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Carbohalogenation

Synergistic Steric Effects in the Development of a Palladium-Catalyzed Alkyne Carbohalogenation: Stereodivergent Synthesis of Vinyl Halides[**]

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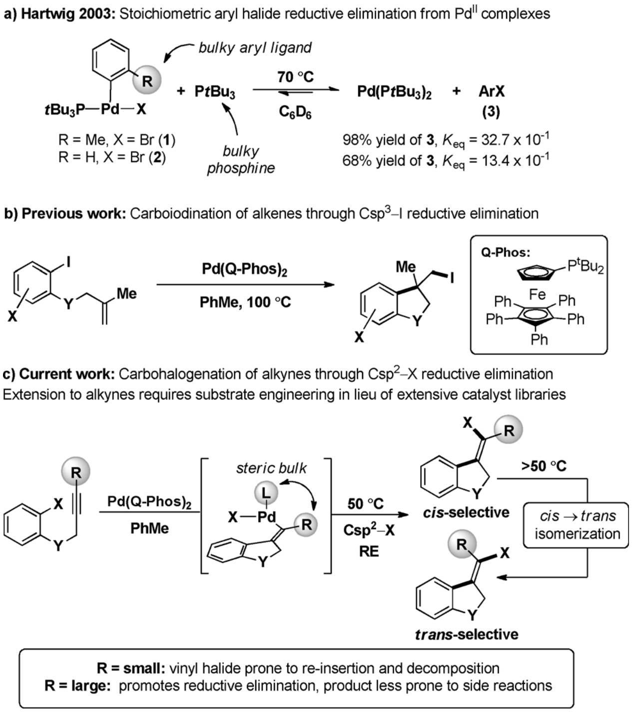
***Abstract:** We report our finding that by exploiting the synergistic steric effects between substrate and catalyst, an intramolecular Pd-catalyzed alkyne carbohalogenation can be achieved. This operationally simple method uses the bulky Pd/Q-Phos combination and allows access to tetrasubstituted vinyl halides from the corresponding aryl chlorides, bromides, and iodides. Steric effects in the substrate play a key role by promoting C_{sp^2}-halogen reductive elimination and enabling catalytic turnover. Through a reversible oxidative addition mechanism, a thermodynamically driven isomerization reaction is observed at elevated temperatures. Thus by changing the reaction temperature, both stereoisomers of the reaction become readily accessible.*



Scheme 1. a) Hartwig's stoichiometric studies on aryl halide reductive elimination; b) Pd^0-catalyzed intramolecular carbohalogenation of alkenes and c) alkynes.

Aryl and vinyl halides are versatile building blocks in organic synthesis due to their applicability toward a vast range of transition-metal-catalyzed cross-coupling reactions. Oxidative addition into an aryl or vinyl halide bond constitutes the first step in many traditional Pd-catalyzed cross-coupling reactions and is generally considered to be an irreversible and thermodynamically favorable step.[1] Consequently, carbon–halogen reductive elimination from Pd^{II} complexes (i.e., the microscopic reverse reaction) is rarely encountered when using conventional ligand sets.[2–4] This long-standing paradigm was shifted when Hartwig reported the stoichiometric reductive elimination of aryl halides from monomeric ArPd^{II}X species in 2003.[3b] Interestingly, this reductive elimination was promoted by the addition of excess PtBu$_3$, an electron-rich and sterically encumbering ligand (Scheme 1a). Typically, electron-poor Pd^{II} complexes are better suited to undergo reductive elimination compared to electron-rich complexes with similar steric properties.[5] However, these studies reveal that unfavorable electronic effects can be overridden in the reductive elimination of C_{sp^2}–X bonds from electron-rich Pd^{II} centers, provided that bulky phosphine ligands are employed. In this study, both K_{eq} and yield are increased upon the use of *ortho*-substituted aryl halide complexes, thus suggesting that substrate sterics may also play an intimate role in promoting this elementary process.

Our group has demonstrated that the use of bulky monodentate phosphine ligands, such as PtBu$_3$ and Q-Phos, can effectively promote C_{sp^3}–I reductive elimination in the Pd^0-catalyzed carboiodination of alkenes (Scheme 1b).[4a–f] To date, the successful realization of an alkyne carbohalogenation reaction has been impeded by a limited library of ligands fitting the criteria for promoting a difficult carbon–halogen reductive elimination step. Furthermore, the reactive nature of the final vinyl halide product presents additional complications, which stem from reinsertion of the Pd^0 catalyst, followed by potential catalyst deactivation, attenuation in turnover numbers and/or the initiation of unwanted coupling or oligomerization processes.

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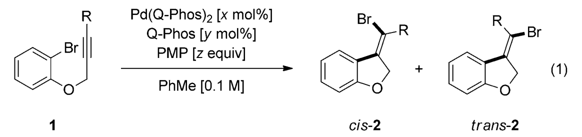
Herein, we report that by systematically tuning the steric properties of the substrate, in addition to using a bulky Pd catalyst, an intramolecular alkyne carbohalogenation can be realized (Scheme 1 c). The bulky alkynyl substituent serves to enhance steric congestion close to the Pd^{II} center, beyond the inherent effects imparted by the ligand, during the key reductive elimination step. In addition to promoting the desired reactivity, the increased steric bulk of the substrate also suppresses product decomposition pathways that are a result of oxidative addition of the Pd catalyst into the product C_{sp^2}–X bond.

This newly developed reaction can be conducted at lower temperatures compared to our previous systems and can be applied to aryl chlorides, bromides, and iodides. Experimental studies suggest that reversible oxidative addition is operative in the catalytic system, which serves to thwart unproductive catalyst consumption pathways and, more interestingly, enables a thermodynamically driven isomerization of vinyl halide product at elevated temperatures. By simply modulating the reaction temperature, both stereoisomers of the reaction can be readily accessed using the same catalyst. To the best of our knowledge, this atom-economical reaction represents the first Pd^0-catalyzed stereodivergent addition of an aryl halide across an alkyne.[6]

Our study commenced with a substrate screening employing previously developed conditions for the carboiodination of diiodinated aromatics [Eq. (1)].[4e] We noticed that the use of bulkier substituents at the terminal position of the alkyne led to increased yields of the desired carbohalogenation product **2** (Table 1, entries 1–3), with substrate **1c** displaying the best reactivity. Notably, an isomeric mixture of **2** was observed under a range of conditions, with the expected *cis*-**2** isomer, resulting from a *cis*-carbopalladation, being the major product.[7] Mechanistic studies suggest that the formation of *trans*-**2**, the product of an apparent *trans*-carbopalladation, is formed through a Pd-mediated olefin isomerization process (see below).[8] Upon further optimization with **1c** (Table S2),[9] we found that the addition of Q-Phos and PMP to the reaction was not necessary for full conversion at higher catalyst loadings (7.5 mol %), and the reaction temperature and time could be decreased to 50 °C and 15 min, respectively (entry 4).

Table 1: Substrate optimization.

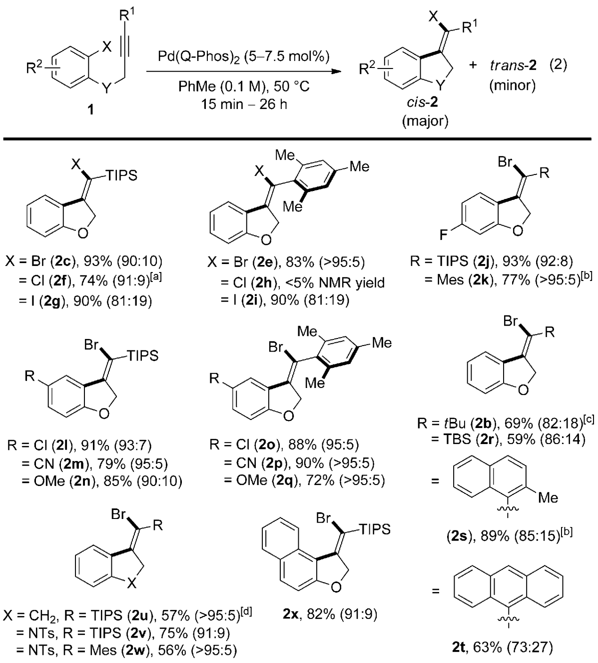


Entry	R (**1**)	*x* [mol %]	Temp [°C]/ (Time [h])	Yield[a] [%]	*cis/trans*[a]
1[b]	Me (**1a**)	5.0	110 (1.0)	40	N/D
2[b]	*t*Bu (**1b**)	5.0	110 (1.0)	83	82:18
3[b]	TIPS (**1c**)	5.0	110 (1.0)	94	87:13
4[c]	**TIPS (1c)**	**7.5**	**50 (0.25)**	**96**	**90:10**
5[c]	TIPS (**1c**)	0	50 (0.25)	0	N/D
6[b]	Ph (**1d**)	5.0	110 (1.0)	<5	N/D
7[c]	**mesityl (1e)**	**5.0**	**50 (18)**	**85**	**$>$95:5**
8[c]	**mesityl (1e)**	**5.0**	**100 (18)**	**90**	**10:90**

[a] Combined yields and *cis/trans*-ratios were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b] Q-Phos (10 mol %), PMP = 1.0 equiv. [c] No Q-Phos or PMP. PMP = 1,2,2,6,6-pentamethylpiperidine; N/D = not determined.

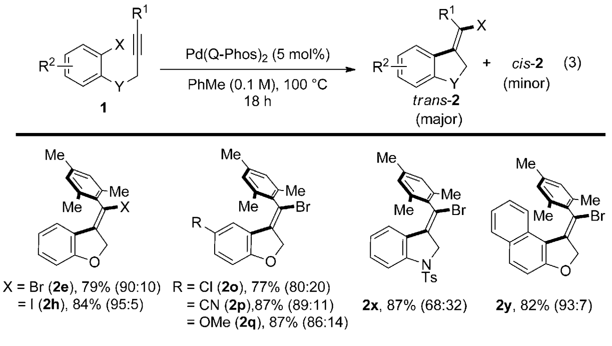
Significant decomposition and trace amounts of the desired product were observed when **1d** was subjected to the unoptimized reaction conditions (entry 6). We speculated that the introduction of *ortho*-substituents on the phenyl ring may favorably increase steric crowding close to the Pd center during the key reductive elimination. Indeed upon screening several *ortho*-substituted derivatives, a dramatic increase in reactivity was observed upon replacing the phenyl ring with a mesityl group (Table S4).[9] Substrate **1e** required more time than **1c** to reach full conversion at 50 °C (entry 7), which is consistent with our rationale that larger substituents promote the C_{sp^2}–X reductive elimination process more effectively (i.e., TIPS > mesityl).[10] At higher reaction temperatures (100 °C), the efficiency of the reaction was not significantly affected, but the stereoselectivity had reversed completely, with high selectivity observed for *trans*-**2e** (entry 8). In situ NMR studies show that the formation of *trans*-**2e**, which is presumably the thermodynamic product, arises primarily from isomerization of the kinetic product, *cis*-**2e**, rather than directly from **1e**.[9]

Having identified optimized conditions for substrates **1c** and **1e**, the substrate scope was investigated (Scheme 2). In addition to aryl bromides, our method could be applied to aryl chlorides (**1f**) and iodides (**1g**, **1i**). Although the use of **1f** required more forcing conditions, this example represents the first disclosure of a Pd^0-catalyzed carbochlorination reaction.



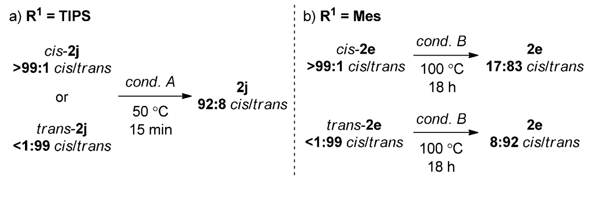
Scheme 2. Substrate scope for *cis*-selective examples. Values in parentheses represent the major/minor isomer ratios. [a] With PMP (0.25 equiv) at 110 °C for 18 h. [b] At 100 °C. [c] With $Pd(Q\text{-}Phos)_2$ (10 mol %), PMP (0.25 equiv) at 110 °C for 1 h. [d] With $Pd(Q\text{-}Phos)_2$ (5 mol %), PMP (1.0 equiv) at 110 °C for 72 h. Ts = tosyl; TBS = *tert*-butyldimethylsilyl ether; TIPS = triisopropylsilyl ether.

Both electron-withdrawing (**1j**, **1k**, **1m**, **1p**) and electron-donating (**1n**, **1q**) substituents on the aryl bromide were well tolerated. Good to modest yields and selectivities were observed upon replacing the TIPS or mesityl groups with other substituents (*cis*-**2r**–*cis*-**2t**), thereby emphasizing the importance of steric bulk at the terminal position. X-ray crystal structures obtained for *cis*-**2c**, *cis*-**2p**, and *trans*-**2p** unambiguously confirm the stereochemistry of the compounds.[11] We also examined if the *cis*-to-*trans* isomerization observed for **1e** at 100 °C could be applied to other substrates, which would allow access to both isomers of the carbohalogenation reaction in a stereodivergent manner [Eq. (3)]. Indeed, at elevated temperature, in a select group of substrates, the *trans*-isomer was obtained as the major product (Scheme 3).

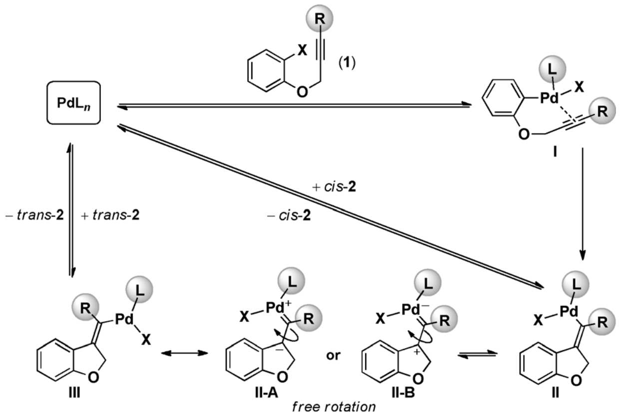


Scheme 3. Substrate scope for *trans*-selective examples. Values in parentheses represent the major/minor isomer ratios.

To gain insight into the olefin isomerization mechanism, isomerically pure samples *cis*-**2j**, *trans*-**2j**, *cis*-**2e**, and *trans*-**2e** were resubjected to the standard reaction conditions, which resulted in olefin isomerization in all cases (Scheme 4). When R^1 = TIPS, the formation of *cis*-**2** seems to be both kinetically and thermodynamically favored. Conversely, when R^1 = Mes, *cis*-**2** is preferentially formed under kinetic conditions, while *trans*-**2** is formed under thermodynamic conditions. In both cases, thermal isomerization is not observed in the absence of a Pd catalyst. Collectively, this data suggests that the isomerization process is Pd-catalyzed and that C_{sp^2}–X oxidative addition and reductive elimination are reversible processes in this system.



Scheme 4. Isomerization experiments. Conditions A: Pd(Q-Phos)$_2$ (7.5 mol%), PhMe (0.1 M); Conditions B: Pd(Q-Phos)$_2$ (5 mol%), PhMe (0.1 M).



Scheme 5. Proposed mechanism.

We propose a mechanism which involves oxidative addition of aryl halide **1**, alkyne insertion to generate a vinyl Pd halide complex **II**, and finally, C_{sp^2}–X reductive elimination to generate *cis*-**2** (Scheme 5). We believe that isomerization occurs via vinyl Pd^{II} intermediate **II**, which can be represented as zwitterionic Pd carbene species **II-A** or **II-B**. The formation of complex **II** may arise from the oxidative addition and alkyne insertion of **1** or directly through the oxidative addition of *cis*-**2**. Analogous Pd carbenes have been implicated as intermediates by the groups of Lipshutz,[12] Cook,[13] and Amatore and Jutand[14] in the stereoisomerization reaction of vinylic Pd^{II} complexes. Either **II-A** or **II-B** can undergo a bond rotation to form vinyl Pd **III**, which upon reductive elimination liberates *trans*-**2**.

In conclusion, we have developed a method for the intramolecular carbohalogenation of hindered alkynes, which employs a Pd/Q-Phos catalyst system. Reactivity is promoted by steric bulk provided by both the ligand and the substrate. The introduction of larger alkynyl substituents increases the propensity for C_{sp^2}–X reductive elimination and concurrently decreases the tendency of the final vinyl halide product to undergo undesired side reactions. Overall, we have established that the combined steric properties of the catalyst and substrate work together to promote this transformation, which would otherwise not be possible if the two strategies were employed independently. Further investigations on the mechanism of this transformation are underway and will be reported in due course.

Experimental Section

An oven-dried 2 dram vial equipped with a stir bar was charged with Pd(Q-Phos)$_2$ (5.0–7.5 mol%) and purged with argon for 5 min. A toluene (1 mL, 0.1 M) solution of **1** (0.100 mmol, 1.00 equiv) was transferred to the vial, which was then sealed with a Teflon-lined cap and placed in a preheated oil bath at the indicated temperature (50–110 °C). After the indicated period of time, the reaction was cooled to room temperature, diluted with Et_2O (1 mL), passed through a plug of silica (eluting with Et_2O) and concentrated. The crude mixture was purified by silica gel flash column chromatography.

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[7] For substrate **1b**, the isomeric products were separated by column chromatography and analyzed by 1D NOE experiments (see the Supporting Information). The *cis*/*trans*-addition ratios for all other substrates were assigned based on analogous chemical shifts in the crude ^{1}H NMR spectra.

[8] The *cis*/*trans* nomenclature for cyclized products **2** reflects the apparent nature of the carbopalladation step. In all cases (except for **2u**), the olefin geometries of *cis*-**2** and *trans*-**2** are *E* and *Z*, respectively.

[9] Refer to the Supporting Information for further experimental details.

[10] At catalyst loadings of 7.5 mol% [Pd], a lower selectivity for *cis*-**2e** was observed (88:12 *cis*/*trans*) compared to 5.0 mol% [Pd] loading (see SI for details).

[11] CCDC 1024942 (*cis*-**2c**), 1024943 (*cis*-**2p**), and 1024944 (*trans*-**2p**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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