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Tandem Catalytic C(sp^3)−H Amination/Sila-Sonogashira–Hagihara Coupling Reactions with Iodine Reagents**

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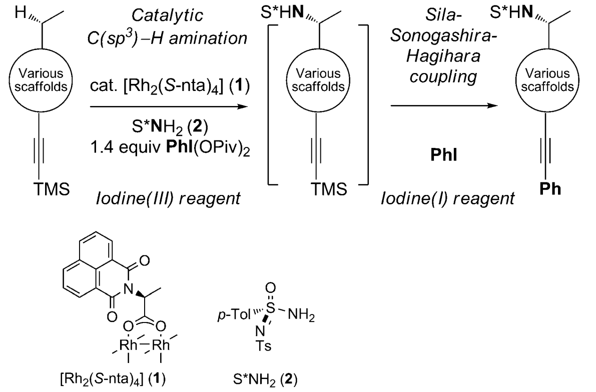
Abstract: *A new tandem C−N and C−C bond-forming reaction has been achieved through Rh^{II}/Pd^0 catalysis. The sequence first involves an iodine(III) oxidant, then the in situ generated iodine(I) by-product is used as a coupling partner. The overall process demonstrates the synthetic value of iodoarenes produced in trivalent iodine reagent mediated oxidations.*

Catalytic tandem reactions are efficient synthetic tools to address the issues of molecular diversity.[1] Their development challenges the creativity of organic chemists, such that new functionalized molecular architectures can be accessed by appropriate sequences of C−C and C−X bond-forming reactions.[2] Tandem reactions are also relevant in the context of sustainable chemistry because their application can offer the opportunity to convert side-products, generated during the first step, in a subsequent transformation of the sequence.[2b,c,3]

The last two decades have witnessed major developments in the chemistry of hypervalent iodine compounds.[4] These compounds are nontoxic reagents, mostly derived from iodobenzene (PhI), which can perform selective transformations.[5] However, a major issue often pointed out in hypervalent iodine chemistry is the low atom economy resulting from the generation of PhI in stoichiometric amounts. To circumvent this drawback, processes involving either catalytic amounts of iodine reagents[5d,6,7] or recyclable iodine compounds[7a,8] have been designed. In the context of sustainability, however, using the iodoarene side-products in tandem catalysis could also be envisioned. This approach could provide rapid access to new molecular building blocks while reducing the production of waste.

Efficient atom-transfer reactions have also been achieved with hypervalent iodine reagents.[9] Of particular relevance is the use of iminoiodinanes as nitrene precursors in the presence of metal complexes.[10] Recent investigations have led to the discovery of efficient catalytic C(sp^3)−H amination[11] and alkene aziridination.[12] In line with the emergence of PhI-catalyzed reactions, studies were aimed at searching for nitrene additions with catalytic amounts of iodine, but these were unsuccessful.[13] Accordingly, we have envisaged an alternate solution which relies on the design of new tandem catalytic reactions. We therefore report herein a C(sp^3)−H amination/sila-Sonogashira–Hagihara coupling sequence which enhances the synthetic value of ArI-based iodine(III) oxidants (Scheme 1).



Scheme 1. Tandem C(sp^3)−H amination/sila-Sonogashira–Hagihara coupling. TMS = trimethylsilyl.

We have recently described a stereoselective C(sp^3)−H amination of hydrocarbons, and it involves the chiral rhodium(II) complex **1** as the catalyst and an iodine(III) reagent as the oxidant.[14] Thus, we hypothesized that the iodobenzene generated from our effective amination reaction could be subsequently used in a metal-catalyzed cross-coupling. We took inspiration from the sila-Sonogashira–Hagihara reaction conditions[15] to investigate the one-pot combination with a catalytic nitrene transfer (Table 1). After the initial step of C(sp^3)−H amination from **3a**, application of the reaction conditions reported by Nagasaka et al.,[15a] however, did not prove successful (entry 1). Pleasingly, by replacing $n\mathrm{Bu_4NCl}$ by $n\mathrm{Bu_4NF}$ (TBAF) and increasing the amount of silver carbonate, the tandem reaction proceeded in a one-pot manner to give the expected product **4aa** in 49% yield (entry 2). Further improvement was obtained with the addition of a base in the reaction mixture. A rapid screening determined that K_2CO_3 was the most suitable base (see Table S1 in the Supporting Information). Thus, adding 3 equivalents of K_2CO_3 generated compound **4aa** in 65% yield (Table 1, entry 3). This result was improved by adjusting the amount of TBAF to 2 equivalents (entry 4). A screening of silver salts and palladium complexes revealed that Ag_2CO_3

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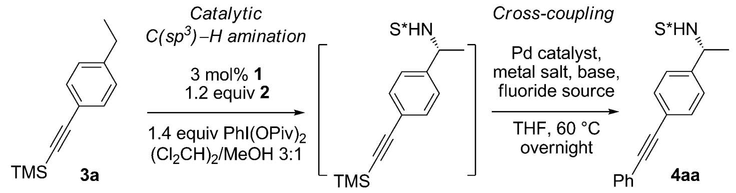
and [Pd(PPh$_3$)$_4$] were the most efficient (Table S1). Interestingly, decreasing the amount of palladium catalyst to 5 mol% did not affect the yield (Table 1, entry 5). We then decided to study the effect of copper salts in the sila-Sonogashira–Hagihara reaction.[16] As revealed by the screening of various copper(I) sources, their use has a beneficial effect on the yield and copper(I) chloride proved to be the most effective (see Table S2).[17,18] Replacing Ag$_2$CO$_3$ by CuCl generated **4aa** in 82% yield (Table 1, entry 6). We then found that the use of an organic base, such as DABCO, afforded **4aa** in higher purity and yields (entries 7–9). Finally, an optimal yield of 89% was reached by running the reaction in THF at 70°C (entry 10). Additionally, application of these reaction conditions prevents the formation of side-products which were observed in the previous experiments with CuCl.[19,20]

Table 1: Screening of reaction conditions for the tandem reactions.[a]



Entry	Pd catalyst (mol%)	Metal salt (equiv)	Base (equiv)	F$^-$ source (equiv)	Yield [%][b]
1	[Pd(PPh$_3$)$_4$] (10)	Ag$_2$CO$_3$ (0.5)	–	nBu$_4$NCl (1.5)	< 5
2	[Pd(PPh$_3$)$_4$] (10)	Ag$_2$CO$_3$ (1)	K$_2$CO$_3$ (3)	nBu$_4$NF (1.5)	49
3	[Pd(PPh$_3$)$_4$] (10)	Ag$_2$CO$_3$ (1)	K$_2$CO$_3$ (3)	nBu$_4$NF (1.5)	65
4	[Pd(PPh$_3$)$_4$] (10)	Ag$_2$CO$_3$ (1)	K$_2$CO$_3$ (3)	nBu$_4$NF (2)	74
5	[Pd(PPh$_3$)$_4$] (5)	Ag$_2$CO$_3$ (1)	K$_2$CO$_3$ (3)	nBu$_4$NF (2)	75
6	[Pd(PPh$_3$)$_4$] (10)	CuCl (1)	K$_2$CO$_3$ (3)	nBu$_4$NF (2)	82[c]
7	[Pd(PPh$_3$)$_4$] (10)	CuCl (1)	DABCO (3)	nBu$_4$NF (2)	82[d]
8	[Pd(PPh$_3$)$_4$] (10)	CuCl (1)	DABCO (4)	nBu$_4$NF (2)	86[d]
9	[Pd(PPh$_3$)$_4$] (5)	CuCl (1)	DABCO (4)	nBu$_4$NF (2)	84[c]
10[e]	[Pd(PPh$_3$)$_4$] (10)	CuCl (1)	DABCO (4)	nBu$_4$NF (2)	89[f]

[a] Reaction conditions: a mixture of **3a** (0.2 mmol), **2** (0.24 mmol), **1** (3 mol%), and PhI(OPiv)$_2$ (0.28 mmol) is stirred at −35°C for 72 h. A base (0.6 to 0.8 mmol), [Pd(PPh$_3$)$_4$] (5 to 10 mol%), THF (1 mL), TBAF (0.6 mmol) and the silver or copper salt (0.2 mmol) are added. The mixture is stirred at 60°C. [b] After flash chromatography. [c] Isolated in mixture with 6% of the side products. [d] Isolated in mixture with 3% of the side products. [e] Run at 70°C. [f] < 1% of the side products. DABCO = l,4-diazabicyclo[2.2.2]octane.

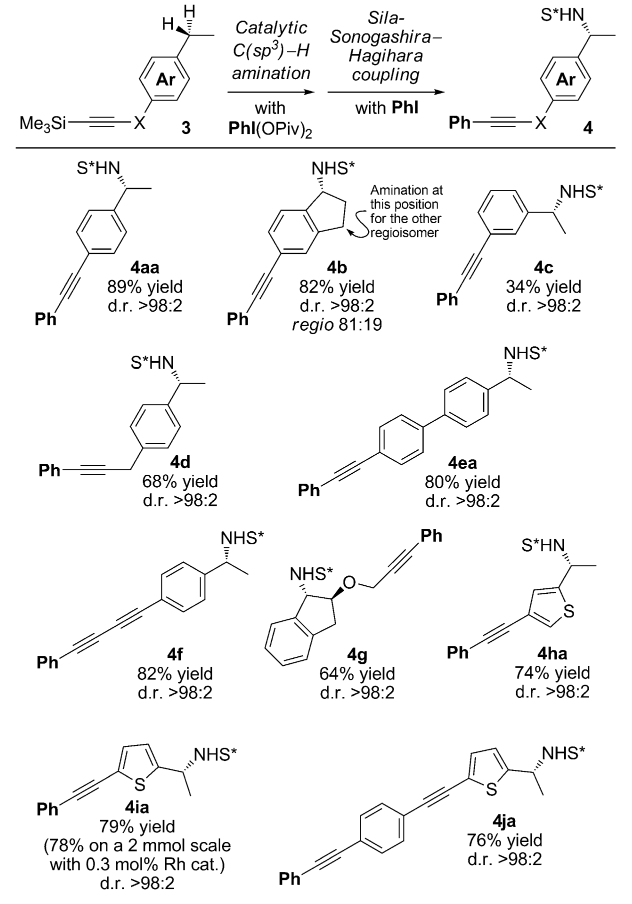
The optimized reaction conditions were applied to various aromatic substrates to investigate the scope of the tandem benzylic C(sp^3)–H amination/palladium-catalyzed coupling reaction (Scheme 2). This method allows the stereoselective preparation of functionalized conjugated systems of potential interest for the development of optoelectronic devices such as organic field effect transistors and organic light-emitting diodes.[21] The expected products **4** were generally obtained as a single isomer with yields in the 64–89% range, except in the case of the *meta*-substituted derivative **4c** which was isolated in 34% yield.[22] This result, however, is in line with the 4:1 ratio of *para/meta* regioisomers observed with the 5-substituted indan **4b**. Worthy of note is the complete chemoselectivity observed for the formation of **4d** despite the presence of two benzylic sites in the starting material.[23] Moreover, in all cases, the alkynes proved inert towards the C(sp^3)–H amination reaction conditions.[24] The overall transformation can be performed on a 2 mmol scale with equal efficiency, even using only 0.3 mol% of the rhodium complex, as shown in the case of **4ia**.

The scope of the tandem reaction was extended to alkenes and adamantane derivatives (Scheme 3). The reaction proceeded with excellent chemo-, regio-, and stereoselectivity to provide the expected products with yields ranging from 62 to 82%. Importantly, the examples displayed in Schemes 2 and 3 show that the presence of a propargyl ether, a vinyl chloride moiety, and even an ester group is well tolerated under these reaction conditions.

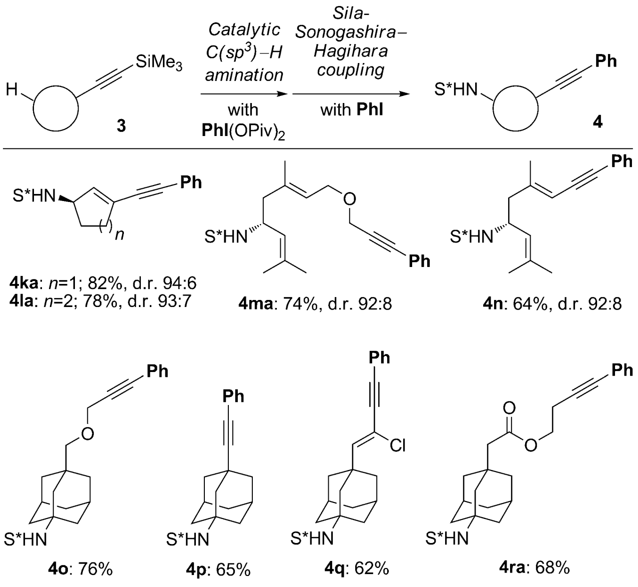
Finally, we can improve the molecular diversity accessible through this process by running the reaction with (diacetoxy)-iodoarenes, thus, allowing the introduction of various aromatic rings on the substrate. The iodine(III) oxidants, substituted either by an electron-withdrawing or electron-donating group, were prepared from the corresponding iodoarenes by a simple reaction with sodium perborate.[25] We were very pleased to observe that the nature of these reagents do not influence the efficiency of the C(sp^3)–H amination and the palladium-catalyzed coupling. The expected products were isolated with comparable yields in the 54–86% range (Scheme 4). Of particular interest is the introduction of a wide range of *ortho*-, *meta*-, and *para*-substituted aromatic rings as well as a naphthyl and a thienyl ring. Thus, this methodology highlights, for the first time, the value of iodoarene-derived oxidants as versatile building blocks in synthesis.[26]

In terms of the mechanism, it is worth mentioning that each step of the tandem process involves iodine reagents which differ by their respective valences (Scheme 5). The catalytic C(sp^3)–H amination, thus, relies on the generation of the metallanitrene **A** through the reaction between the amide **2** and the iodine(III) oxidant, in the presence of the rhodium(II) complex **1**. One equivalent of the monovalent iodoarene is then released whereas nitrene C(sp^3)–H insertion affords the compound **6**. The latter undergoes desilylation to deliver the alkynylcopper species **7** in the presence of TBAF, CuCl, and DABCO. The compound **7** enters the second catalytic cycle through a transmetalation step with the arylpalladium(II) intermediate **B** generated by the oxidative addition of the palladium(0) complex to ArI. Isomerization of **C** into **D** followed by reductive elimination, finally leads to the expected product **4**.

In conclusion, we have described a new tandem catalytic reaction which provides an efficient solution to use the ArI moiety generated in iodine(III)-oxidant-based processes.[27] The sequence combines a catalytic C(sp^3)–H nitrene insertion with a palladium-catalyzed C–C cross-coupling to afford complex nitrogenous molecules with very good yields and complete stereoselectivity. This work highlights the value of the iodoarene part of iodine(III) oxidants as a relevant building block in synthesis. In addition, the process is a rare

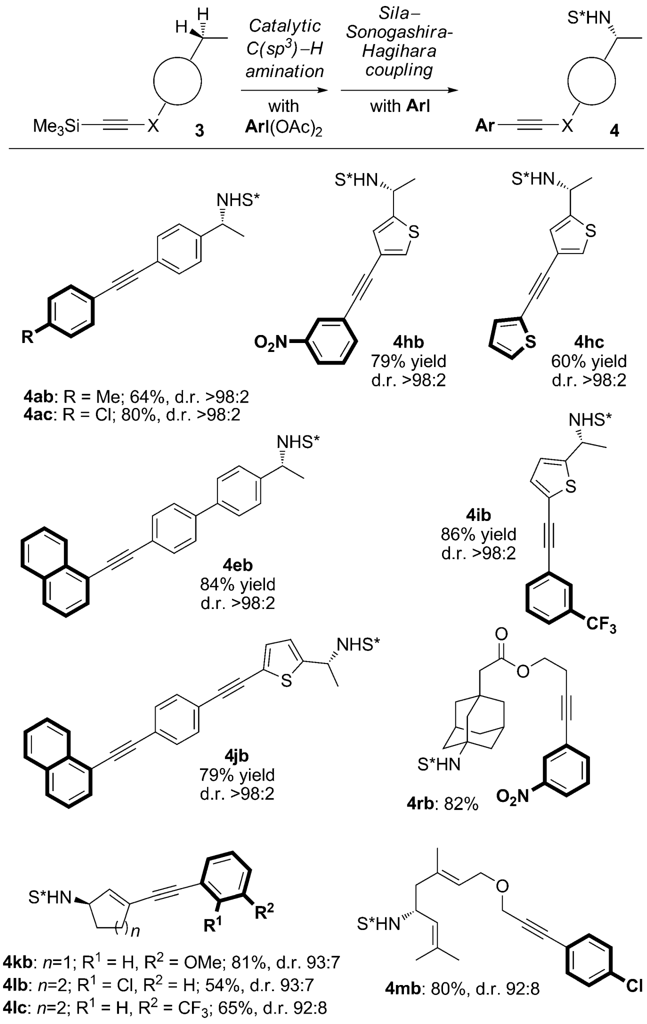


Scheme 2. Tandem reaction with aromatic substrates.



Scheme 3. Tandem reaction with alkenes and alkanes.

example of rhodium(II)/palladium(0) tandem catalysis which is complementary to those reported with either rhodium(I) or

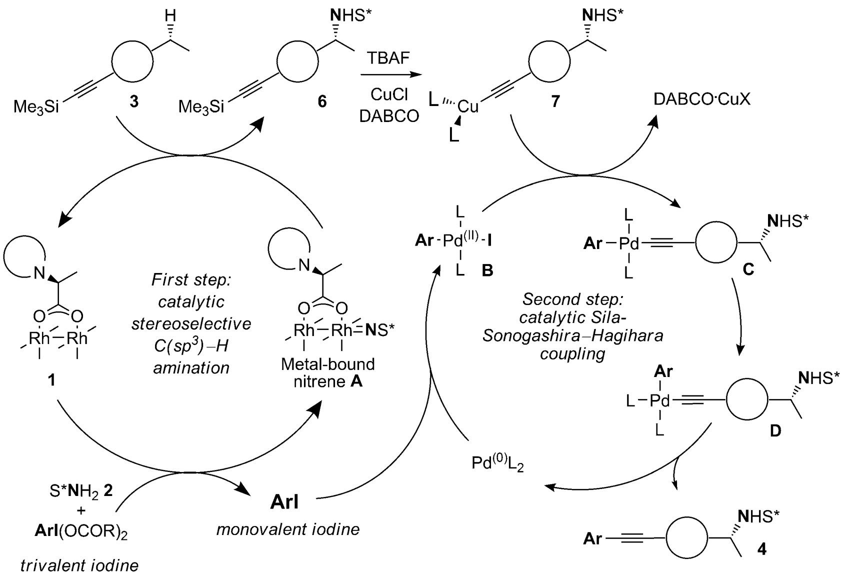


Scheme 4. Tandem reaction with various iodoarene-derived reagents.

rhodium(III) complexes.[28] We are currently extending the concept of hypervalent iodine compounds as double reagents to other types of tandem reactions.

Experimental Section

General procedure for the catalytic tandem reaction: In an oven-dried sealable tube were introduced activated 4 Å molecular sieves (100 mg), $Rh_2[(S)\text{-nta}]_4$ (**1**; 0.006 mmol, 3 mol%), the *S*-sulfonimidamide **2** (0.24 mmol, 1.2 equiv) and the substrate (0.2 mmol, 1 equiv). 1,1,2,2-Tetrachloroethane (0.75 mL) and methanol (0.25 mL) were added under argon. The tube was cooled to −78 °C, and PhI(OPiv)$_2$ (0.28 mmol, 1.4 equiv) was added in one portion. The mixture was stirred at −35 °C for 72 h. The tube was then allowed to warm at room temperature. DABCO (0.8 mmol, 4 equiv), $[Pd(PPh_3)_4]$ (0.02 mmol, 10 mol%), THF (1 mL) and TBAF ($c = 1$ M in THF, 0.4 mmol, 2 equiv) were added, followed by CuCl (0.2 mmol, 1 equiv). The solution was stirred at 70 °C overnight. After cooling to RT, the resulting mixture was filtered over celite and the filtrate was evaporated under reduced pressure. The oily residue was purified by flash chromatography (CH_2Cl_2/EtOAc).



Scheme 5. Postulated mechanism of the tandem reaction.

Keywords: C–H Activation · cross-coupling · homogeneous catalysis · hypervalent compounds · synthetic methods

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[18] The application of the reaction conditions to the nonsilylated analogue of **3a** leads to the expected product with a lower yield of 45%.

[19] The side products correspond to the *Z*- and *E*-1,2-dichloroenynes derived from the TMS-alkyne **3a** (see the Supporting Information).

[20] Following the suggestion of a referee, tandem reactions have been performed with an aryl iodide which allows using a terminal alkyne in the coupling. However, these reactions give lower yields and/or lead to mixtures of products (see the Supporting Information).

[21] The tandem reaction leads to the introduction of electron-donating and electron-withdrawing groups at both ends of the molecules in a one-pot manner. This could allow rapid and efficient access to a large variety of donor–bridge–acceptor

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