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Letter

Designing Homogeneous Copper-Free Sonogashira Reaction through a Prism of Pd−Pd Transmetalation

Bruno A. Martek, Martin Gazvoda, Damijana Urankar, and Janez Košmrlj*

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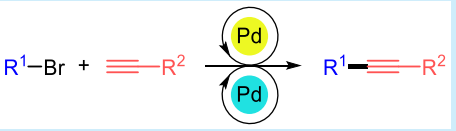
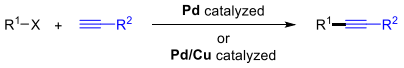
ABSTRACT: Simultaneous introduction of two different palladium (pre)catalysts, one tuned to promote oxidative addition to (hetero)aryl bromide and another to activate terminal alkyne substrate, leads to productive Pd−Pd transmetalation, subsequent reductive elimination, and formation of disubstituted alkyne. This conceptually novel rational design of copper-free Sonogashira reaction enabled facile identification of the reaction conditions, suitable for the synthesis of alkyl, aryl, and heteroaryl substituted alkynes at room temperature with as low as 0.125 mol % total Pd loading.



Although the palladium catalyzed C−C bond formation between aryl or vinyl halides and terminal alkynes by Heck[1] and Cassar[2] evolved into the most effective tool for the synthesis of disubstituted alkynes, it is the copper cocatalyzed variant that has mostly entered industrial applications (Scheme 1).[3,4]

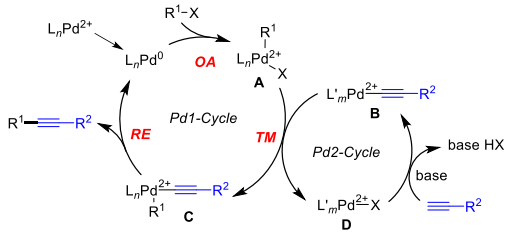
Scheme 1. General Representation of Pd-Catalyzed and Copper Cocatalyzed Alkynylation Reaction



This is exemplified by the synthesis of many Food and Drug Administration (FDA) approved active pharmaceutical ingredients (APIs),[3a,d] including Terbinafine (Sandoz, squalene epoxide inhibitor),[5] Ponatinib (Ariad Pharmaceuticals, tyrosine-kinase inhibitor),[6] Tazarotene (Allergan, receptor-selective retinoid),[7] and Eniluracil (GlaxoSmithKline, dihydropyrimidine dehydrogenase inactivator).[8] As reported by Sonogashira et al.,[9] alkynylation in the presence of copper salts proceeds under much milder conditions.[3,4,10] Copper additives, however, promote Glaser−Hay[11] competitive homocoupling of alkyne and interfere with some functional groups potentially present in the coupling partners like azide, amine, and alkyne. During the isolation process, removal of copper cocatalyst may complicate the workup and purification, especially in the synthesis of APIs.[12,13] When it comes to a bulk industrial process, recovery of the precious metal from spent catalysts is more challenging for the copper cocatalyzed than the copper-free process.[14,15] Although homogeneous copper-free alkynylation has witnessed tremendous improvements, it mostly benefited from development of novel ligands[3,4,10b,16] and technologies. Aqueous micellar catalysis developed by the groups of Lipshutz,[17] and Sparr and Parmentier[18] is a notable example of the latter.

Contrary to a previous belief, it has been recently postulated by us[19,20] and others[21] that the mechanism of copper-free alkynylation operates through a process that resembles copper cocatalyzed variant, but the role of copper is played by palladium (Scheme 2). It builds on transmetalation (TM)

Scheme 2. General Representation of Bicyclic Mechanism of Copper-Free Alkynylation That Is Synergistically Catalyzed by Two Pd Species



between two distinct palladium species, oxidative addition (OA) intermediate **A** that is generated within *Pd1-Cycle*, and acetylide **B** from the *Pd2-Cycle*. Ideally for the productive alkynylation, the concentrations of both reactive intermediates in the reaction mixture are kept equimolar throughout the process. Increasingly favorable formation of **A** over **B** from the single (pre)catalyst decelerates or even terminates the cross-coupling and promotes undesired homocoupling side reaction into biaryls instead. Likewise, acetylide **B** as a (pre)catalyst sink potentially leads to 1,3-diyne and/or enyne byproducts. This condition, however, is rather difficult to meet rationally by

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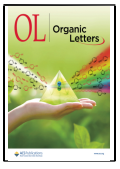

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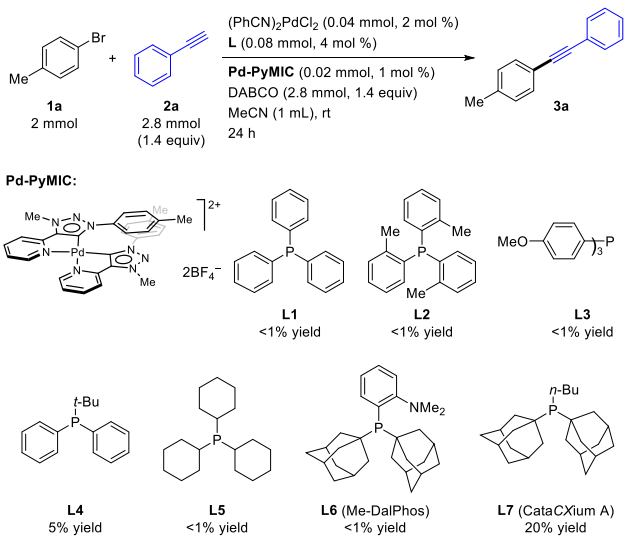
introducing a single palladium source/ligand combination that has so far been exclusively applied for the copper-free alkynylation.[3,4]

Based on the mechanistic rationale, herein we present a novel concept for the design of palladium catalyzed copper-free alkynylation. It features simultaneous introduction of two different palladium (pre)catalysts into the reaction mixture, one tuned to facilitate oxidative addition to aryl halide in *Pd1-Cycle*, and another one to activate terminal alkyne in *Pd2-Cycle*.

Initially, we selected $(PhCN)_2PdCl_2$ as a source of palladium to operate in the *Pd1-Cycle* and set a brief screening (*vide infra*) through a selection of commercially available phosphine-based ligands shown in Table 1. These Pd/ligand combinations have already proven to promote the formation of catalytically active Pd^0 species, subsequent oxidative addition, and reductive elimination (RE) in a range of cross-couplings.[3,4,10b,16d,22]

Table 1. Phosphine Ligand Evaluation in Model Alkynylation Reaction[a]



[a]NMR yields are reported as determined from at least two consecutive runs.

To build on *Pd2-Cycle*, we decided to avoid the phosphine-based palladium complexes. Although their ability to activate terminal alkynes into acetylides of type **B** is well-established,[10b,23] the propensity of phosphines to dissociate and exchange[24] could lead to undesired scrambling between the reactive palladium species from both cycles, leading to uncontrolled side reactions or even termination of the process. Instead, we selected N-heterocyclic carbene (NHC) ligand of a pyridine (Py) functionalized mesoionic (MIC) structure (PyMIC),[19,25] possessing coordination abilities to a metal beyond phosphines and even NHCs. **B**-like NHC acetylide Pd^{2+} complexes are well-documented,[26] and their formation is also evident from many Pd-NHC promoted copper-free and copper cocatalyzed alkynylations.[27] All of the above applies to the **Pd-PyMIC** complex (Table 1) that has proven to have an exceptional stability, promoting copper-free alkynylation in hot water under aerobic conditions.[19]

For the test reaction, we selected 4-bromotoluene (**1a**, 1 equiv) and phenylacetylene (**2a**, 1.4 equiv) as the model substrates (Table 1). The reaction conditions employed $(PhCN)_2PdCl_2$ (2 mol %), phosphine ligand **L** (4 mol %), **Pd-PyMIC** (1 mol %), and 1,4-diazabicyclo[2.2.2]octane (DABCO, 1.4 equiv) as a base in acetonitrile at room temperature. We aimed to design the reaction conditions that would enable cross-coupling at room temperature (22 °C). By screening through the ligands **L**, only CataCXium A (**L7**) provided reasonable conversion to product **3a** (20%). Triphenylphosphine-based ligands **L1**−**L3** promoted conversions of **2a** into the products that were tentatively identified as enynes as based on the ^1H NMR resonances appearing in the olefinic regions of spectra (Supplementary Figure S1), with **1a** remaining unconsumed. This is not surprising because the formation of enynes from terminal alkynes in the presence of palladium and bulky phosphine ligands was previously reported by Trost et al.[23] and Colacot et al.[10b]

As indicated in the systematic investigation by Mårtensson et al.,[28] solvent composition and base are important for copper-free alkynylation. With **L7** as the ligand of choice, under the same reaction conditions as indicated in Table 1, 1,4-dioxane afforded the highest 35% conversion to **3a** over the other tested solvents: MeCN (affording 20% of **3a**), *N*-methylpyrrolidone (NMP, 13%), *N*,*N*-dimethylformamide (DMF, 17%), MeOH (15%), *i*-PrOH (14%), EtOAc (22%), tetrahydrofuran (THF, 19%), and toluene (<1%). Prolonged reaction time in 1,4-dioxane from 24 to 72 h increased the conversion to 50% (Supplementary Table S1).

With 1,4-dioxane as the solvent of choice, the effect of the base was evaluated. Different organic amines (pyrrolidine, NEt_3, *t*-$BuNH_2$, *i*-Pr_2NEt, Cy_2NMe, DBU, DBN, TMG, and DABCO), organic and inorganic carbonates (KOAc, KOPiv, K_2CO_3, Cs_2CO_3), phosphate (K_3PO_4), and hydroxide (KOH) were tested under the reaction conditions from Table 1 (see Supplementary Table S1). Notable 35 and 38% conversions could only be achieved with DABCO and K_2CO_3, respectively. By prolonging the reaction time to 72 h, K_2CO_3 (70% conversion) turned out to be more effective over DABCO (50% conversion).

Finally, the effect of the palladium source was briefly evaluated in the reaction between **1a** (2 mmol) and **2a** (2.8 mmol) under the same reaction conditions as above [**L7** (0.08 mmol, 4 mol %), **Pd-PyMIC** (0.02 mmol, 1 mol %), K_2CO_3 (2.8 mmol), 1,4-dioxane (1 mL), rt, 24 h] with other Pd^{2+} complexes (0.04 mmol, 2 mol %) including $(PhCN)_2PdBr_2$ (affording 17% yield of **3a**), $(MeCN)_2PdCl_2$ (7%), $Pd(OAc)_2$ (22%), and $Pd(TFA)_2$ (29%), as well as $Pd(dba)_2$ (10%) as an example of Pd^0 source. Initially selected $(PhCN)_2PdCl_2$ affording 38% of **3a** proved superior (Supplementary Table S2). The reduction of Pd^{2+} to Pd^0 has been addressed elsewhere,[3,4,10b,16d,22] whereas in the *Pd2-Cycle*, palladium remains in Pd^{2+}.

To ascertain whether under the above optimized reaction conditions the double-palladium manifold indeed plays the anticipated role in the catalysis from Scheme 2, we conducted the following test experiments (Table 2). A mixture of **1a**, **2a**, and K_2CO_3 in 1,4-dioxane was exposed to 2 mol % of $(PhCN)_2PdCl_2$, 4 mol % of **L7**, and 1 mol % of **Pd-PyMIC** for 24 h, affording **3a** in 38% yield (Table 2, entry 1). An excess of $(PhCN)_2PdCl_2$ over **Pd-PyMIC** (**B** from Scheme 2) was employed because the formed is a precatalyst, which must undergo several transformations before turning into the catalytically active species **A**, including Pd^{2+} to Pd^0 reduction, ligand **L7** coordination, and oxidative addition to **1a**. Repeating the reaction in the absence **Pd-PyMIC** but with higher 3 mol % loading of $(PhCN)_2PdCl_2$ (and 6 mol % of **L7**)

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Table 2. Test Experiments Proving the Concept[a]

entry	$(PhCN)_2PdCl_2$/**L7** (mol %, mol %)	**Pd-PyMIC** (mol %)	total Pd content (mol %)	base	yield (%)[b]
1	2, 4	1	3	K_2CO_3	38
2	2, 4	1	3	DABCO	35
3	3, 6		3	K_2CO_3	9
4	3, 6		3	DABCO	<1
5		3	3	K_2CO_3	<1
6		3	3	DABCO	<1

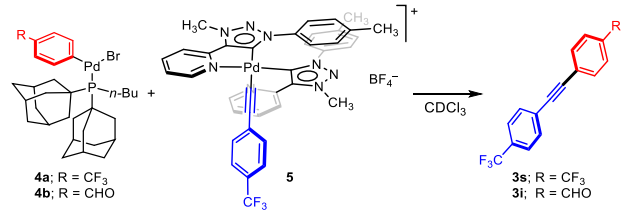
[a]Conditions: **1a** (2 mmol), **2a** (2.8 mmol), $(PhCN)_2PdCl_2$ (0−3 mol %), **L7** (0−6 mol %), **Pd-PyMIC** (0−3 mol %), base (2.8 mmol), 1,4-dioxane (1 mL), rt, 24 h. [b]NMR yields determined from at least two consecutive runs.

to keep the same overall concentration of Pd (3 mol %) the same as above gave significantly lower 9% yield of **3a** (Table 2, entry 3). Finally, the reaction with 3 mol % of **Pd-PyMIC**, but in the absence of $(PhCN)_2PdCl_2$ and **L7**, resulted in only trace amounts of product **3a** formation (entry 5). The results were consistent with those obtained by using DABCO in place of K_2CO_3, where only minute amounts of **3a** could be detected either in the absence of $(PhCN)_2PdCl_2$/**L7** or **Pd-PyMIC** (compare entries 2, 4, and 6). Some product **3a** formation in entry 3 is not unexpected as it is known that palladium precatalyst formed from **L7** promotes copper-free alkynylation in micellar medium.[18] Nevertheless, significantly faster reactions in the presence of **Pd-PyMIC** as well as the proof of concept can be grasped from Table 2.

At this point, the scope of alkynylation was evaluated with different bromides **1** and alkynes **2** (Table 3). Based on several experiments with these coupling partners, aimed at increasing the yields of **3**, decreasing Pd loading and confirming reproducibility of the process, some observations were made, as follows. (i) Although K_2CO_3 performed better in the model reaction between **1a** and **2a** into **3a** (Supplementary Table S1), DABCO was more efficient to produce **3b**, **d**, **e** and was used for the syntheses of **3c**, **f**−**s** (Table 3). (ii) In some instances, the above identified $(PhCN)_2PdCl_2$/**L7**/**Pd-PyMIC** loadings of 2.0/4.0/1.0 mol % (*Conditions A*) could even be lowered to 0.25/0.50/0.25 mol % (*Conditions B*). *Conditions B* are generally efficient to couple electronically less demanding partners, i.e., electron-deficient aryl bromides with electron-rich alkynes. As evident from Table 3, cross-couplings between various combinations of electron-rich, electron deficient, and sterically demanding (hetero)aryl bromides and different terminal alkynes were achieved at room temperature.

To provide evidence that Pd−Pd transmetalation is indeed operating, independently prepared oxidative addition adduct **4a** and palladium acetylide **5** were let to react in isolated segment of the catalytic cycle from Scheme 2 (Scheme 3).

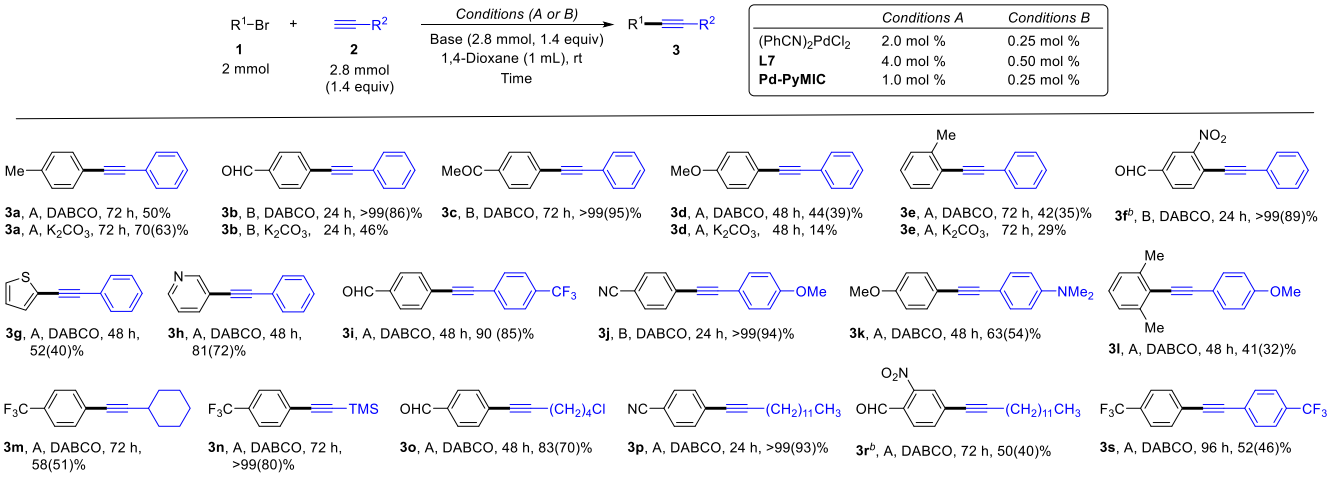
Scheme 3. Reaction between Independently Prepared Complexes 4 and 5



Trifluoromethyl functionalized substrates and $CDCl_3$ as a reaction solvent were selected to enable sensitive monitoring of the reaction by NMR. A mixture of **4a** and **5** in a 1:1 molar ratio turned from colorless to dark brown immediately after dissolution in $CDCl_3$ at room temperature. NMR spectra indicated consumption of both **4a** and **5**, and complete conversion to diarylalkyne **3s** as judged by ^1H and $^{19}F\{H\}$ NMR (Figure 1, Supplementary Figures S37 and S38). The results were consistent with those obtained by reacting **4b** and **5**, leading to nonsymmetrical alkyne **3i** (Supplementary Figures S39 and S40).

As a part of our anticancer investigations,[29] we have been interested in multitargeted antifolate LY231514 (Eli Lilly and Company), which is FDA approved for chemotherapy in combination with other platinum drugs. Multi kilogram scale preparation of synthetic intermediate **3t** was achieved by Pd/Cu cocatalyzed coupling between **1m** with **2i** at 50 °C in 83% yield (Scheme 4).[30] With herein identified $(PhCN)_2PdCl_2$/**L7**/**Pd-PyMIC** system, starting compounds **1m** and **2i** reacted

Table 3. Substrate Scope Screening[a]



[a]NMR yield determined from at least two consecutive runs. The figure in parentheses refers to isolated pure product. [b]2.5 mL of 1,4-dioxane was used.

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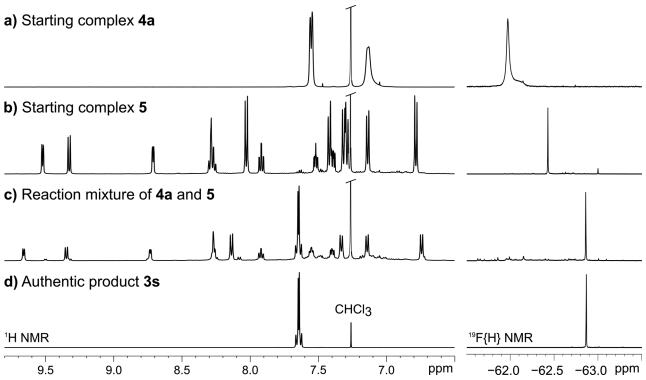
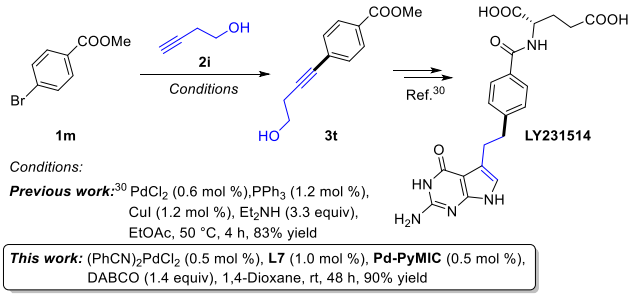


Figure 1. Selected regions of ^{1}H (left) and $^{19}F\{H\}$ NMR (right) $CDCl_3$ spectra of (a) complex **4a**, (b) complex **5**, (c) an equimolar mixture of **4a** and **5** (Scheme 3), 20 min after dissolution, and (d) authentic product **3s**.

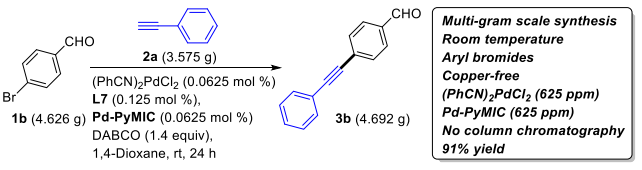
Scheme 4. Alkynylation is a Step in the Synthesis of LY231514



in the absence of copper additives already at room temperature to afford **3t** in 90% yield of isolated pure product (Scheme 4).

Scalability of the double-palladium manifold was tested in the reaction of **1b** (25 mmol scale) with **2a** to form **3b**. Analytically pure product **3b** (4.692 g) was obtained with no need of column chromatography purification. In addition, the overall palladium content could be decreased from 0.50 mol % (Table 3, *Conditions B*) down to 0.125 mol % (Scheme 5). Increasing the scale also resulted in the increase of the yield of **3b** from 86% (Table 3, *Conditions B*) to 91% (Scheme 5).

Scheme 5. Multigram Scale Synthesis of 3b



It is noteworthy that the results from Schemes 4 and 5 address the limitations of the Cu-catalyzed and copper free process as described in the introduction, although this may be a challenge on the scale the reactions are performed.

In summary, the recently proposed bicyclic mechanism for the palladium catalyzed alkynylation has enabled rational design of the catalytic manifold that relies on simultaneous application of two discrete palladium systems, each operating within the corresponding cycle. Cross-couplings between various combinations of electron-rich, electron deficient, and sterically demanding (hetero)aryl bromides and different terminal alkynes were achieved at room temperature and low total Pd loadings. Pd−Pd transmetalation has been confirmed by reactions of independently prepared reactive intermediates, i.e., oxidative addition adducts and palladium acetylide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01227.

Experimental procedures and analytic data for the compounds described and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Janez Košmrlj − *Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia;* orcid.org/0000-0002-3533-0419; Email: janez.kosmrlj@fkkt.uni-lj.si

Authors

Bruno A. Martek − *Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia;* orcid.org/0000-0001-8387-0519

Martin Gazvoda − *Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia;* orcid.org/0000-0003-3421-0682

Damijana Urankar − *Faculty of Chemistry and Chemical Technology, University of Ljubljana, SI-1000 Ljubljana, Slovenia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01227

Notes

The authors declare no competing financial interest.

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