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Palladium(0)-Catalyzed Alkynylation of C(sp³)-H Bonds

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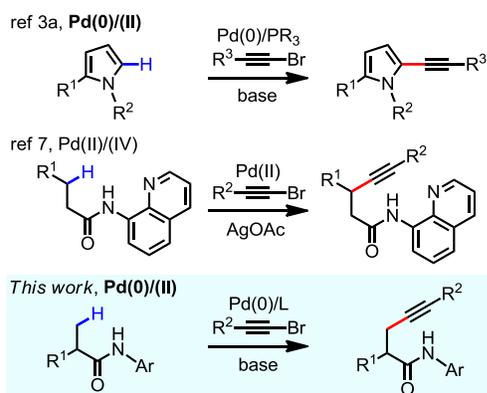
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Abstract: The alkynylation of β -C(sp³)-H bonds in aliphatic amides with alkynyl halides has been enabled using Pd(0)/*N*-heterocyclic carbene (NHC) and Pd(0)/phosphine (PR₃) catalysts. This is the first example of utilizing [AlkynylPd(II)L_n] complexes to activate C(sp³)-H bonds.

The Pd(0)-catalyzed Sonogashira coupling reaction, which couples alkynes with aryl halides or pseudohalides, is a pivotal C-C bond forming reaction in modern organic synthesis.¹ The development of complementary methods to convert C-H bonds into C-alkynyl bonds is highly attractive, as the alkyne moiety remains an essential functional group in many cross-coupling, metathesis and cycloaddition reactions.² In a pioneering study, Gevorgyan demonstrated the feasibility of coupling heterocyclic C(sp²)-H bonds with alkynyl halides using Pd(0)/PR₃ catalysts.^{3a} Pd(II)/Pd(0) catalysis has also been successfully employed in the cross-coupling of heterocycles with alkynes.⁴ However, despite a number of reports concerning C(sp²)-H alkynylation reactions,³⁻⁷ methods to convert inert C(sp³)-H bonds to C(sp³)-alkynyl bonds remain rare, with only a single example reported by Chatani illustrating the Pd(II)-catalyzed coupling of C(sp³)-H bonds with alkynyl halides via Pd(II)/Pd(IV) catalysis.⁸ Herein, we report the first example of Pd(0)/NHC and Pd(0)/PR₃-catalyzed alkynylation of β -C(sp³)-H bonds using an *N*-arylamide auxiliary.

Scheme 1. C-H Alkynylation using Pd(II) and Pd(0) Catalysts



Recently, substantial progress has been made in the development of Pd(II)-catalyzed C(sp³)-H activation reactions.^{8,9} In contrast, Pd(0)/PR₃-catalyzed intermolecular C(sp³)-H bond activation remains underdeveloped, with only one example of β -arylation of amides reported by our group in 2009.¹⁰ Since Pd(0)/Pd(II)-catalysis is compatible with a wide range of ligands and does not require co-oxidants, we embarked on expanding the scope of C(sp³)-H activation reactions using Pd(0)/Pd(II)-catalysis. We envisioned that β -alkynylation of C(sp³)-H bonds would be highly desirable, as it installs a versatile handle for further structural elaboration of aliphatic acid derivatives. However, unlike the active [ArylPd(II)L_n] species generated from ArX/Pd(0) catalysis,^{11,12} [AlkynylPd(II)L_n] complexes formed *via*

oxidative addition of alkynyl halide have not been demonstrated to cleave inert C(sp³)-H bonds. In addition, upon C(sp³)-H activation, reductive elimination to generate the desired C(sp³)-alkynyl bond from a Pd(II) center has no precedent, although a rare example of Sonogashira coupling with alkyl halides was achieved by Fu.¹³

With these considerations in mind, we initiated our investigation of the Pd(0)-catalyzed β -C(sp³)-H alkynylation of *N*-arylamide **1a**. Initial screening of the ligands (0.2 equiv.) was carried out by reacting 0.1 mmol of amide **1a** with 10 mol% of Pd(OAc)₂, 2 equiv. of TIPS-alkynyl iodide and 2 equiv. of Cs₂CO₃ in toluene at 80 °C under nitrogen for 8 hours (Table 1). To our delight, using PCy₃·HBF₄ as the ligand,¹⁴ we obtained the desired alkynylation product **2a** in 41% yield; however, we also identified that **2a** could undergo Pd-catalyzed aminoalkynylation of the initially installed alkynyl group to give the undesired product **3a** (Table 1, entry 1).¹⁵ In order to suppress this undesired side reaction, we changed the alkynyl iodide to the corresponding bromide, which gave 40% of **2a** and improved the product ratio between **2a** and **3a** to 5:1 (Table 1, entry 2). TIPS-alkynyl chloride yielded no product, presumably due to its sluggish oxidative addition onto Pd(0). Subsequently, we carried out an extensive screening of solvents using PCy₃·HBF₄ and TIPS-alkynyl bromide to find that freshly distilled Et₂O gave the best yield of **2a** in 61% yield while affording only 2% of **3a** (Table 1, entry 8). Polar, strongly coordinating solvents such as DMF and DMSO promoted the decomposition of the alkynyl bromide and gave no desired product.

Table 1. Screening of Alkynyl Halide and Solvent^{a,b}

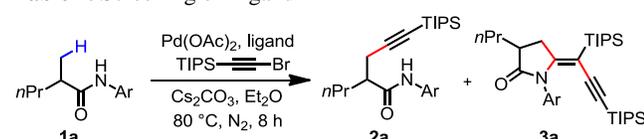
Entry	X	Solvent	¹ H NMR yield (%)		Entry	X	Solvent	¹ H NMR yield (%)	
			2a	3a				2a	3a
1 ^c	I	PhMe	41	17	6	Br	<i>n</i> -hexane	43	3
2	Br	PhMe	40	8	7	Br	THF	28	12
3 ^d	Cl	PhMe	0	0	8	Br	Et ₂ O	61	2
4	Br	PhCF ₃	37	5	9	Br	DMF	0	0
5	Br	C ₆ F ₆	17	1	10	Br	DMSO	0	0

^a Conditions: substrate (0.1 mmol), Pd(OAc)₂ (10 mol%), PCy₃·HBF₄ (20 mol%), alkynyl halide (2.0 equiv.), Cs₂CO₃ (2.0 equiv.), Et₂O (0.5 mL), 80 °C, 8 h. ^b The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard. ^c 6 h. ^d 24 h.

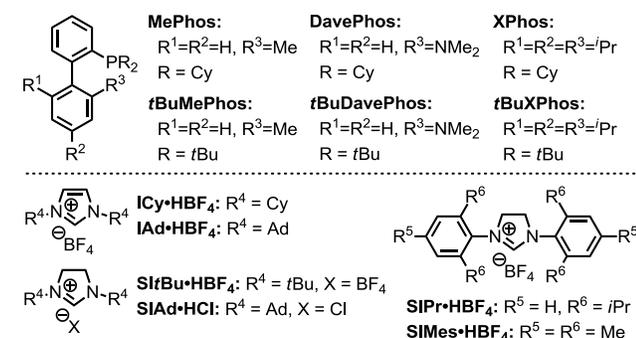
Having identified the optimal alkynyl halide and solvent, we screened a wide range of PR₃ and NHC ligands (Table 2). The trialkyl phosphine ligands, such as P^tPr₃·HBF₄ and PdAd₂*n*Bu·HBF₄ both gave **2a** in 55% yields, while suppressing the

formation of **3a**. $\text{PrBu}_2\text{Ph}\cdot\text{HBF}_4$ diminished the yield to 7%; in contrast, Buchwald ligands that possess dialkyl-biaryl phosphine backbone gave improved yields. In particular, highly sterically hindered and electron-donating $t\text{BuXPhos}\cdot\text{HBF}_4$ afforded **2a** in 73% yield. Notably, unprotected phosphine ligand such as DavePhos was not as effective as its HBF_4 salt¹⁴ and gave a significantly lower yield (Table 2, entries 7–8). Subsequently, we investigated the use of a range of NHC ligands. Although cyclohexyl- and aryl-substituted NHC ligands led to poor yields (Table 2, entries 11–13), we were delighted to find that *tert*-butyl-substituted $\text{SI}t\text{Bu}\cdot\text{HBF}_4$, adamantyl-substituted $\text{IAd}\cdot\text{HBF}_4$, and $\text{SIAd}\cdot\text{HCl}$ ligands were as effective as $t\text{BuXPhos}\cdot\text{HBF}_4$, furnishing the desired product **2a** in over 70% yield (Table 2, entries 14–16). Overall, $\text{IAd}\cdot\text{HBF}_4$ gave the best yield and selectivity for **2a**. Further tuning of the reaction conditions were carried out using $\text{IAd}\cdot\text{HBF}_4$. We found that the use of $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (5 mol%) as the catalyst and running the reaction at 85 °C improved the yield of **2a** to 81% (see Supporting Information). Diisopropyl ether (*i*- Pr_2O) with higher boiling point was also tested as a solvent to run the reaction of substrate **1a** and the desired product **2a** was obtained in 84% yield.

Table 2. Screening of Ligand^a



Entry	Ligand	¹ H NMR yield (%) 2a	3a	Entry	Ligand	¹ H NMR yield (%) 2a	3a
1	PPh_3	11	3	10	$t\text{BuMePhos}\cdot\text{HBF}_4$	45	1
2	$\text{PCy}_3\cdot\text{HBF}_4$	61	2	11	$t\text{BuDavePhos}\cdot\text{HBF}_4$	57	6
3	$\text{P}i\text{Pr}_3\cdot\text{HBF}_4$	55	2	12	$t\text{BuXPhos}\cdot\text{HBF}_4$	73	2
4	$\text{PA}_{d_2}n\text{Bu}\cdot\text{HBF}_4$	55	1	13	$\text{ICy}\cdot\text{HBF}_4$	7	0
5	$\text{PrBu}_2\text{Ph}\cdot\text{HBF}_4$	7	0	14	$\text{SI}i\text{Pr}\cdot\text{HBF}_4$	23	8
6	$\text{MePhos}\cdot\text{HBF}_4$	41	2	15	$\text{SIMes}\cdot\text{HBF}_4$	44	5
7	DavePhos	35	1	16	$\text{SI}t\text{Bu}\cdot\text{HBF}_4$	76	4
8	$\text{DavePhos}\cdot\text{HBF}_4$	58	3	17	$\text{IAd}\cdot\text{HBF}_4$	75	2
9	$\text{XPhos}\cdot\text{HBF}_4$	27	1	18	$\text{SIAd}\cdot\text{HCl}$	70	1



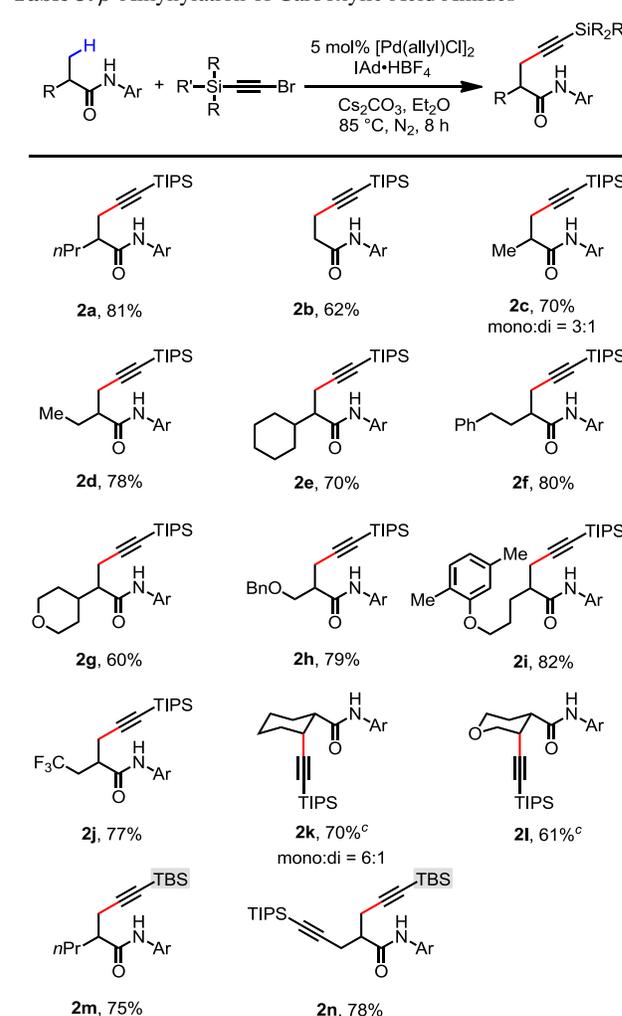
^a The reaction conditions are identical to those described in Table 1.

With the optimized reaction conditions in hand, we converted a variety of commercially available carboxylic acids into the corresponding amides to examine the scope of the alkylation protocol. Amides derived from aliphatic acids (**1a–e**) gave the corresponding alkylation products (**2a–e**) in good yields. For substrates with both β -methyl $\text{C}(\text{sp}^3)\text{–H}$ bonds and β -methylene $\text{C}(\text{sp}^3)\text{–H}$ bonds (**1a**, **1d**, **1f**, **1h**, **1i**, and **1n**), the β -methyl $\text{C}(\text{sp}^3)\text{–H}$ bond was selectively functionalized to give the corresponding products. Ethers were well tolerated and afforded the alkylation products (**2g**, **2h**, **2i** and **2l**) in good yields. The substrate containing a β -trifluoromethyl group could also be alkynylated to

form **2j** in 77% yield. This method was also found to be effective for the activation of cyclohexyl and tetrahydropyranyl $\text{C}(\text{sp}^3)\text{–H}$ bonds. Alkynylation of *N*-arylcyclohexanecarboxamide **1k** gave a mixture of mono- and di-alkynylated products (**2k mono**, **2k di**) in 70% combined yield; **2k mono** was isolated as a single *cis*-substituted diastereomer. Tetrahydropyran **1l** could also be alkynylated to provide a mono-*cis*-alkynylated product **2l** without further di-alkynylation.

TBS-alkynyl bromide was also used for alkylation of **1a** and **2c mono** to give **2m** and **2n** in 75% and 78%, respectively. However, other less hindered bromoalkynes were not reactive, most likely due to their propensity of coordinating with Pd center *via* the π bonds. Importantly, the TBS group was readily removed by treatment with TBAF to fashion the terminal alkyne unit, which could be utilized for further synthetic elaborations (see SI). It is worth noting that alkynyl group in substrate **2c mono** is tolerated, allowing for the installation of two distinct alkynyl groups in product **2n**. At this stage, amides derived from pivalic acid and other aliphatic acids that possess a quaternary α -carbon center gave poor yields. We presume that these sterically hindered amide substrates prevent coordination of the large $[\text{AlkynylPd}(\text{II})\text{L}_n]$ complex to the auxiliary, thus retarding $\text{C}(\text{sp}^3)\text{–H}$ activation. Further screenings of ligands and alkynyl halides are ongoing to overcome this limitation.

Table 3. β -Alkynylation of Carboxylic Acid Amides^{a,b}

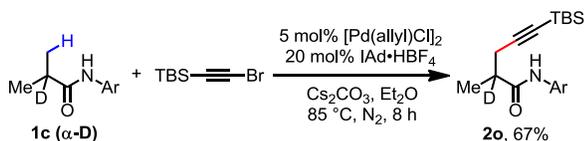


^a Conditions: substrate (0.1 mmol), $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (5 mol%), $\text{IAd}\cdot\text{HBF}_4$ (20 mol%), alkyne bromide (2.0 equiv.), Cs_2CO_3 (2.0 equiv.), Et_2O (0.5 mL), 85 °C, 8 h. ^b Isolated yields. ^c Single *cis*-diastereoisomer was obtained.

The mechanistic implications of this intermolecular C–H alkylation reaction merit discussion. To probe whether the

palladation at the acidic α -position and subsequent β -hydride elimination was responsible for the observed reactivity, we have prepared α -deutero substrate **1c** (α -D) and subjected it to the alkylation reaction conditions (Scheme 2). The product obtained (**2c** (α -D), 67%) fully retained the α -deuterium, thus suggesting that the Baudoin's β -hydride elimination pathway in the presence of LiNCy_2 is unlikely in our alkylation reactions.¹⁶ Since the cleavage of $\text{C}(\text{sp}^3)\text{-H}$ bonds by alkynylpalladium complexes has not been shown before, we prepared these complexes from Pd(0) and bromoalkynes in the presence of $t\text{BuXPhos-HBF}_4$ and reacted them with substrates under standard conditions. The formation of the desired product further supports the Pd(0)-catalyzed C-H activation reaction pathway (see SI).

Scheme 2. Deuterium Labeling in $\text{C}(\text{sp}^3)\text{-H}$ Alkylation



In summary, alkylation of $\text{C}(\text{sp}^3)\text{-H}$ bonds with alkynyl bromides has been achieved using Pd(0)/NHC and Pd(0)/ PR_3 catalysts without the use of co-oxidants. This illustrates the first example of utilizing $[\text{AlkynylPd}(\text{II})\text{L}_n]$ complexes to activate and alkynylate $\beta\text{-C}(\text{sp}^3)\text{-H}$ bonds of carboxylic acid derivatives. The extension of this method to effect enantioselective $\text{C}(\text{sp}^3)\text{-H}$ alkylation reactions by the use of optically active NHC and PR_3 ligands is currently underway in our laboratory.

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

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