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Palladium(0)-Catalyzed Alkynylation of C(sp^3)−H Bonds

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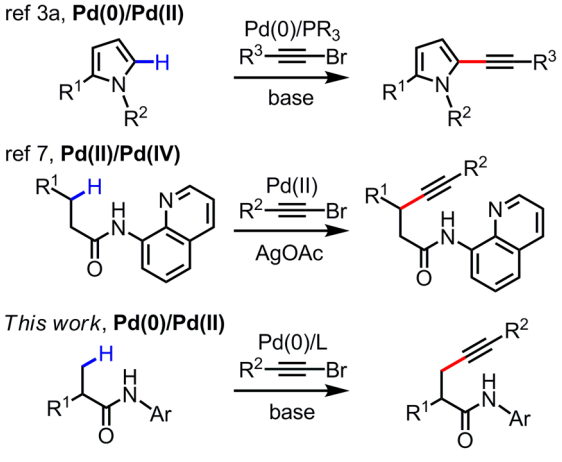
Supporting Information

ABSTRACT: The alkynylation of β-C(sp^3)−H bonds in aliphatic amides with alkynyl halides has been enabled using Pd(0)/*N*-heterocyclic carbene (NHC) and Pd(0)/phosphine (PR_3) catalysts. This is the first example of utilizing [AlkynylPd(II)L_n] complexes to activate C(sp^3)−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(sp^2)−H bonds with alkynyl halides using Pd(0)/PR_3 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(sp^2)−H alkynylation reactions,[3−7] methods to convert inert C(sp^3)−H bonds to C(sp^3)−alkynyl bonds remain rare, with only a single example reported by Chatani illustrating the Pd(II)-catalyzed coupling of C(sp^3)−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)/PR_3-catalyzed alkynylation of β-C(sp^3)−H bonds using an *N*-arylamide auxiliary (Scheme 1).

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(sp^3)−H activation reactions.[8,9] In contrast, Pd(0)/PR_3-catalyzed intermolecular C-(sp^3)−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(sp^3)−H activation reactions using Pd(0)/Pd(II) catalysis. We envisioned that β-alkynylation of C(sp^3)−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(sp^3)−H bonds. In addition, upon C(sp^3)−H activation, reductive elimination to generate the desired C(sp^3)−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(sp^3)−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 Cs_2CO_3 in toluene at 80 °C under nitrogen for 8 h (Table 1). To our delight, using $PCy_3{\cdot}HBF_4$ as the ligand,[14] we obtained the desired alkynylation product **2a** in 41% yield; however, we also identified that **2a** could undergo Pd-catalyzed amino-alkynylation of the initially installed alkynyl group to give the undesired product **3a** (Table 1, entry 1).[15] 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 $PCy_3{\cdot}HBF_4$ and TIPS−alkynyl bromide to find that freshly distilled Et_2O 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.

Having identified the optimal alkynyl halide and solvent, we screened a wide range of PR_3 and NHC ligands (Table 2). The trialkyl phosphine ligands, such as $PiPr_3{\cdot}HBF_4$ and $PAd_2nBu{\cdot}HBF_4$, both gave **2a** in 55% yields, while suppressing the formation of **3a**. $PtBu_2Ph{\cdot}HBF_4$ diminished the yield to 7%;

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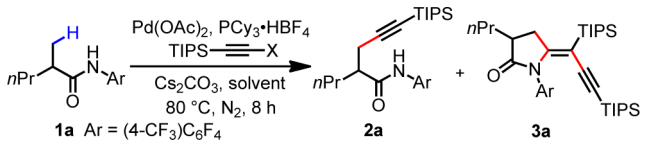
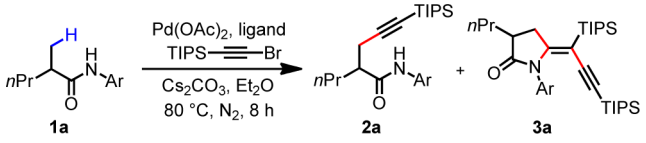
Table 1. Screening of Alkynyl Halide and Solvent[a,b]



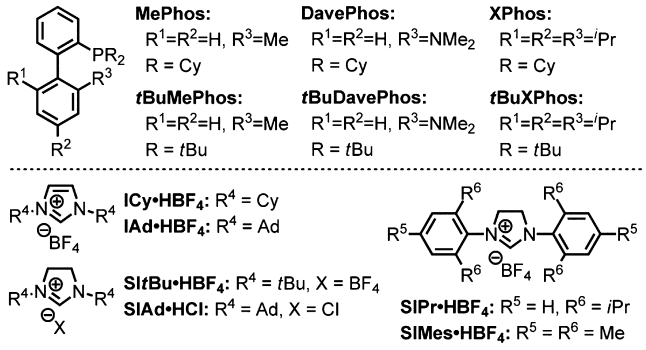
Entry	X	Solvent	^{1}H NMR yield (%) 2a	3a	Entry	X	Solvent	^{1}H NMR yield (%) 2a	3a
1[c]	I	PhMe	41	17	6	Br	*n*-hexane	43	3
2	Br	PhMe	40	8	7	Br	THF	28	12
3[d]	Cl	PhMe	0	0	8	Br	Et_2O	61	2
4	Br	$PhCF_3$	37	5	9	Br	DMF	0	0
5	Br	C_6F_6	17	1	10	Br	DMSO	0	0

[a]Conditions: substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol %), PCy_3·HBF_4 (20 mol %), alkynyl halide (2.0 equiv), Cs_2CO_3 (2.0 equiv), Et_2O (0.5 mL), 80 °C, 8 h. [b]The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c]6 h. [d]24 h.

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*BuMePhos•HBF_4	45	1
2	PCy_3•HBF_4	61	2	11	*t*BuDavePhos•HBF_4	57	6
3	$PiPr_3$•HBF_4	55	2	12	*t*BuXPhos•HBF_4	73	2
4	PAd_2nBu•HBF_4	55	1	13	ICy•HBF_4	7	0
5	$PtBu_2Ph$•HBF_4	7	0	14	SIPr•HBF_4	23	8
6	MePhos•HBF_4	41	2	15	SIMes•HBF_4	44	5
7	DavePhos	35	1	16	SI*t*Bu•HBF_4	76	4
8	DavePhos•HBF_4	58	3	17	IAd•HBF_4	75	2
9	XPhos•HBF_4	27	1	18	SIAd•HCl	70	1



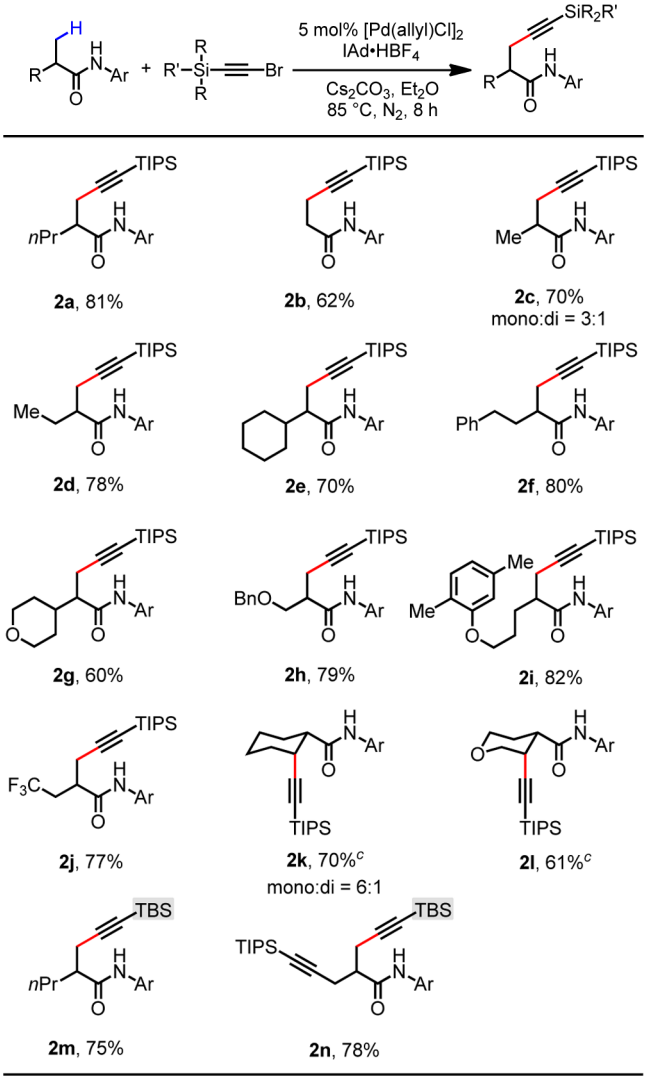
[a]The reaction conditions are identical to those described in Table 1.

in contrast, Buchwald ligands that possess dialkyl-biaryl phosphine backbone gave improved yields. In particular, highly sterically hindered and electron-donating *t*BuXPhos·HBF_4 afforded **2a** in 73% yield. Notably, unprotected phosphine ligand such as DavePhos was not as effective as its HBF_4 salt[14] and gave a significantly lower yield (Table 2, entries 7 and 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 13−15), we were delighted to find that *tert*-butyl-substituted SI*t*Bu·HBF_4, adamantyl-substituted IAd·HBF_4, and SIAd·HCl ligands were as effective as *t*BuXPhos·HBF_4, furnishing the desired product **2a** in over 70% yield (Table 2, entries 16−18). Overall, IAd·HBF_4 gave the best yield and selectivity for **2a**. Further tuning of the reaction conditions were carried out using IAd·HBF_4. We found that the use of $[Pd(allyl)Cl]_2$ (5 mol %) as the catalyst and running the reaction at 85 °C improved the yield of **2a** to 81% (see Supporting Information (SI)). 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.

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 alkynylation protocol (Table 3). Amides derived from aliphatic

Table 3. β-Alkynylation of Carboxylic Acid Amides[a,b]



[a]Conditions: substrate (0.1 mmol), $[Pd(allyl)Cl]_2$ (5 mol %), IAd·HBF_4 (20 mol %), alkynyl 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.

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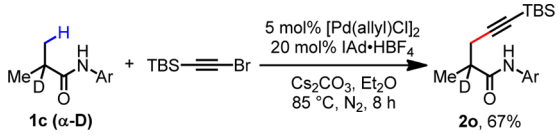
acids (**1a**–**e**) gave the corresponding alkynylation products (**2a**–**e**) in good yields. For substrates with both β-methyl C(sp^3)–H bonds and β-methylene C(sp^3)–H bonds (**1a**, **1d**, **1f**, **1h**, **1i**, and **1n**), the β-methyl C(sp^3)–H bond was selectively functionalized to give the corresponding products. Ethers were well tolerated and afforded the alkynylation 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 C(sp^3)–H bonds. Alkynylation of *N*-arylcyclohexanecarboxamide **1k** gave a mixture of mono- and dialkynylated 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 dialkynylation.

TBS–alkynyl bromide was also used for alkynylation of **1a** and **2c mono** to give **2m** and **2n** in 75% and 78%, respectively. However, other less hindered alkynyl bromides 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 [AlkynylPd(II)L_n] complex to the auxiliary, thus retarding C(sp^3)–H activation. Further screenings of ligands and alkynyl halides are ongoing to overcome this limitation.

The mechanistic implications of this intermolecular C–H alkynylation 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 alkynylation reaction conditions (Scheme 2). The product

Scheme 2. Deuterium Labeling in C(sp^3)–H Alkynylation



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 alkynylation reactions.[16] Since the cleavage of C(sp^3)–H bonds by alkynylpalladium complexes has not been shown before, we prepared these complexes from Pd(0) and alkynyl bromides in the presence of *t*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).

In summary, alkynylation of C(sp^3)–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 [AlkynylPd(II)L_n] complexes to activate and alkynylate β-C(sp^3)–H bonds of carboxylic acid derivatives. The extension of this method to effect enantioselective C(sp^3)–H alkynylation reactions by the use of optically active NHC and PR_3 ligands is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. 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.

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