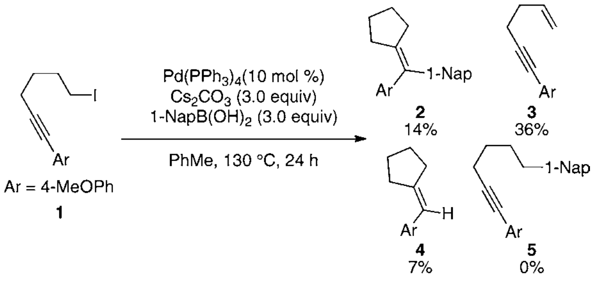
Previous pioneering work has established migratory insertion as an alternative mechanistic pathway to *β*-hydride elimination for alkylpalladium species. For example, carbon monoxide undergoes rapid migratory insertion into alkylpalladium species en route to a carbonylative Heck reaction.[7] Additionally, migratory insertion of olefins into alkylpalladium intermediates has been shown to produce a viable alkyl-Heck reaction.[8] However, the reaction conditions that facilitated olefin insertion required sterically encumbered N-heterocyclic carbenes as ligands or elevated temperatures (110−130 °C). Since alkynes have been reported to insert more rapidly than olefins into acylpalladium bonds,[9] we reasoned a tethered alkyne might be used to intercept a transient alkylpalladium species prior to *β*-hydride elimination (Scheme 1). Following migratory insertion of the alkyne, a new vinyl carbopalladium intermediate would provide an opportunity for an additional cross-coupling reaction. Such a process would allow for the regioselective synthesis of tetrasubstituted olefins, known to be challenging targets for organic synthesis.[10]

Scheme 1. Alkyne Migratory Insertion as an Alternative Reaction Pathway to *β*-Hydride Elimination in Alkylpalladium Species



To test the viability of the cascade alkyne insertion/cross-coupling reaction, alkyl iodide **1** was subjected to 10 mol % $Pd(PPh_3)_4$, Cs_2CO_3, and 1-napthalene boronic acid at 130 °C in toluene (Scheme 2). Gratifyingly, tetrasubstituted olefin **2** was formed in 14% yield along with two expected side products, terminal olefin **3** (36% yield) and trisubstituted olefin **4** (7% yield). The direct Suzuki cross-coupled product **5** was not observed.[4d,11] Similar tetrasubstituted olefins would be inaccessible using conventional olefination strategies[12] or alternative palladium-catalyzed reactions.[13]

Scheme 2. Initial Result for Novel Alkyne Insertion/Suzuki Reaction



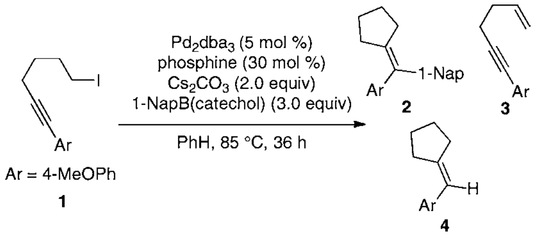
Following this initial result, we continued with optimization efforts to suppress the formation of side products **3** and **4** (see SI for additional details). Lowering the reaction temperature and reducing the amount of Cs_2CO_3 combined to inhibit the *β*-hydride elimination pathway leading to terminal olefin **3**. Identifying the hydride source required for the formation of trisubstituted olefin **4** proved difficult, but changing the solvent from toluene to benzene at 85 °C dramatically reduced the amount of **4**, while the addition of exogenous water had little

Received: August 5, 2012
Published: September 7, 2012

effect on the product distribution. Furthermore, the use of $Pd_2(dba)_3$ (commercial or freshly prepared)[14] and exogenous triphenylphosphine led to higher yields than freshly prepared $Pd(PPh_3)_4$, with optimal reaction rates obtained with a palladium:phosphine ratio of 1:3. Appropriate control reactions excluding palladium, phosphine, Cs_2CO_3, and aryl nucleophile resulted in little to no desired tetrasubstituted olefin **2**.

Further examination of ligands revealed electron-rich arylphosphines, such as $P(4\text{-}MePh)_3$ and $P(4\text{-}MeOPh)_3$, increased the overall reaction rate but compromised the yield of tetrasubstituted olefin **2** (entries 1 and 2, Table 1). More sterically encumbered, electron-rich alkylphosphines, such as $P(t\text{-}Bu)_3$ or $P(t\text{-}Bu)_2Me$, led to fast consumption of starting iodide **1** without the formation of an appreciable amount of tetrasubstituted olefin **2**, even at lower temperatures. On the other hand, electron-deficient arylphosphines such as $P(4\text{-}ClPh)_3$, $P(4\text{-}FPh)_3$, and $P(4\text{-}CF_3Ph)_3$ afforded both slower reaction rates and higher yields of desired tetrasubstituted olefin **2** (entries 4–6, Table 1). Of these, $P(4\text{-}ClPh)_3$ provided the highest conversion and yield, thereby making it the preferred ligand for this palladium-mediated cascade reaction.

Table 1. Electronic Effects of the Phosphine Ligand[a]

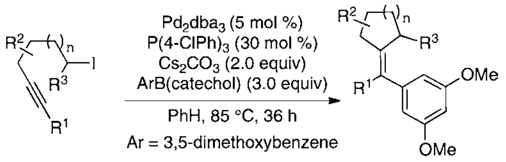


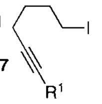
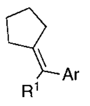
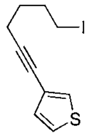
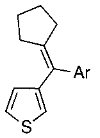
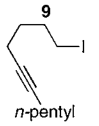
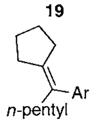
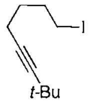
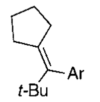
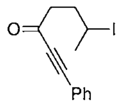
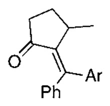
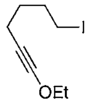
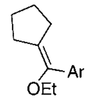
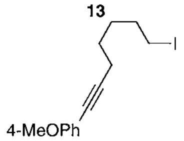
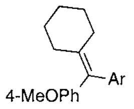
entry	phosphine	conv (%)	yield (%)		
			2	3	4
1	$P(4\text{-}MePh)_3$	100	74	6	12
2	$P(4\text{-}MeOPh)_3$	100	76	7	11
3	PPh_3	100	81	3	10
4	$P(4\text{-}FPh)_3$	95	84	2	8
5	$P(4\text{-}CF_3Ph)_3$	87	76	0	6
6	$P(4\text{-}ClPh)_3$	100	90	0	8

[a] ^1H NMR yields based on 1,3,5-trimethoxybenzene as an internal standard.

With optimal reaction conditions achieved, the substrate scope of alkynyl iodides was evaluated (Table 2). Varying the electronic properties of the internal alkyne with electron-rich and -deficient aromatic groups had little effect on the reaction, providing high yields in all cases (entries 1–5, Table 2). Alkynes substituted with alkyl groups, regardless of steric bulk, proceeded cleanly and in high yield (entries 6 and 7, Table 2). Interestingly, secondary iodide **12** provided the tetrasubstituted olefin **22** in good yield, even at lower temperature (70 °C, entry 8, Table 2). This constitutes a rare example of oxidative addition into unactivated secondary halides by palladium.[4e] Likewise, the tetrasubstituted enol ether **23** was accessed through the reaction of alkyl iodide **14** (entry 9, Table 2). The reaction also proved applicable in the construction of a six-membered ring in compound **24** (entry 10, Table 2). Unfortunately, attempts to access four- and seven-membered rings under the optimized reaction conditions led to significantly lower yields.

Table 2. Alkyne Insertion/Suzuki Substrate Scope



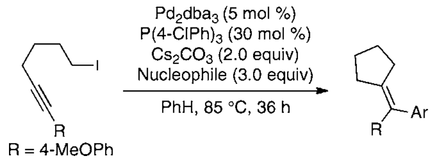
entry	substrate	product	% yield[a]
1	R^1 = 4-MeOPh **1** 	 **15-18**	86
2	= Ph **6**		85
3	= 4-Me_2NPh **7**		78
4	= 4-CF_3Ph **8**		72
5	 **9**	 **19**	88
6	 **10**	 **20**	94
7	 **11**	 **21**	91[b]
8	 **12**	 **22**	84[c]
9	 **13**	 **23**	71[b,c]
10	 **14**	 **24**	75

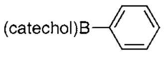
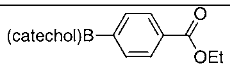
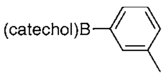
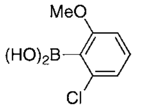
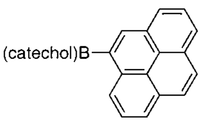
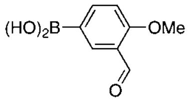
[a] Isolated yield. [b] Reaction time = 48 h. [c] Reaction performed at 70 °C.

Cursory investigation of aryl boronic nucleophiles demonstrated the expected substrate scope for a competent Suzuki reaction. For example, electronically neutral aryl substrates proceeded cleanly with high yields (entries 1–3, Table 3). Aryl nucleophiles containing electron-rich or -deficient aromatic groups also provided good yields (entries 4–6, Table 3). Additionally, the use of a sterically congested, ortho-disubstituted aryl boronic acid also led to high yield (87%, entry 5, Table 3). Both catechol esters and free boronic acids worked well for the cross-coupling reaction. The reaction proved compatible with functional groups such as aldehydes, esters, ethers, and aryl chlorides (entries 4–6, Table 3). Unfortunately, attempts to use aryl nucleophiles bearing nitro, carboxylic acid, or alcohol functional groups resulted in low yields of the desired tetrasubstituted olefin.

Oxidative addition at palladium(0) with alkyl halides has been shown to proceed through both S_N2[4d,8a] and radical-mediated pathways.[8b,15] To probe the mechanism of oxidative addition, deuterium-labeled substrate **25** was prepared and subjected to standard reaction conditions (Scheme 3).[8a] Under these conditions, the formation of a single *syn* diastereomer **26**

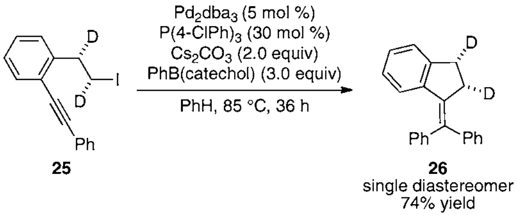
Table 3. Scope of Boron Nucleophile in Alkyne Insertion/Suzuki Reaction



entry	Nucleophile	% yield[a]	entry	Nucleophile	% yield[a]
1		90	4		67
2		82	5		87
3		84	6		61

[a]Isolated yield.

Scheme 3. Deuterium Labeling Demonstrates Inversion of Stereochemistry at the Carbon Electrophile

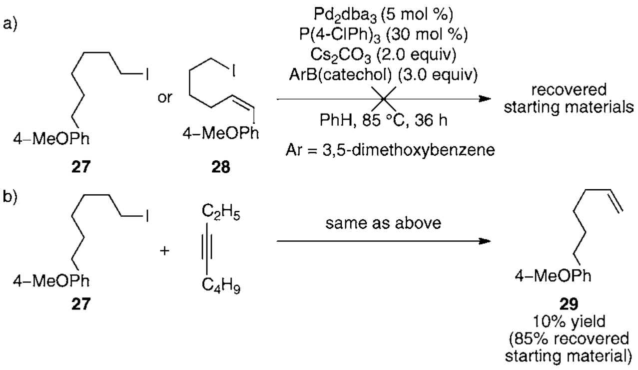


suggests an S_N2 oxidative addition for this reaction. Furthermore, running the reactions in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or azobisisobutyronitrile (AIBN) under the standard conditions had little effect on rate or yield, thereby arguing against free radical initiation of the reaction.[8b]

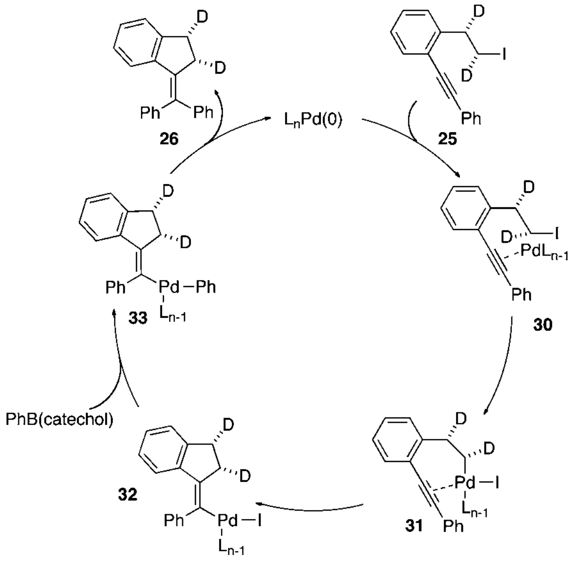
Since the overall transformation reported here occurs at lower temperatures (70–85 °C) than the previously reported alkyl Heck reaction with aryl phosphines (110–130 °C),[8b] we sought to establish whether the alkyne facilitated oxidative addition, the putative rate-determining step for the reaction.[5a,c] To that end, when substrates **27** and **28** were prepared and separately subjected to the standard reaction conditions, quantitative recovery of starting material was observed without formation of the expected *β*-hydride elimination products (Scheme 4a). Additionally, when alkyl iodide **27** was subjected to the same reaction conditions in the presence of 3-octyne, terminal olefin **29** was obtained in 10% yield along with 85% recovered iodide **27** (Scheme 4b). Finally, when a mixture of internal alkyne **1** and reduced alkyl iodide **27** was subjected to the standard reaction conditions, clean formation of desired product **2** was observed along with the recovery of iodide **27** and trace quantities of *β*-hydride elimination product **29**. While additional experiments are necessary, clearly the presence of the alkyne promotes oxidative addition, likely through palladium precoordination to the alkyne.

With these results, a putative catalytic cycle is proposed in Scheme 5. Precoordination of the palladium catalyst to the alkyne promotes an intramolecular S_N2 oxidative addition consistent with the inversion of stereochemistry observed for deuterated substrate **26**. Following the oxidative addition to form Csp^3–Pd(II) intermediate **31**, migratory insertion of the tethered alkyne proceeds more rapidly than *β*-hydride elimination to give vinylpalladium **32**. Transmetallation with boronic ester provides intermediate **33**, which reductively eliminates to give tetrasubstituted olefin product **26**. Studies to further elucidate the mechanism are underway.

Scheme 4. (a) Primary Alkyl Iodides Lacking a Pendant Alkyne Fail To Undergo Oxidative Addition under the Optimized Reaction Conditions; (b) The Presence of an Exogenous Alkyne Promotes the Oxidative Addition of Alkyl Iodides



Scheme 5. Putative Catalytic Cycles for the Alkyne Insertion/Suzuki Reaction



In summary, we have demonstrated that migratory insertion of alkynes into Csp^3–palladium species can out-compete *β*-hydride elimination without exotic ligands. This process allowed the development of a tandem alkyne insertion/Suzuki reaction of unactivated alkyl iodides. The reaction has broad substrate scope: applicable to both primary and secondary alkyl iodides and useful in the construction of both five-membered and six-membered rings. Cursory mechanistic studies have led to the proposal of a plausible catalytic cycle. The overall transformation provides rapid access to regio- and stereo-defined, unsymmetrical, tetrasubstituted olefins through a mechanistically unique reaction manifold which complements existing methods.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful for generous financial support by Indiana University and the Petroleum Research Fund, administered by the American Chemical Society. We thank Andrea Patterson for experimental support.

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