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Stereoselective Synthesis of Methylene Oxindoles via Palladium(II)-Catalyzed Intramolecular Cross-Coupling of Carbamoyl Chlorides

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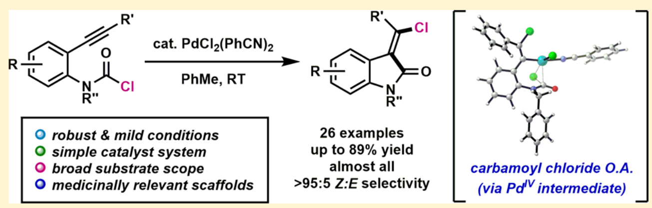
Supporting Information

ABSTRACT: We report a highly robust, general and stereoselective method for the synthesis of 3-(chloromethylene)oxindoles from alkyne-tethered carbamoyl chlorides using $PdCl_2(PhCN)_2$ as the catalyst. The transformation involves a stereo- and regioselective chloropalladation of an internal alkyne to generate a nucleophilic vinyl Pd^{II} species, which then undergoes an intramolecular cross-coupling with a carbamoyl chloride. The reaction proceeds under mild conditions, is insensitive to the presence of moisture and air, and is readily scalable. The products obtained from this reaction are formed with >95:5 *Z*:*E* selectivity in nearly all cases and can be used to access biologically relevant oxindole cores. Through combined experimental and computational studies, we provide insight into stereo- and regioselectivity of the chloropalladation step, as well as the mechanism for the C−C bond forming process. Calculations provide support for a mechanism involving oxidative addition into the carbamoyl chloride bond to generate a high valent Pd^{IV} species, which then undergoes facile C−C reductive elimination to form the final product. Overall, the transformation constitutes a formal Pd^{II}-catalyzed intramolecular alkyne chlorocarbamoylation reaction.



INTRODUCTION

Methylene oxindoles represent a privileged scaffold in medicinal chemistry, as they are prevalent in a range of pharmaceutical agents and biologically active molecules (Figure 1).[1] In addition to their therapeutic value, they are also useful intermediates in total synthesis, frequently exploited in cycloaddition reactions to gain access to spirocyclic oxindole natural products.[2] Despite numerous reports outlining the synthesis of methylene oxindoles,[3] there are a limited number of highly stereoselective methods to access 3-(halomethylene)oxindoles **1**—an attractive entry point to libraries of medicinally relevant molecules.[4]

In 2007, Li and co-workers disclosed a Pd^{II}-catalyzed carbonylative annulation reaction with 2-alkynylanilines using $CuCl_2$ as a stoichiometric oxidant (Scheme 1a).[4a] Depending on the substrate employed, the *E*:*Z*-selectivities varied between 2.7:1 and >99:1. Complementary to the work of Li and others,[4b−f] our group recently demonstrated that alkyne-tethered carbamoyl chlorides are also suitable precursors for the synthesis of 3-(chloromethylene)oxindoles via a Pd^0-catalyzed intramolecular chlorocarbamoylation reaction (Scheme 1b).[4g] The use of hindered alkynes, in combination with a bulky phosphine ligand (PA-Ph = 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phospha-adamantane), was crucial for promoting the final Csp^2−Cl reductive elimination step and enabling exclusive *trans*-selectivity in the cyclization. The importance of having steric bulk at the terminal alkynyl position is exemplified by substrate **1b′** (R = Ph), which failed to undergo the desired chlorocarbamoylation

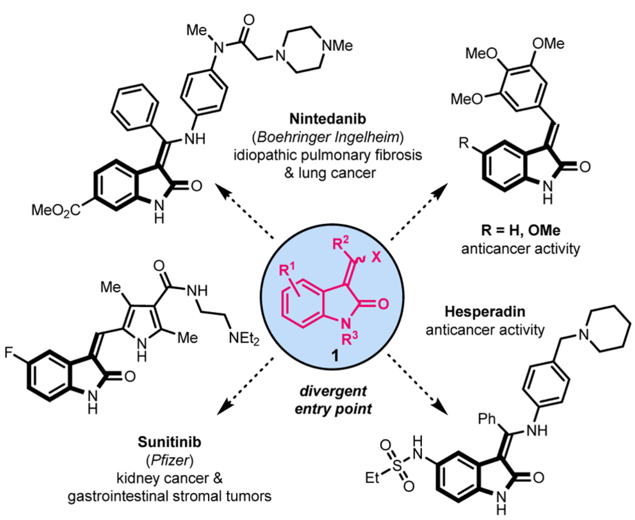


Figure 1. Potential entry to biologically active oxindoles via functionalization of 3-(halomethylene)oxindoles **1**.

reaction with a range of Pd^0 catalysts commonly employed for carbon−halogen reductive eliminations.[5]

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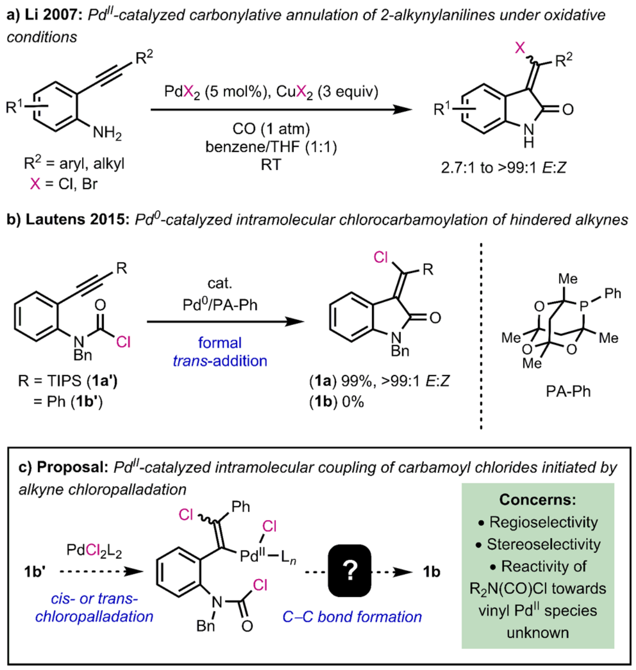
Scheme 1. Methods for the Synthesis of 3-(Halomethylene)oxindoles

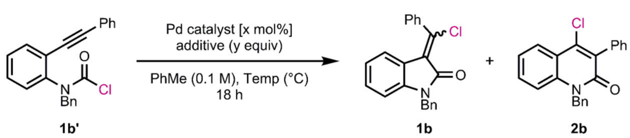


In an effort to increase the diversity of products obtained—particularly scaffolds of high pharmaceutical value—we were prompted to investigate alternative reaction pathways, wherein the difficult Csp^2–Cl reductive elimination could be avoided. Cognizant of the well-established reactivity of Pd^{II} alkyne complexes,[6] we envisaged generating a nucleophilic vinyl Pd^{II} species in situ via alkyne chloropalladation,[7] which could subsequently activate the carbamoyl chloride through a C–C bond-forming process (Scheme 1c). The proposed method offers several advantages, as it would avoid the use of air-sensitive Pd^0 catalysts, toxic CO gas, and/or oxidative conditions. At the outset of this project, we were concerned about the ability to achieve high regio- and stereoselectivities for the chloropalladation step, which has proven to be very challenging with unactivated, unsymmetrical internal alkynes.[8] Although the trapping of vinyl or aryl Pd^{II} species with various unsaturated polar functional groups (e.g., aldehydes, ketones, esters, and nitriles) has been previously reported,[9−13] the analogous reaction with carbamoyl chlorides remains a challenge.[14,15] Despite these aforementioned issues, we herein present our development of an intramolecular Pd^{II}-catalyzed alkyne chlorocarbamoylation reaction, for which the key step proceeds through the intramolecular coupling of a carbamoyl chloride with an in situ-generated vinyl Pd species.

■ RESULTS AND DISCUSSION

To establish a protocol for the cyclization of **1b′**, a number of Pd catalysts, commonly employed in the chloropalladation of alkynes, were screened (Table 1). We found that both $PdCl_2(MeCN)_2$ and $PdCl_2(PhCN)_2$ were effective for this transformation, giving full conversion of the starting material and providing *Z*-**1b** as the major product (entries 1 and 2). The use of either $PdCl_2$ or $PdBr_2(PhCN)_2$ led to inferior results, which can be attributed to their low solubility in toluene (entries 3 and 4). Upon switching the solvent to THF, $PdBr_2(PhCN)_2$ could promote the desired transformation, albeit with lower yields and *Z*:*E*-selectivities (entry 5). By ^{1}H NMR analysis, we did not observe significant quantities of the brominated oxindole or quinolinone products for entry 5. Our calculations reveal that the $PdBr_2(PhCN)_2$ catalyst can undergo halide exchange with carbamoyl chloride **1b′** to form a mixed PdClBr(PhCN) species, which slightly favors chloropalladation over bromopalladation in the alkyne insertion step ($\Delta\Delta G^\ddagger$ = 0.3 kcal/mol).[16] As the reaction progresses, an increasing amount of $PdCl_2(PhCN)$ is formed, leading to mainly chloride incorporation in the products.[17] Although $Pd(OAc)_2$ was a competent catalyst for this reaction, lower yields and regio- and stereoselectivities were also observed in this case (entry 6). The use of Na_2PdCl_4 led to poor results, demonstrating the benefit of using neutral over anionic Pd catalysts (entry 7). Upon further reaction

Table 1. Reaction Optimization[a]



entry	conditions	conv (%)	NMR yield **1b** (%)	ratio **1b**:**2b**	ratio *Z*-**1b**:*E*-**1b**
1	$PdCl_2(MeCN)_2$ [10], 50 °C	100	76	84:16	>95:5
2	$PdCl_2(PhCN)_2$ [10], 50 °C	100	80	83:17	>95:5
3	$PdCl_2$[10], 50 °C	25	18	78:22	94:6
4	$PdBr_2(PhCN)_2$ [10], 50 °C	0	-	-	-
5[b]	$PdBr_2(PhCN)_2$ [10], 50 °C	92	60	>95:5	75:25
6	$Pd(OAc)_2$ [10], 50 °C	100	65	81:19	82:18
7	Na_2PdCl_4 [10], 50 °C	25	17	77:23	90:10
8[c]	***$PdCl_2(PhCN)_2$ [5], RT***	***100***	***84***	***84:16***	**>95:5**
9[c]	entry 8 with 1 equiv of LiCl	84	71	87:13	>95:5
10[c]	entry 8 with 1 equiv of CuCl	100	84	86:14	>95:5
11[c]	entry 8 with 1 equiv of $CuCl_2$	100	83	85:15	>95:5
12[c,d]	entry 8 with 1 equiv of 12-crown-4	24	13	87:13	93:7
13[c,d]	entry 8 with 1 equiv of $^n Bu_4NCl$	6	0	-	-
14[c]	no catalyst, RT	0	-	-	-

[a]Conversions, NMR yields, and isomeric ratios determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b]With THF as solvent. [c]Reaction concentration = 0.2 M; reaction conducted under air. [d]Reaction conducted at 50 °C.

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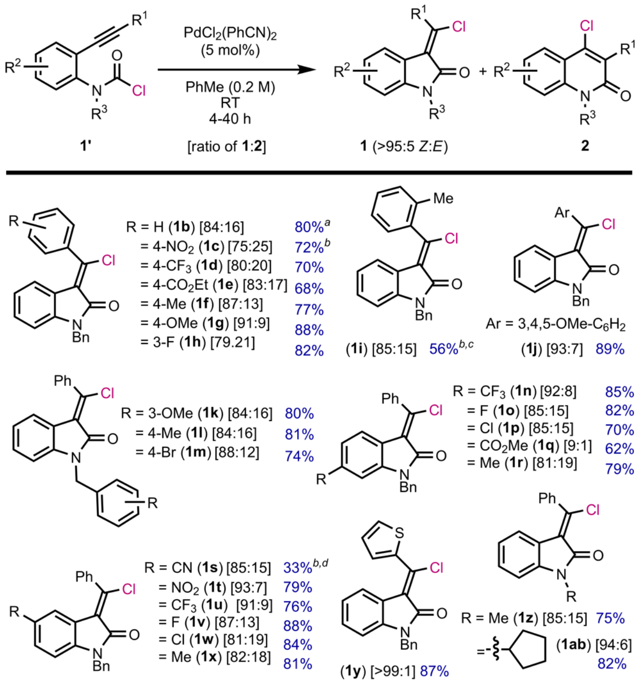
optimization, we found that $PdCl_2(PhCN)_2$ slightly outperformed $PdCl_2(MeCN)_2$ at lower catalyst loadings and ambient reaction temperatures, furnishing **1b** in 82% yield (>95:5 *Z*:*E*) and quinolinone **2b** in 16% yield by ^{1}H NMR (entry 8). It should be highlighted that the reaction is complete within 8 h and is unaffected by the presence of air and moisture, thus greatly simplifying the experimental setup.

In stark contrast to previous reports on the chloropalladation of alkynes, increasing the free chloride concentration with various additives did not influence the *Z*:*E*-selectivities (entries 9−11). In fact, attempts to increase the chloride solubility in toluene by employing a combination of LiCl/12-crown-4 or ^{n}Bu$_4$NCl led to a further decrease or complete shut-down in reactivity (entries 12 and 13). This observation suggests that internal chloride delivery via *cis*-chloropalladation predominates over external chloride delivery via *trans*-chloropalladation under these reaction conditions.[18] As expected, in the absence of the Pd catalyst, no reaction occurs (entry 10). In general, the use of highly coordinating solvents or phosphine or amine ligands proved to be detrimental to the reaction, thus emphasizing the importance of having a coordinatively unsaturated Pd catalyst.[16] The stereoselectivity of the reaction is particularly noteworthy, as it is complementary to all other previous reports on the synthesis of 3-(halomethylene)oxindoles.[4] Additionally, the regioselectivity of the chloropalladation step, represented by the ratio of **1b**:**2b**, is higher than one would expect for a relatively unbiased diarylacetylene substrate.[4a,19] Though it is possible that the carbamoyl group can direct the chloropalladation step by coordinating to the Pd catalyst,[20] steric effects likely have a greater influence on this addition process (see Mechanistic and Computational Studies, below).

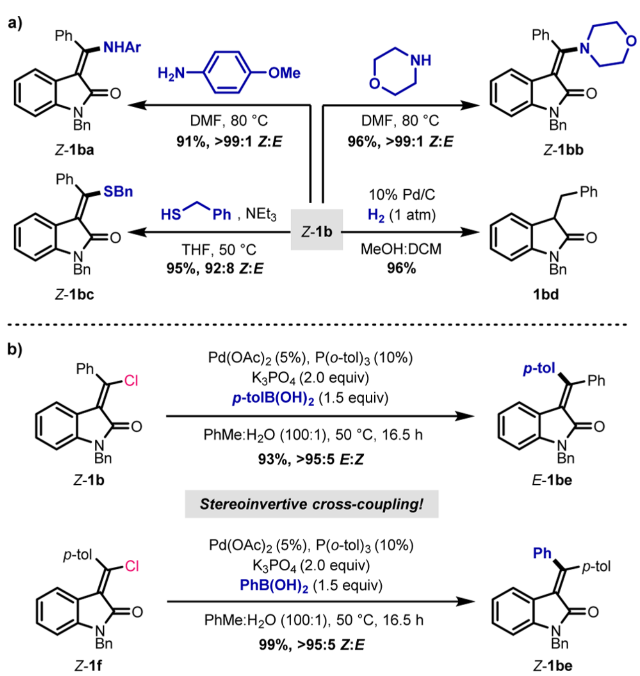
With the optimized conditions in hand, we evaluated the substrate scope (Table 2). Overall, the reaction tolerates a diverse range of substituents at the distal alkynyl position R^1, including a biologically relevant scaffold in **1j** and a 2-thienyl group in **1y**. With the exception of **1i**, which possesses a sterically hindered aryl ring, >95:5 *Z*:*E* selectivity was observed in all cases. It should be mentioned that literature examples featuring highly selective *cis*-chloropalladation pathways remain rare, thus illustrating the potential utility of this method.[21] Substrates bearing alkyl chains at the R^1 position also demonstrated excellent reactivity and stereoselectivity in the cyclization; however, full separation of the regioisomers by silica gel chromatography could not be achieved in these cases.[16] Polyhalogenated oxindoles **1m**, **1p**, and **1w** can be readily accessed using this method, owing to the stability of Csp^2−X bonds under Pd^{II} catalysis, thereby providing the potential for further derivatization via cross-coupling. In addition, different N-protecting groups and substitution patterns on the aromatic backbone were accommodated without any adverse effects on yield and selectivity. However, diminished reactivity was observed with **1s′**, likely due to competitive binding of the nitrile group with the Pd catalyst. Notably, we were able to gain access to the core scaffold of the anticancer drug nintedanib using this protocol (**1q**). Although not shown in Table 2, substrates possessing heteroatoms in close proximity to the reacting alkyne showed poor reactivity, possibly due to unproductive chelation with the catalyst. Furthermore, the reaction can be conducted on gram scale with carbamoyl chloride **1b′** using only 2 mol% [Pd]. To confirm our structural and stereochemical assignments, X-ray crystal structures of methylene oxindole *Z*-**1v** and quinolinone **2z** were obtained, while the isomeric ratios for all other examples were determined by comparing analogous chemical shifts in the ^{1}H NMR spectra.[16]

Table 2. Substrate Scope



Unless otherwise stated, reactions were conducted on a 0.25 mmol scale under air with 5 mol% [Pd]. Combined isolated yields for **1** are reported. Values in brackets represent ratios of **1**:**2** which were determined by ^{1}H NMR analysis of the crude reaction mixture. [a]Reaction conducted on gram scale (2.90 mmol) with 2 mol% [Pd]. [b]Reaction conducted at 50 °C. [c]72:28 *Z*:*E* ratio. [d]85% yield brsm.

Scheme 2. Synthetic Transformations of 3-(Chloromethylene)oxindoles



To demonstrate the synthetic utility of the products obtained from this protocol, various transformations of 3-(chloromethylene)oxindole *Z*-**1b** were conducted (Scheme 2a). Nucleophilic substitution reactions using *p*-anisidine (**1ba**), morpholine

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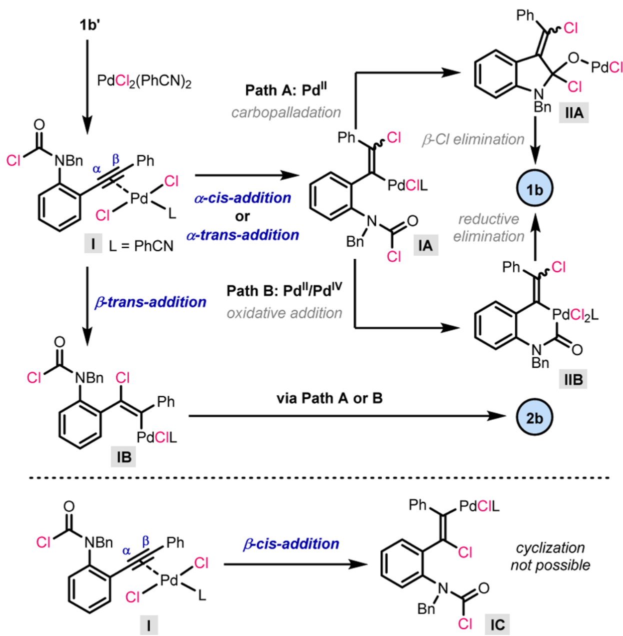
(**1bb**), and benzyl mercaptan (**1bc**) proceeded in high yields with excellent *Z*-selectivity in all cases. The stereochemical assignments were confirmed by selective 1D or 2D NOESY experiments and by X-ray crystallographic analysis in the case of *Z*-**1bc**.[16] The vinyl chloride moiety can also be fully reduced using Pd/C and H_2 to give 3-substituted oxindole **1bd**. Interestingly, subjecting *Z*-**1b** to standard Suzuki cross-coupling conditions[22] using *p*-tolylboronic acid resulted in the formation of *E*-**1be** with >95:5 selectivity, which is the opposite of the isomer we expected (Scheme 2b). We reasoned that this may be due to an in situ olefin isomerization to the more stable isomer in either the starting material or product. However, when we tested *Z*-**1f** under identical conditions using phenylboronic acid instead, *Z*-**1be** was formed with >95:5 selectivity. This stereoinversion could be a result of a *cis* → *trans* vinyl Pd^{II} isomerization after oxidative addition into the C−Cl bond of *Z*-**1**,[23] or a mechanism involving carbopalladation of the olefin in *Z*-**1** by an $ArPd^{II}X$ species, followed by stereospecific *syn*-β-Cl elimination (see section 5.2 in the Supporting Information). At this stage, further studies on the mechanism of this cross-coupling process are warranted. Nevertheless, we have shown that both 3-(diarylmethylene)-oxindole isomers can be readily accessed by using the appropriate coupling partners.

■ MECHANISTIC AND COMPUTATIONAL STUDIES

Proposed Mechanism. A general catalytic cycle for this transformation begins with complexation of **1b′** with the electrophilic Pd^{II} catalyst, followed by chloropalladation of the coordinated alkyne (Scheme 3). Ultimately, the regioselectivity

Scheme 3. Proposed Mechanism

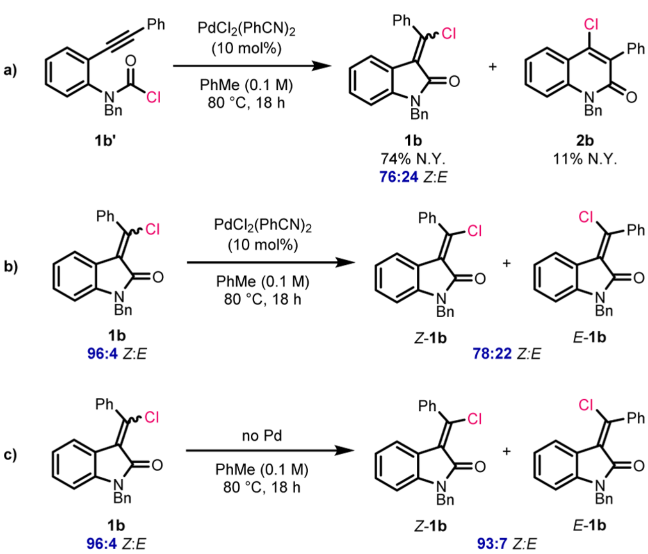


(α vs β) and stereoselectivity (*cis* vs *trans*) of this insertion process is what determines the final product distribution. In the α-addition pathway, Pd ends up in the α position of the alkyne, proximal to the carbamoyl chloride. Under all circumstances, α-*cis*-addition is the predominant pathway, leading to high selectivities for *Z*-**1b**. In the β-addition pathway, chloropalladation occurs with the opposite regioselectivity, in which Pd ends up distal to the carbamoyl chloride. While this step can also occur with either *cis*- or *trans*-selectivity, only one intermediate (**IB**) is able to cyclize, while the other species (**IC**) leads to a potentially unproductive pathway. We cannot rule out the possibility of vinyl Pd^{II} species **IC** undergoing a *cis* → *trans* isomerization to form **IB**, which can then cyclize to furnish product **2b**. The stereoisomerization of similar vinyl Pd^{II} complexes is well documented in the literature.[23b−j] Regardless of the regiomeric outcome, a nucleophilic vinyl Pd species is produced (**IA** or **IB**), which can subsequently react with the carbamoyl chloride in an intramolecular fashion to give methylene oxindole **1b** or quinolinone **2b**.

Two possible mechanisms (paths **A** or **B**) can be envisaged for this C−C bond-forming step. Analogous to the reactivity of aldehydes and ketones with nucleophilic Pd^{II} species, carbopalladation of the carbonyl functionality (path **A**) leads to Pd alkoxide species **IIA**,[9,10] which can then undergo β-Cl elimination to form the final product.[7,24] An alternative pathway involves oxidative addition into the carbamoyl chloride bond (path **B**) to form a high-valent Pd^{IV} species (**IIB**), which upon C−C reductive elimination furnishes the product and regenerates the divalent Pd catalyst.[25] To gain deeper insight into the mechanism of this transformation, as well as the regio- and stereoselectivities observed, we describe combined experimental and computational studies in the following sections.

Stereoselectivity of Chloropalladation Step. It is certainly possible that the formation of *E*-**1b** could arise from an in situ *Z* → *E* isomerization of *Z*-**1b**. To assess the feasibility of this process, the reaction was first conducted at 80 °C instead of room temperature, which led to significant amounts of *E*-**1b** being formed after 18 h (76:24 *Z*:*E*) (Scheme 4a). When an isolated

Scheme 4. Isomerization Studies



sample of **1b** (96:4 *Z*:*E*) was subjected to the same reaction conditions, a similar isomeric ratio was obtained (78:22 *Z*:*E*) (Scheme 4b). However, in the absence of the electrophilic Pd^{II} catalyst, the extent of this isomerization was minimal (93:7 *Z*:*E*) (Scheme 4c). Overall, these studies suggest that, while α-*trans*-chloropalladation pathways may be occurring in concert with α-*cis*-chloropalladation, *E*-**1b** can also be formed through a Pd^{II}-mediated isomerization of *Z*-**1b**, which occurs more readily at elevated temperatures.[26,27] Regardless of the exact mechanism for the formation of the *E*-isomer, it should be reiterated that only

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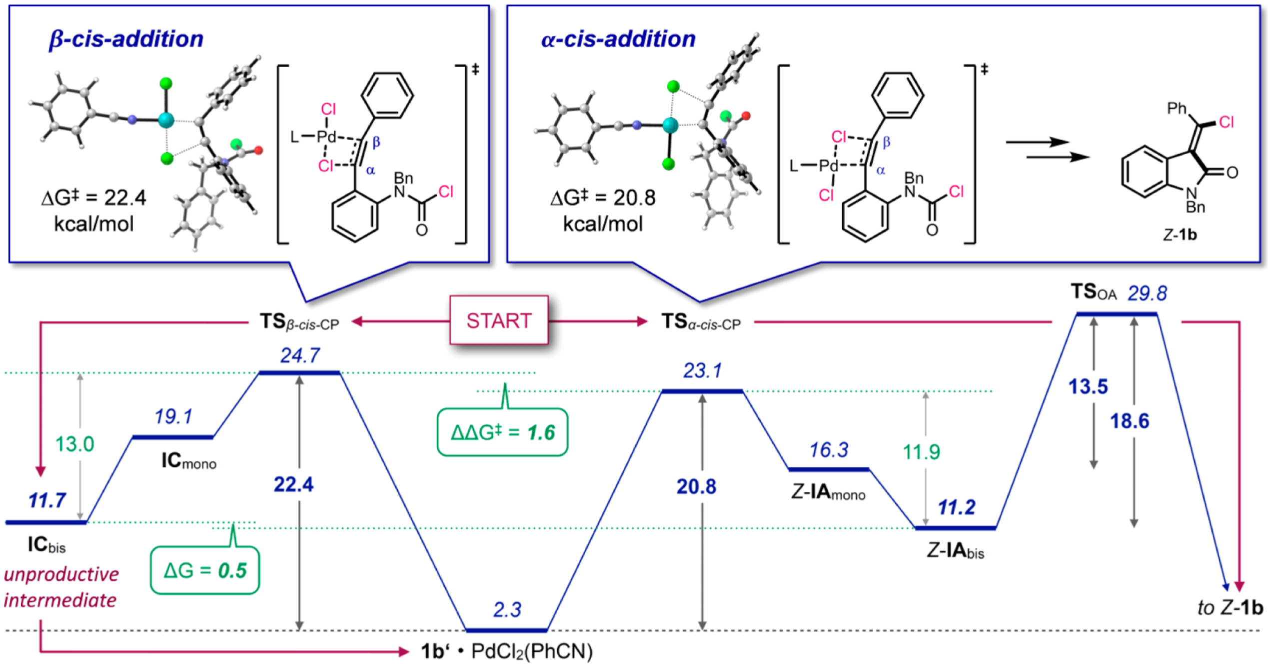
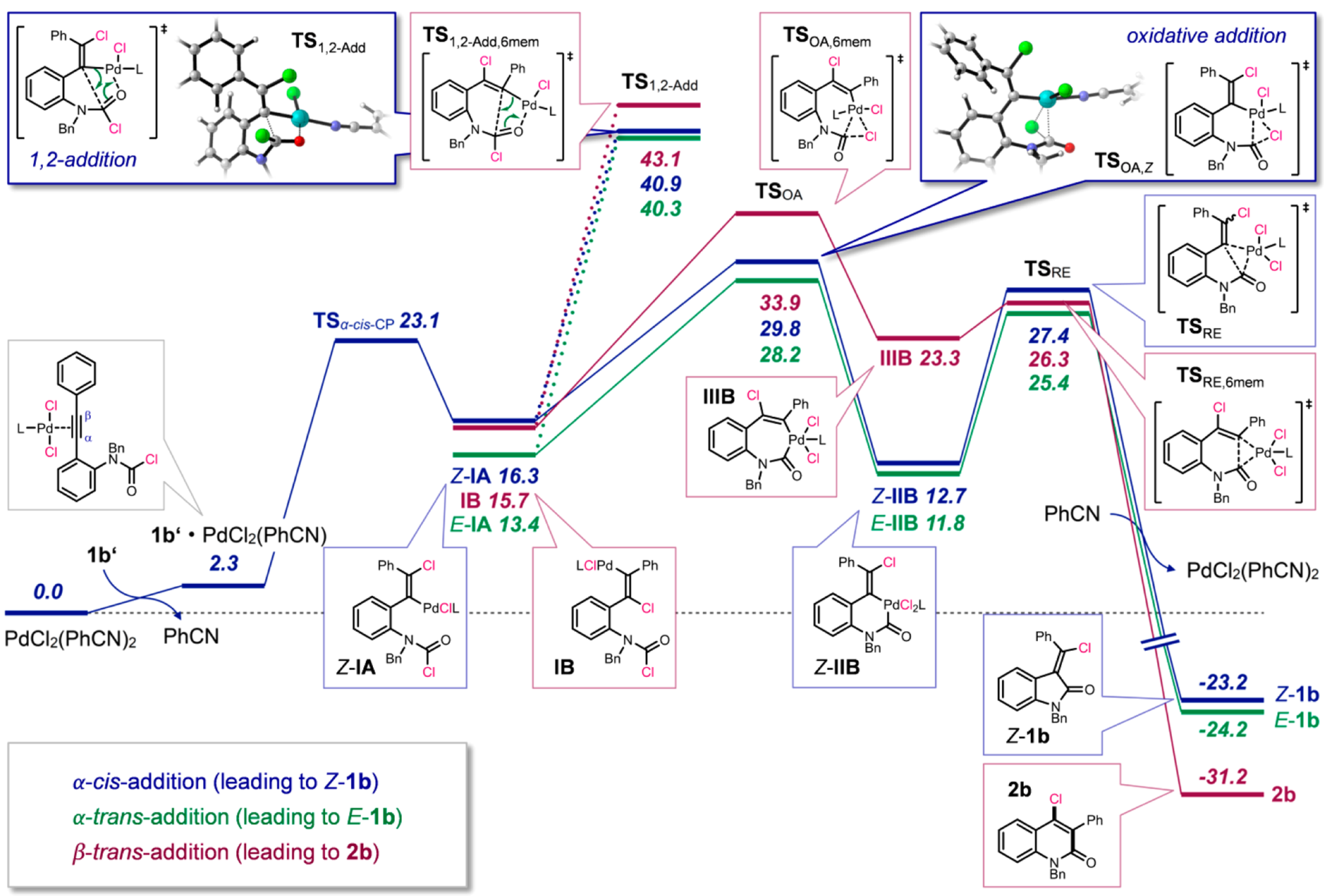
Scheme 5. Calculated Selectivities of *cis*-Chloropalladation: *α*- (Right) versus *β*-*cis*-Addition (Left)[a]



[a]Gibbs free energies (in kcal/mol, relative to isolated reactants, $PdCl_2(PhCN)_2$ and substrate) at the CPCM (toluene) M06L/def2-TZVP//B3LYP/6-31G(d) (LANL2DZ) level of theory.

Scheme 6. Full Energetic Pathways for the Formation of *Z*- and *E*-1b as Well as Side Product 2b[a]



[a]Gibbs free energies (in kcal/mol, relative to the isolated reactants, $PdCl_2(PhCN)_2$ and substrate) calculated at the CPCM (toluene) M06L/def2-TZVP//B3LYP/6-31G(d) level of theory.

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very small amounts of this product (<5%) are observed under the standard conditions.

Regioselectivity of Chloropalladation Step. While we anticipated that the carbamoyl moiety may act as a directing group in steering regioselectivity (*α*- vs *β*-addition), calculations at the CPCM (toluene) M06L/def2-TZVP//B3LYP/6-31G(d) level of theory[28,29] indicate that the most favorable interaction of the Pd^{II} catalyst is its coordination to the alkyne. All additional interactions with the carbamoyl group, as well as the sole coordination of Pd^{II} to carbamoyl group, were found to be energetically unfavorable, i.e., led to energetically less stable species. For the catalyst $PdCl_2(PhCN)_2$ to be able to coordinate to the alkyne, one of the benzonitrile ligands needs to dissociate to render monoacetonitrile $PdCl_2(PhCN)$ as the catalytically active species. After coordination of the catalyst to the alkyne, chloropalladation (i.e., alkyne insertion) can occur with *α*- or *β*-selectivity via an internal, concerted transition state (Scheme 5). Calculations suggest that, while *α*-addition is kinetically favored by $\Delta\Delta G^{\ddagger}$ = 1.6 kcal/mol, both *α*- and *β*-chloropalladation are fully reversible, and *α*-addition is favored due to a slight thermodynamic preference of ΔG = 0.5 kcal/mol. Since *β*-addition results in the formation **IC**, which cannot undergo direct intramolecular cross-coupling, the reaction can reverse and undergo the favorable *α*-addition.

Mechanism for Intramolecular Activation of Carbamoyl Chloride. Two mechanistic scenarios could be envisioned for the C−C bond-forming event (Scheme 3). Carbopalladation (i.e., 1,2-addition) of the carbamoyl group would result in the formation of a Pd^{II} alkoxide that could then undergo *β*-Cl elimination to form **1b** (path **A**). Alternatively, oxidative addition of Pd^{II} to the C−Cl bond of the carbamoyl chloride would form a Pd^{IV} intermediate, and subsequent C−C bond formation could take place via reductive elimination (path **B**). Both mechanistic pathways were studied by means of computations, which indicate that the formation of Pd^{IV} via oxidative addition (path **B**) is favored over 1,2-addition (path **A**) by $\Delta\Delta G^{\ddagger}$ = 11.0 kcal/mol.

Both oxidative addition and reductive elimination display facile activation barriers, $\Delta G^{\ddagger}$ = 13.5 and 14.7 kcal/mol, respectively. Due to the necessity of an empty coordination site at the Pd^{II} center, both oxidative addition and 1,2-addition occur via a monoacetonitrile-coordinated transition state. In contrast, mono- and bis-acetonitrile transition states were considered for reductive elimination, which demonstrated the monoligated transition state to be favored by $\Delta\Delta G^{\ddagger}$ = 15.3 kcal/mol.

Full Energetic Pathway. Full energetic pathways were calculated at the CPCM (toluene) M06L/def2-TZVP//B3LYP/6-31G(d) level of theory using Gaussian 09, revision D.01 (Scheme 6).[28,29] Both *Z*-**1b** and *E*-**1b** form via analogous routes from initial *cis* (blue) or *trans* (green) *α*-chloropalladation, respectively. Subsequent C−C bond formation is predicted to occur via an oxidative addition/reductive elimination sequence involving the formation of Pd^{IV} intermediate **IIB**. Alternative pathways involving 1,2-addition/*β*-Cl elimination were found to be energetically disfavored by $\Delta\Delta G^{\ddagger}$ = 11.0 and 12.1 kcal/mol for *Z*- and *E*-**1b**, respectively.

Side product **2b** could arise from initial *β*-*trans*-chloropalladation (red) to form intermediate **IB**.[30] Analogous to the formation of the five-membered ring in **1b**, two mechanistic pathways for the formation of the six-membered ring in **2b** are plausible. C−C bond formation can occur via either Pd^{II} or Pd^{II}/Pd^{IV} pathways. Similar to **1b**, an oxidative addition/reductive elimination sequence involving the formation of a Pd^{IV} intermediate was shown to be favored over the alternative 1,2-addition/*β*-Cl elimination by $\Delta\Delta G^{\ddagger}$ = 9.2 kcal/mol. While oxidative addition to form the 7-membered Pd^{IV} intermediate (leading to **2b**) displays a larger activation barrier compared to the analogous formation of six-membered **IIB** (leading to **1b**; $\Delta G^{\ddagger}_{OA}$ = 18.2 and 13.5 kcal/mol, respectively), the subsequent reductive elimination to form the 6-membered ring in **2b** is much more facile ($\Delta G^{\ddagger}_{RE}$ = 3.0 kcal/mol) than for the corresponding formation of the 5-membered ring in **1b** ($\Delta G^{\ddagger}_{RE}$ = 14.7 kcal/mol). Overall, calculations indicate oxidative addition (TS_{OA}) to be the reactivity-limiting step and C−C bond formation to occur via a Pd^{II}/Pd^{IV} pathway rather than a redox-neutral Pd^{II}-catalyzed cycle.

■ CONCLUSION

In conclusion, we have developed a highly stereoselective method for the synthesis of 3-(chloromethylene)oxindoles that takes advantage of an in situ-generated vinyl Pd^{II} species. Excellent regio- and stereoselectivities are observed for the alkyne chloropalladation step, which is particularly rare for relatively unbiased, internal alkynes. High regioselectivities are achieved by virtue of the reversibility of the *cis*-chloropalladation step. We demonstrate that the vinyl chloride functionality in the products can be functionalized through a variety of transformations, thus providing a divergent route to access a library of medicinally relevant scaffolds. Our calculations support a mechanism involving a $Pd^{II/IV}$ cycle, wherein C−C bond reductive elimination is the driving force for the reaction. Overall, carbamoyl chlorides are extremely versatile intermediates in organic synthesis, and their application in Pd-catalyzed cross-couplings can provide efficient entry to a range of nitrogen-containing heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08925.

Experimental procedures, computational details, spectral data for all new compounds, and crystallographic data (PDF)

X-ray crystallographic data for *Z*-**1v** (CIF)

X-ray crystallographic data for **2z** (CIF)

X-ray crystallographic data for *Z*-**1bc** (CIF)

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Notes

The authors declare no competing financial interest.

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