Synthetic Methods

International Edition: DOI: 10.1002/anie.201507883
German Edition: DOI: 10.1002/ange.201507883

An Exclusively *trans*-Selective Chlorocarbamoylation of Alkynes Enabled by a Palladium/Phosphaadamantane Catalyst

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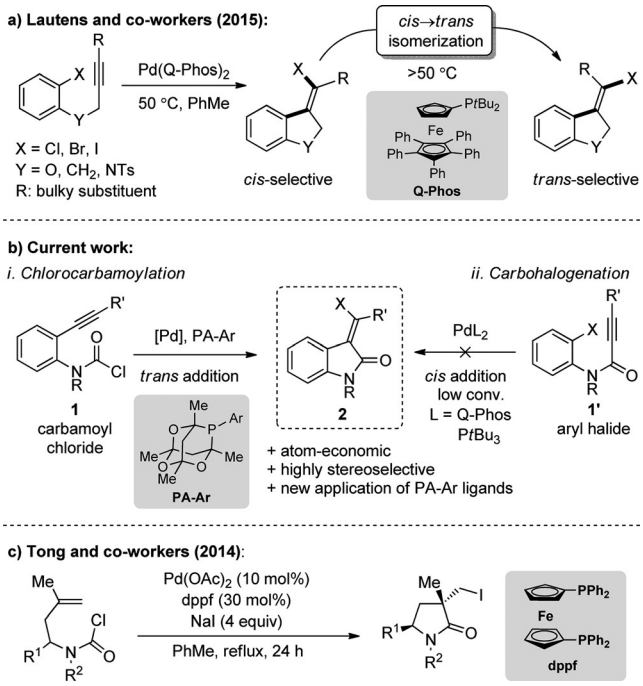
Abstract: *Pharmaceutically relevant methylene oxindoles are synthesized by a palladium(0)-catalyzed intramolecular chlorocarbamoylation reaction of alkynes. A relatively underexplored class of caged phosphine ligands is uniquely suited for this transformation, enabling high levels of reactivity and exquisite trans selectivity. This report entails the first transition-metal-catalyzed atom-economic addition of a carbamoyl chloride across an alkyne.*

The palladium-catalyzed carbohalogenation of unsaturated C–C bonds has emerged as a robust method for the synthesis of organic halides.[1] Although significant advances in the area of alkene carbohalogenation have been demonstrated,[2] reports using alkynes remain scarce.[3] To this end, we recently described a stereodivergent Pd-catalyzed alkyne carbohalogenation reaction using aryl halides, which relied on the combined steric bulk of both catalyst and substrate to promote the desired reactivity (Scheme 1 a).[3c] Depending on the nature of the terminal alkyne substituent and the temperature of the reaction, both the *cis* and *trans* vinyl halide products could be accessed by a Pd-mediated isomerization process. During this investigation, we noticed that aryl halides **1′** bearing an amide tether were not suitable substrates for this transformation, giving only trace amounts of methylene oxindole **2** under various conditions (Scheme 1 b). Our motivation for accessing this structural manifold lies in its frequent occurrence in a number of bioactive molecules and pharmaceuticals[4] as well as its synthetic utility in target-oriented synthesis.[5] Considering the limited number of methods available to access 3-(halomethylene)oxindoles in a highly stereoselective fashion, we sought to access this motif through an alternative disconnection employing carbamoyl chlorides **1** as precursors.[6]

An analysis of the literature revealed that in contrast to acid chlorides and chloroformates,[7] carbamoyl chlorides have not been frequently exploited in transition-metal-catalyzed alkyne addition reactions, despite their potential for accessing valuable N-containing heterocycles.[8] Moreover,



Scheme 1. a) Stereodivergent vinyl halide synthesis by Pd-catalyzed alkyne carbohalogenation. b) Alternative synthetic routes towards the 3-(halomethylene)oxindole scaffold. c) Palladium-catalyzed formal carboiodination of alkenes using aliphatic carbamoyl chlorides.

the proposed chlorocarbamoylation reaction is a completely unknown process.[9] A recent report by Tong and co-workers illustrated the synthetic potential of alkene-tethered carbamoyl chlorides in a Pd-catalyzed formal carboiodination reaction (Scheme 1 c).[2f] It should be noted that in the absence of NaI, the organochloride product could not be obtained, suggesting that Pd/dppf is not a suitable catalyst for promoting the elusive C_{sp^3}–Cl reductive-elimination step.

Herein, we report that aryl phosphaadamantane (PA-Ar) ligands (PA-Ar = 1,3,5,7-tetramethyl-2,4,8-trioxa-6-aryl-6-phosphaadamantane) are uniquely suited to promote the Pd^0-catalyzed intramolecular chlorocarbamoylation of alkynes, representing the first application of these caged phosphine ligands in a C–Cl bond-forming reaction.[10] Furthermore, the transformation proceeds with exquisite *trans* selectivity, which seemingly disobeys the requirement for a *cis* carbopalladation in the alkyne insertion step. Although the *cis*→*trans* isomerization of vinyl palladium species has been well-documented in intermolecular cross-couplings,[11] there are few systems that enable the exclusive formation of the *trans* isomer in intramolecular alkyne addition reactions.[12]

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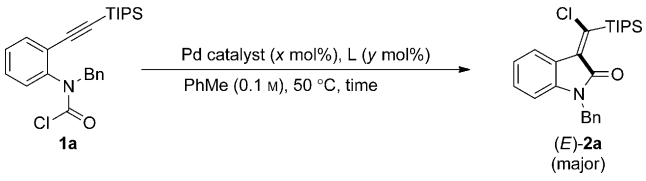
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201507883.

Taking into account the importance of steric bulk in promoting carbon–halogen reductive elimination, carbamoyl chloride **1a** was chosen for the reaction optimization (Table 1). Initial screening revealed that both $Pd(PtBu_3)_2$ and $Pd(Q\text{-}Phos)_2$ were inefficient catalysts for the chlorocarbamoylation reaction, giving low yields of **2a** (entries 1 and 2). Upon switching to $Pd(PtBu_2Ph)_2$, a significant increase in reactivity was observed (entry 3). Attempts to push the reaction to full conversion by switching to higher temperatures and/or catalyst loadings were met with failure. It should be noted that in all cases, the *E* isomer, formally resulting from a *trans* addition process, was observed as the major product. In search of a more efficient catalyst, we were prompted to investigate ligands based on the phosphaadamantane core, as its steric bulk and electronic properties are comparable to those of a $PtBu_2$ group and a $P(OR)_2$ group, respectively.[13] Furthermore, these ligands are stable to air, moisture, and column chromatography, making them particularly attractive for reaction development. After screening a variety of PA-Ar ligands (Supporting Information, Scheme S1), PA-Ph proved to be the best, providing **2a** in 99% yield ($E/Z > 99{:}1$) after 3 h (entry 4).[14] At higher concentration and longer reaction times, the catalyst loading could be decreased to 1.25 mol% (entry 5). Entries 6 and 7 demonstrate that maintaining a 1:2 Pd/L ratio is crucial for the reactivity, and that the reaction does not proceed in the absence of Pd. Notably, applying Tong's conditions[2f] to substrate **1a** led to inferior results (entry 8).

Table 1: Reaction optimization.

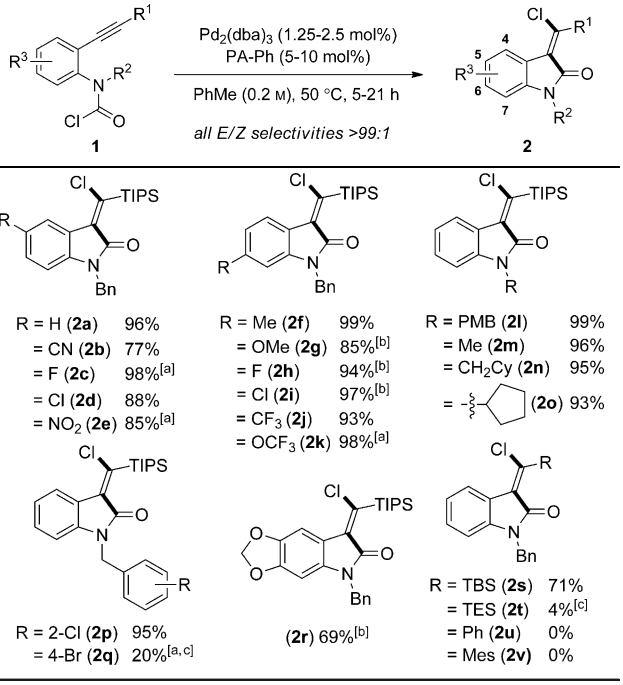


Entry	Pd catalyst (*x* mol%)	Ligand (*y* mol%)	Time [h]	Conv.[a] [%]	Yield[a] [%]	*E*/*Z*[a] [%]
1	$Pd(PtBu_3)_2$ (5)	–	18	19	12	N.D.[b]
2	$Pd(Q\text{-}Phos)_2$ (5)	–	18	28	21	N.D.[b]
3	$Pd(PtBu_2Ph)_2$ (5)	–	18	92	86	>99:1
4	Pd_2dba_3 (2.5)	PA-Ph (10)	3	100	99	>99:1
5[c]	*Pd_2dba_3 (1.25)*	*PA-Ph (5)*	*5*	*100*	*99*	*>99:1*
6[c]	Pd_2dba_3 (1.25)	PA-Ph (5)	21	26	8	>99:1
7[c]	–	PA-Ph (5)	5	7	0	–
8[d]	$Pd(OAc)_2$ (10)	dppf (30)	24	24	<2	N.D.

[a] Conversions, NMR yields, and *E*/*Z* ratios were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. NMR yields of the major isomer are given. [b] Formation of other side products prevented clear determination of the *E*/*Z* ratios by ^{1}H NMR analysis of the crude reaction mixture. [c] Concentration: 0.2 M. [d] With NaI (4.0 equiv), 0.067 M, reflux. N.D. = not determined.

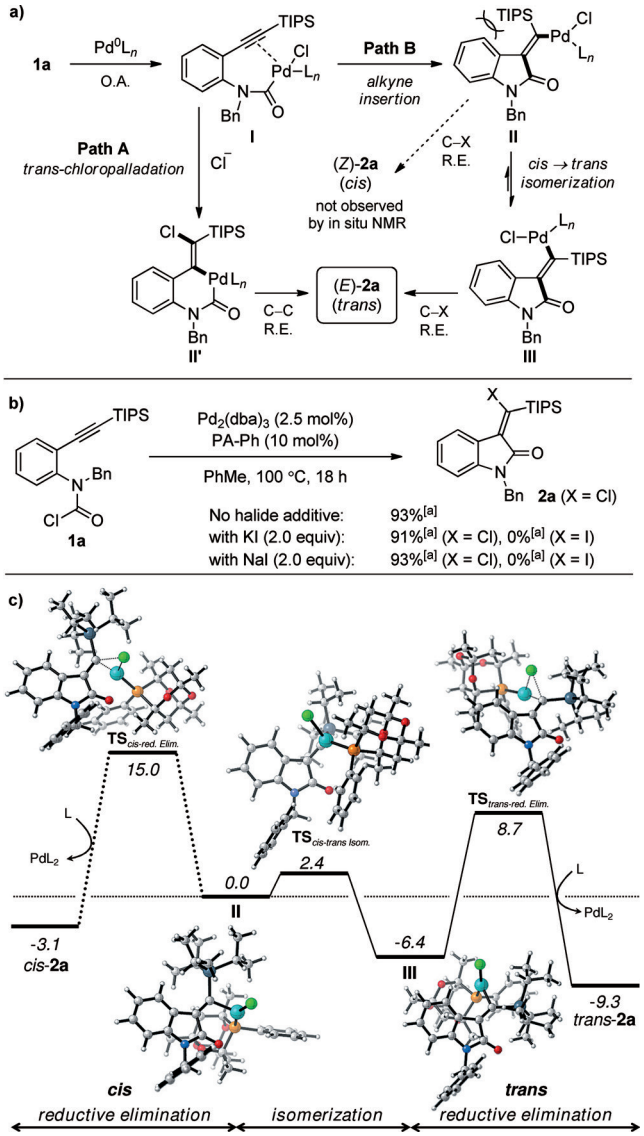
With our optimized conditions in hand, we then investigated the substrate scope (Table 2). Substrates with electron-withdrawing substituents at the 5- (**1b**, **1c**, **1e**) or 6-position (**1h**, **1j**, **1k**) were well tolerated. Substrate **1f** demonstrated excellent reactivity, but more electron-rich carbamoyl chlorides (**1g** and **1r**) were significantly less reactive under the standard conditions. Having additional Cl atoms on either the aromatic backbone (**1d**, **1i**) or the benzyl group (**1p**) did not compromise the reaction. However, the presence of a more reactive C_{sp^2}–Br bond (**1q**) did have a negative impact on the yield. The reaction efficiency was minimally impacted upon changing the nature of the N-protecting group (**1l**–**1o**), but having a bulky silyl alkynyl substituent proved to be necessary (**1s** vs. **1t**). Aryl substituents were incompatible with the standard reactions conditions (**1u** and **1v**). In all examples, exclusive selectivity for the *E* isomer (>99:1) was observed. To confirm our stereochemical assignment, an X-ray crystal structure of (*E*)-**2b** was obtained, and the *E*/*Z* ratios for all other examples were determined by comparing analogous chemical shifts in the ^{1}H NMR spectra.[15]

Table 2: Substrate scope.



[a] $Pd_2(dba)_3$ (2.5 mol%), PA-Ph (10 mol%). [b] $Pd_2(dba)_3$ (2.5 mol%), PA-Ph (10 mol%), 100 °C. [c] Yield determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

To account for the high *trans* selectivity, we propose two possible mechanistic pathways (A or B) and present experimental and computational data that support pathway B (Scheme 2a).[16] Both catalytic cycles begin with oxidative addition of Pd^0 into the carbamoyl chloride bond. In pathway A, an in situ released chloride ion (from another molecule of **1a**) could trap intermediate **I** by a *trans* chloropalladation process, which, upon C–C reductive elimination, would give (*E*)-**2a**. To test the feasibility of an ionic pathway, we conducted the reaction in the presence of exogenous halide additives (KI or NaI, Scheme 2b).[17] In both cases, **1a** was fully converted into **2a** (X = Cl) with no halide exchange products observed in the ^{1}H NMR spectrum of the crude reaction mixture, thus disfavoring pathway A. Alternatively,



Scheme 2. a) Proposed mechanism. b) Halide exchange experiments. [a] NMR yield determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. c) Gibbs free energy pathway calculated at the CPCM (toluene) M06L/def2-TZVP//B3LYP/6-31G(d)(LANL2DZ) level of theory (in kcal mol^{-1}).

in pathway B, *cis* carbopalladation would generate vinyl Pd species **II**. C–Cl reductive elimination would initially lead to (*Z*)-**2a**, which could re-enter the catalytic cycle and undergo a Pd-mediated isomerization process. When the reaction was monitored by in situ NMR spectroscopy, we did not observe the formation of (*Z*)-**2a** at the time intervals examined.[14] In fact, we observed the exclusive and immediate formation of (*E*)-**2a** at a rate comparable to the rate of starting-material disappearance. This suggests that direct C–Cl reductive elimination from **II** is highly disfavored, and that a fast *cis*→*trans* isomerization (**II**→**III**) occurs.

To gain further insight, we undertook computational studies of path B in Scheme 2, employing the method M06L/def2-TZVP along with the solvation model CPCM (for toluene).[18,19] Following oxidative addition, alkyne insertion in intermediate **I** was calculated to proceed with a barrier of $\Delta G^{\ddagger} = 14.7$ kcal mol^{-1}. The subsequent *cis*→*trans* isomerization of **II** to the more stable intermediate **III** was found to be facile ($\Delta G^{\ddagger} = 2.4$ kcal mol^{-1}) and hence significantly favored over direct reductive elimination from **II** (Scheme 2c). Overall, isomerization followed by reductive elimination from **III** is the kinetically and thermodynamically favored pathway. The TIPS group was found to be crucial in easing the *cis*→*trans* isomerization as well as lowering the energetic span,[20] thereby improving catalytic efficiency. The latter was also found to be the likely origin of the superior activity of the PA-Ph ligand.

In conclusion, we have developed a highly efficient palladium-catalyzed intramolecular chlorocarbamoylation reaction that provides access to methylene oxindole scaffolds. The steric bulk and electron-deficient nature of the PA-Ar ligands make them ideal for promoting difficult reductive eliminations. The developed method demonstrates exquisite selectivity for the *E* isomer, thus representing a rare instance of a highly selective formal *trans* carbopalladation pathway.[12]

Experimental Section

A 2 dram vial was charged with Pd_2dba_3 (2.9 mg, 0.00313 mmol, 1.25 mol%), PA-Ph (3.7 mg, 0.0125 mmol, 5 mol%), and **1a** (106.5 mg, 0.25 mmol, 1.0 equiv). After purging the reaction mixture with a flow of argon for 15 min, anhydrous toluene (1.25 mL) was added. The vial was sealed with a Teflon-lined cap and placed in a pre-heated oil bath at 50 °C. After 5 h, the reaction mixture was cooled to room temperature and passed through a plug of silica gel, washing with Et_2O. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography.

Acknowledgments

We thank Alphora Inc., the Natural Sciences and Engineering Research Council of Canada (NSERC), and the University of Toronto (U of T) for financial support. M.L. (O.C.) thanks the Canada Council for the Arts for a Killam Fellowship. C.M.L. thanks NSERC for a postgraduate scholarship. We thank Cytec for the donation of phosphines, Johnson Matthey for Pd catalysts, Dr. Paul Murray (Paul Murray Catalysis Consulting Ltd.) for conducting ligand mapping studies and pointing us towards the PA-Ar ligands, Dimitry Pichugin (U of T) for assistance with NMR studies, and Dr. Alan J. Lough (U of T) for obtaining the crystal structure of **2b**. F.S. and T.S. thank the RWTH Aachen, MIWF NRW, and the Evonik foundation (scholarship to T.S.) for funding.

Keywords: chlorocarbamoylation · cyclization · homogenous catalysis · palladium · phosphaadamantane

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 15897–15900
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[14] See the Supporting Information for details.

[15] CCDC 1419478 (**2b**) contains 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.

[16] See the Supporting Information for studies that disfavor a radical pathway.

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Received: August 23, 2015
Revised: September 30, 2015
Published online: November 20, 2015

