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 and Cassar 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). This is exemplified by the synthesis of many Food and Drug Administration (FDA) approved active pharmaceutical ingredients (APIs), including Terbinafine (Sandoz, squalene epoxide inhibitor), Ponatinib (Ariad Pharmaceuticals, tyrosine-kinase inhibitor), Tarzotene (Allergan, receptor-selective retinoid), and Eniluracil (GlaxoSmithKline, dihydropyrroimidine dehydrogenase inactivator). As reported by Sonogashira et al., alkynylation in the presence of copper salts proceeds under much milder conditions. Copper additives, however, promote Glaser–Hay 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. Copper free alkynylation is synergistically catalyzed by two Pd species through a Prism of Pd–Pd Transmetalation 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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introducing a single palladium source/ligand combination that has so far been exclusively applied for the copper-free alkylation.

Based on the mechanistic rationale, herein we present a novel concept for the design of palladium catalyzed copper-free alkylation. 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 alkylene in Pd2-Cycle.

Initially, we selected (PhCN)2PdCl2 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 combina
tions have already proven to promote the formation of catalytically active Pd0 species, subsequent oxidative addition, and reductive elimination (RE) in a range of cross-couplings.1,4,10b,16d,22

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 (PyMIC), possessing coordination abilities to a metal beyond phosphines and even NHCs. Pd2+ complexes are well-documented, and their formation is reported by Trost et al.23 and Colacot et al.22

As indicated in the systematic investigation by Mårtensson et al., solvent composition and base are important for copper-free alkylation. 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-methylpyrrrolidone (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, N,N't-BuNH2, N,N'-NET, Cy2NMMe, DBU, DBN, TMG, and DABCO), organic and inorganic carbonates (KOAc, KOPiv, K2CO3, CS2CO3), phosphate (K3PO4), 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 K2CO3, respectively. By prolonging the reaction time to 72 h, K2CO3 (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 %), K2CO3 (2.8 mmol), 1,4-dioxane (1 mL), rt, 24 h) with other Pd2+ complexes (0.04 mmol, 2 mol %) including (PhCN)2PdBr2 (affording 17% yield of 3a), (MeCN)2PdCl2 (7%), Pd(OAc)2 (22%), and Pd(TFA)2 (29%), as well as Pd(db)2 (10%) as an example of Pd0 source. Initially selected (PhCN)2PdCl2 affording 38% of 3a proved superior (Supplementary Table S2). The reduction of Pd2+ to Pd0 has been addressed elsewhere, whereas in the Pd2-Cycle, palladium remains in Pd2+

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 K2CO3 in 1,4-dioxane was exposed to 2 mol % of (PhCN)2PdCl2, 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)2PdCl2 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 Pd2+ to Pd0 reduction, ligand L7 coordination, and oxidative addition to 1a. Repeating the reaction in the absence of Pd-PyMIC but with higher 3 mol % loading of (PhCN)2PdCl2 (and 6 mol % of L7)
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)2PdCl2 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 K2CO3 where only minute amounts of 3a could be detected either in the absence of (PhCN)2PdCl2 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 alkylation 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 alkylation 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 experiments with these coupling partners, aimed at increasing the yields of reactions in the presence of Pd-PyMIC as well as the proof of concept can be grasped from Table 2. 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).

\[ \text{PhCN} \text{PdCl}_2 / L7 (\text{mol} \text{ %, base}) \quad \text{pd-PyMIC (mol %)} \quad \text{Total Pd content (mol %)} \quad \text{yield (mol %)} \]

| entry | 1 | 2 | 3 | base | yield (mol %) |
|-------|---|---|---|------|---------------|
| 0.25/0.50/0.25 mol % (Conditions B) | 2.0/4.0/1.0 mol % (Conditions B) | 0.25/0.50/0.25 mol % (Conditions B) |
| 1 | 2 | 4 | 1 | 3 | K2CO3 | 38 |
| 2 | 2 | 4 | 1 | 3 | DABCO | 35 |
| 3 | 3 | 6 | 1 | 3 | K2CO3 | 9 |
| 4 | 3 | 6 | 1 | 3 | DABCO | <1 |
| 5 | 3 | 3 | 1 | 3 | K2CO3 | <1 |
| 6 | 3 | 3 | 1 | 3 | DABCO | <1 |

*\(^a\)Conditions: 1a (2 mmol), 2a (2.8 mmol), (PhCN)2PdCl2 (0–3 mol %), L7 (0–6 mol %), Pd-PyMIC (0–3 mol %), base (2.8 mmol), 1,4-dioxane (1 mL), rt, 24 h. NMR yield determined from at least two consecutive runs.*

**Table 2. Test Experiments Proving the Concept**

| Conditions A | Conditions B |
|--------------|--------------|
| (PhCN)2PdCl2 | (PhCN)2PdCl2 |
| 2.0 mol % | 2.0 mol % |
| 0.25 mpy | 0.25 mpy |
| 0.25 mpy | 0.25 mpy |
| L7 | L7 |
| 4.0 mol % | 4.0 mol % |
| 0.25 mpy | 0.25 mpy |
| 0.25 mpy | 0.25 mpy |
| Pd-PyMIC | Pd-PyMIC |
| 1.0 mol % | 1.0 mol % |
| 0.25 mpy | 0.25 mpy |
| 0.25 mpy | 0.25 mpy |

**Table 3. Substrate Scope Screening**

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).

\[ \text{PhCN} \text{PdCl}_2 / L7 (\text{mol} \text{ %, base}) \quad \text{pd-PyMIC (mol %)} \quad \text{Total Pd content (mol %)} \quad \text{yield (mol %)} \]

| entry | 1 | 2 | 3 | base | yield (mol %) |
|-------|---|---|---|------|---------------|
| 0.25/0.50/0.25 mol % (Conditions B) | 2.0/4.0/1.0 mol % (Conditions B) | 0.25/0.50/0.25 mol % (Conditions B) |
| 1 | 2 | 4 | 1 | 3 | K2CO3 | 38 |
| 2 | 2 | 4 | 1 | 3 | DABCO | 35 |
| 3 | 3 | 6 | 1 | 3 | K2CO3 | 9 |
| 4 | 3 | 6 | 1 | 3 | DABCO | <1 |
| 5 | 3 | 3 | 1 | 3 | K2CO3 | <1 |
| 6 | 3 | 3 | 1 | 3 | DABCO | <1 |

*\(^a\)Conditions: 1a (2 mmol), 2a (2.8 mmol), (PhCN)2PdCl2 (0–3 mol %), L7 (0–6 mol %), Pd-PyMIC (0–3 mol %), base (2.8 mmol), 1,4-dioxane (1 mL), rt, 24 h. NMR yield determined from at least two consecutive runs.*

**Table 3. Substrate Scope Screening**

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**Scheme 3. Reaction between Independently Prepared Complexes 4 and 5**

Trifluoromethyl functionalized substrates and CDCl3 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 CDCl3 at room temperature. NMR spectra indicated consumption of both 4a and 5, and complete conversion to diarylalkyne as judged by 1H and 19F{H} NMR (Figure 1, Supplementary Figures S37 and S38). The results were consistent with those obtained by reacting 4b and 5, leading to nonsymmetrical alkyn 5 (Supplementary Figures S39 and S40).

**Table 3. Substrate Scope Screening**

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). With herein identified (PhCN)2PdCl2/ L7/Pd-PyMIC system, starting compounds 1m and 2i reacted 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).
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).

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 alkylation 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.

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