Multicatalytic Reactions

DOI: 10.1002/anie.201103692

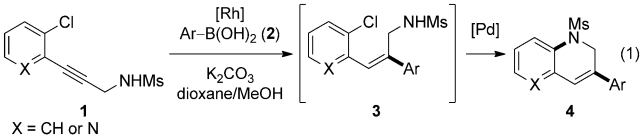
Domino Rhodium-Catalyzed Alkyne Arylation/Palladium-Catalyzed N Arylation: A Mechanistic Investigation**

*Jane Panteleev, Lei Zhang, and Mark Lautens**

Domino processes, in which one reagent or catalyst promotes a series of reactions in a defined order, have become increasingly used in organic synthesis.[1] In the majority of cases, the functionality produced from the first step makes the subsequent step possible, and as a result, single products are formed rather than complex mixtures. In recent years, the idea of combining two different catalysts in a single vessel to promote domino reactions has become more common.[2] Organo-/metal catalysis, sequential biocatalysis, bio-/metal catalysis, and metal/metal catalysis have all been reported.[2,3]

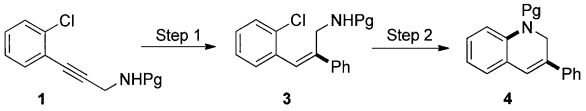
In the majority of examples in which two metals catalyze sequential processes, the presence of the second metal does not expand the range of transformations that are possible.[3] We now report an example in which two different metals with two different phosphine ligands promote two out of three possible reactions and do so in a time-resolved way, thus leading to an efficient preparation of dihydroquinolines.[4] Importantly, we show that one of the two phosphine ligands is selective in binding to only one of the metals, and the other ligand is nondiscriminating in its binding properties; yet one of the two metal–phosphine complexes is far more reactive and selectivity is observed. This study raised the more general question of matching ligands and metals in order to efficiently promote only the desired reaction rather than competing processes. Thus, complex sequences of reactions that contain multiple catalytically active species can ultimately be created in a single reaction vessel.

Our work in this area arose from our studies on the rhodium-catalyzed addition of boronic acids to pyridinyl alkenes and alkynes.[5] We saw the potential to construct heterocyclic motifs **4** by starting from appropriately substituted alkynes **1** [Eq. (1)]. Herein, we report the realization of this idea through a successful combination of a two-metal/two-ligand catalyst system, featuring a rhodium-catalyzed alkyne arylation and palladium-catalyzed C–N coupling.[6,7] This synthetic sequence proceeds in one vessel, in which both catalysts exist concurrently and display correct reactivity even though other reaction pathways, including a Suzuki reaction, are available.



We began our investigation by optimizing the individual steps of the sequence (Table 1). Racemic binap was found to be the optimal ligand for the alkyne arylation of **1**, resulting in product **3** in 60–80% yield (Table 1, entries 3–5).[6,8] Addition of methanol to the reaction was crucial in improving the yield and regioselectivity (> 20:1 versus 10:1; Table 1, entries 4 and 5). The methanesulfonyl protecting group gave the best yields (Table 1, entry 5). When we examined the C–N bond

Table 1: Optimization of the two-step dihydroquinoline synthesis.[a]



Step 1: $[Rh(cod)OH]_2$ (5 mol % [Rh]), ligand (5.2 mol %)
$Ph\text{-}B(OH)_2$ (2 equiv), K_2CO_3 (1.1 equiv), dioxane/additive

Step 2: $Pd(OAc)_2$ (2 mol %), ligand (4 mol %)
K_2CO_3 (1.1 equiv) or Cs_2CO_3 (1.4 equiv), dioxane

Entry	Step	Ligand	Additive	T [°C]	Pg	**3** [%][b]	**4** [%][b]
1	1	dppp	H_2O	60	Ts	(24)	–
2	1	$P(4\text{-}FC_6H_4)_3$	H_2O	60	Ts	54	–
3	1	binap	H_2O	60	Ts	63[c]	–
4	1	binap	MeOH	60	Ts	67[d]	–
5	1	binap	MeOH	60	Ms	77[d]	–
6[e]	2	Xantphos	–	100	Ts	(66)	–
7[e]	2	Davephos	–	100	Ts	(47)	(6)
8[e]	2	X-Phos	–	100	Ts	0	70
9	2	X-Phos	MeOH	90	Ts	0	83
10	2	X-Phos	MeOH	90	Ms	0	92
11[f]	1 + 2	binap + X-Phos	MeOH	90	Ms	8	69
12	1	no ligand	MeOH	60	Ms	–[g]	–
13	1	X-Phos	MeOH	90	Ms	(5)	–
14	2	binap	MeOH	90	Ms	(84)	(4)

[a] See Table 3 for representative reaction conditions. [b] Yields of isolated products; yields in parentheses indicate yields determined by NMR spectroscopy. [c] 10:1 regioisomeric ratio (r.r.) determined by NMR spectroscopy of the crude product. In the minor isomer, arylboronic acid is added to the opposite end of the alkyne. [d] > 20:1 r.r. [e] Cs_2CO_3 (1.5 equiv) was used. [f] Domino reaction using K_2CO_3 (2.2 equiv). [g] A complex mixture of by-products was observed. binap = racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, cod = 1,5-cyclooctadiene, DavePhos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, dppp = propane-1,3-diylbis(diphenylphosphane), Ms = methanesulfonyl, Ts = toluene-4-sulfonyl, X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, XantPhos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

[*] J. Panteleev, L. Zhang, Prof. Dr. M. Lautens
Davenport Research Laboratories
Department of Chemistry, University of Toronto
80 St George St. Toronto, Ontario, M5S 3H6 (Canada)
E-mail: mlautens@chem.utoronto.ca

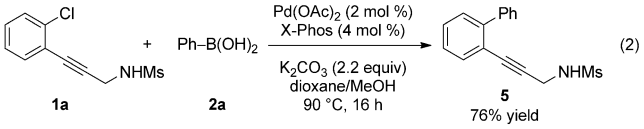
[**] The authors wish to thank the Natural Sciences and Engineering Research Council (NSERC), Merck for an Industrial Chair, and the University of Toronto for financial support. J.P. thanks NSERC for a CGSD scholarship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201103692.

formation we obtained excellent yields (92%) of **4** by using the X-Phos ligand (Table 1, entries 8–10).[9] Notably, both of the reactions proceeded in 1,4-dioxane as the solvent when using a weak carbonate base.

We were interested in combining the two steps in a single reaction vessel, and in order to simplify the system, the ligand–metal solutions were prepared separately prior to the addition of the substrates.[10] To our gratification, the overall transformation proceeded in a combined yield that was similar to the two independent reaction steps (69% versus 71%; Table 1, entry 11). Examples of domino reactions catalyzed by two transition metals are rare, thus we elected to further investigate the interactions between the two catalyst systems.

To survey the reactivity of the possible metal–ligand combinations, we carried out several control experiments on each step [Table 1, Eq. (2)]. Use of phosphine-free [Rh(cod)OH]$_2$ led primarily to the decomposition of **1a** (Table 1, entry 12). The arylation reaction using X-Phos as a ligand led to a low yield of **3a** (5%) and a significant amount of decomposition (40%; Table 1, entry 13). Subjecting substrate **1a** to only [Pd(binap)] or [Pd(X-Phos)] did not lead to **3a** or **4a**; instead, [Pd(X-Phos)] furnished the Suzuki cross-coupling product **5** in good yield [76%; Eq. (2)].[11,12] The reaction of **3a** with [Pd(binap)] yielded only trace amounts of **4a** (Table 1, entry 14). From these control experiments it was apparent that use of [Rh(binap)] resulted in the desired product, and phosphine-free rhodium led to decomposition of **1a**. The ability to form [Pd(X-Phos)] was equally important since [Pd(binap)] was catalytically inactive in C–N coupling.



Both reactions utilize specialized phosphine ligands, which have the potential to exchange between the metal centers. We observed that Pd(OAc)$_2$ forms discrete complexes with both binap and X-Phos.[13] Based on ^{31}P NMR spectroscopy, it was apparent that [Pd(binap)] and [Pd(X-Phos)] exist in an equilibrium. While rhodium is known to bind binap, no complexation of rhodium and X-Phos was indicated by ^{31}P NMR spectroscopy.[10,13] Our NMR experiments suggested that palladium could bind both phosphine ligands, however rhodium could only complex binap.

We further examined the effect of Pd(OAc)$_2$ or X-Phos addition on the rate of the alkyne arylation reaction (Figure 1). When the reaction was carried out with X-Phos present in the catalyst solution, a minimal effect on the rate of the reaction was observed (Figure 1, entry 2 versus entry 1). In contrast, addition of 5 mol% of Pd(OAc)$_2$ led to the formation of only a trace of **3a** (5%; Figure 1, entry 3), while the conversion of **1a** returned to more than 70% with the addition of 5 mol% of [Pd(X-Phos)] solution to the reaction mixture (Figure 1, entry 4). With a higher [Pd(X-Phos)] loading, the Suzuki product **5** was formed in substantial amounts (Figure 1, entry 5). Interestingly, no Suzuki products containing the arylated alkene, such as **6**, were ever observed

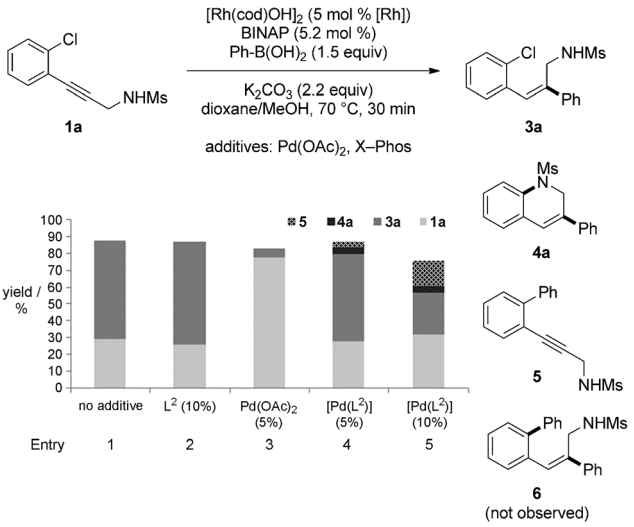


Figure 1. Effect of step 2 components on step 1 conversion. L^2 = X-Phos.[14]

in the optimized reaction, thus indicating that even if an excess of the aryl boronic acid is used, the Suzuki coupling is slower than the intramolecular C–N coupling in **3a**.

Similarly, we examined the C–N coupling step (Figure 2). While 92% yield of product was achieved when using [Pd(X-Phos)], only 4% of product was obtained when [Pd(binap)] was utilized (Table 1, entry 14). This observation had a significant implication on the domino process, considering that any ligand interchange between rhodium and palladium could be deleterious to the C–N bond formation. In fact, when the reaction was carried out using a premixed [Pd(X-Phos)] catalyst solution with 5 mol% of binap added, the yield plummeted from 92% to 3% (Figure 2, entry 2). When we looked at the reaction of **3a** with 5 mol% of [Rh(binap)] as the additive, the yield returned to 91% (Figure 2, entry 4). With higher rhodium loading (10 mol%, Figure 2, entry 5) a decrease in conversion was observed, possibly resulting from binap inhibition.

Ligand interference was further confirmed when we examined the Rh/Pd ratio in the domino reaction (Figure 3). When increasing the loading of the [Rh(binap)] catalyst, progressively less product **4a** was formed and the reaction stalled at the intermediate stage. Varying the ligand

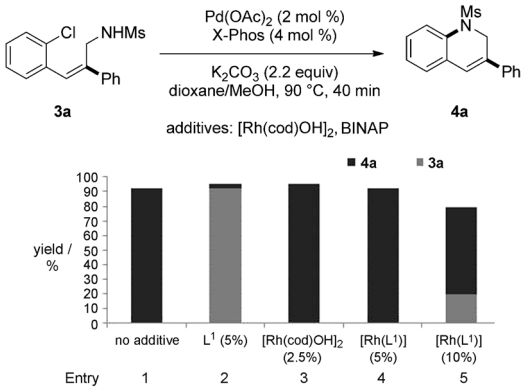


Figure 2. Effect of step 1 components on step 2 yield. L^1 = binap.[14]

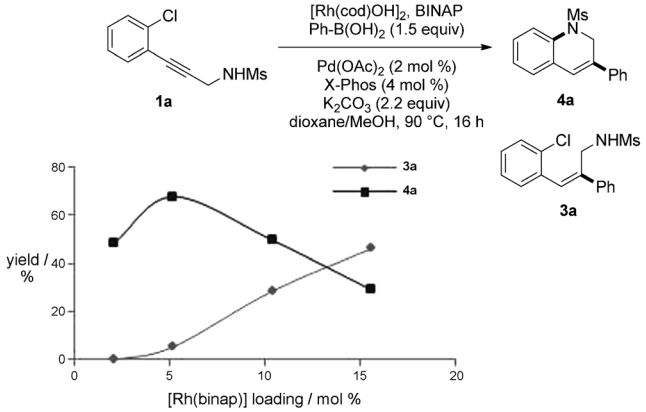
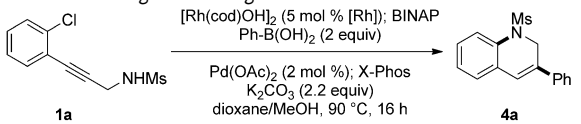


Figure 3. Effect of the Rh/Pd Ratio on the yield of the reaction.[14] 1.05 equivalents of binap with respect to [Rh] were used.

equivalents showed similar trends (Table 2). With binap loading exceeding 5.5 mol%, the reaction stalled at the intermediate stage (Table 2, entries 1–4). Addition of an excess of X-Phos did not remedy this effect; in fact, further equivalents of X-Phos resulted in lower yields (Table 2, entries 4–6). While counterintuitive at first, this result is consistent with the inverse rate dependence that is often observed with bulky phosphine ligands and is caused by saturation of the coordination sites on the palladium center.[15]

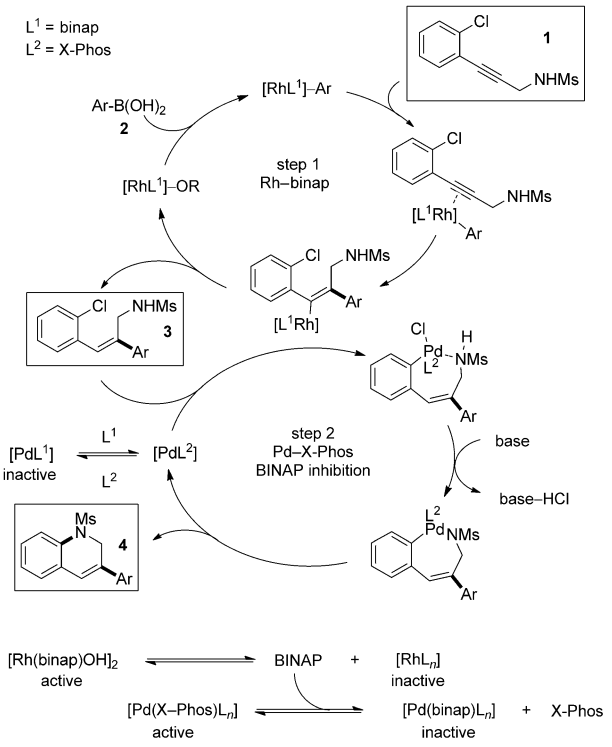
The experiments described above gave us some insight into the mechanism of the reaction (Scheme 1). It appears that the two catalytic cycles occur independently, and no direct interaction between the two active metal complexes exists. Initially, substrate **1** reacts rapidly under rhodium catalysis to yield **3**, which can then cyclize through a palladium-catalyzed C–N coupling to result in product **4**. An alternative reaction pathway occurs where **1** undergoes Suzuki cross-coupling, but with optimized catalyst ratios this pathway is suppressed. Additionally, inhibition of the C–N coupling by binap is observed. We propose that the [Rh(binap)OH]$_2$ solution is a source of trace amounts of free binap, but Rh/binap binding largely remedies the inhibitory effect of the free ligand.

Table 2: Effect of ligand loading on the domino reaction.[a]



Entry	binap [mol%]	X-Phos [mol%]	**3a** [%][b]	**4a** [%][b]	**3a**:**4a**
1	5.2	4	6	69	1:11
2	5.5	4	22	47	1:2.1
3	7.5	4	38	33	1.2:1
4	10	4	55	27	2:1
5	10	2	47	36	1.3:1
6	10	6	61	21	2.9:1
7	10	8	75	6	12.5:1

[a] See Table 3 for reaction conditions. [b] Yields determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

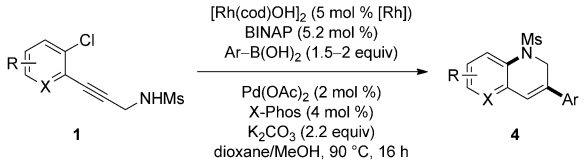


Scheme 1. Proposed mechanism of the domino dihydroquinoline synthesis.

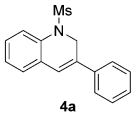
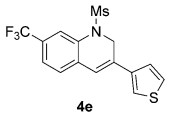
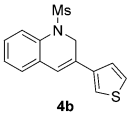
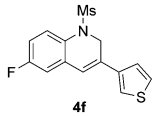
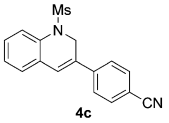
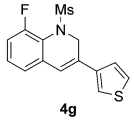
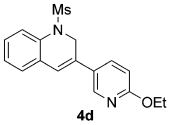
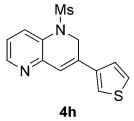
The domino reaction proceeded in an overall yield of 69%, in comparison to the two-step combined yield of 71%. However, isolation of the intermediate in good yield and purity was often problematic because of the presence of minor by-products. Preliminary investigations of the scope show that electron-rich and electron-poor aryl and heteroaryl boronic acids could be used to give good overall yields (Table 3). Performing the reaction in two-stage heating (60°C for 1.5 h, then 90°C) had a subtle beneficial effect (81% versus 78%; Table 3, entries 5 and 6). We observed significantly higher yields when utilizing 3-thiophenylboronic acid **2b** as the nucleophile (Table 3, entry 1 versus entry 2). A competition experiment indicated that this boronic acid is approximately five times more reactive than **2a**.[16]

Domino reactions try to address the need for less wasteful and more time- and cost-efficient synthetic pathways. Currently, the use of multiple transition-metal-catalyzed transformations in domino processes is rare. A domino multicatalytic synthesis of dihydroquinolines was realized, wherein the products of a rhodium-catalyzed arylation were cyclized by palladium-promoted C–N coupling. While some inhibition of the palladium-catalyzed C–N coupling by the rhodium arylation ligand was observed, the domino reaction proceeded in equivalent yields as the independent reaction steps. Our work provides a rare example of a system where two transition-metal complexes with different phosphine ligands capable of dissociation function along a desired pathway, even when other reaction pathways are available. We look forward to a more thorough investigation of this concept and its application to other synthetic systems.

Table 3: Preliminary scope of the domino reaction.[a]



1 4

Entry	Product	Yield [%][b]	Entry	Product	Yield [%][b]
1	 **4a**	69	5 6[c]	 **4e**	78 81
2	 **4b**	78	7	 **4f**	70
3	 **4c**	68	8	 **4g**	73
4	 **4d**	65	9	 **4h**	45

[a] Stock catalyst solutions ($[Rh]_2$ (0.005 M) with BINAP (1.05 equiv with respect to [Rh]), and $Pd(OAc)_2$ (0.008 M) with X-Phos (2 equiv with respect to [Pd])), were mixed separately in dioxane at 50 °C for 15 min. 0.5 mL of each solution was added to a vial containing **1** (0.2 mmol, 49 mg), **2** (0.4 mmol, 49 mg), K_2CO_3 (61 mg), and MeOH (100 μL) in dioxane (1 mL). The mixture was stirred at 90 °C for 16 h. [b] Yield of isolated product for the domino process. [c] Reaction carried out at 60 °C over 1.5 h, then at 90 °C for 14.5 h.

Received: May 30, 2011
Published online: August 24, 2011

Keywords: chemoselectivity · dihydroquinolines · domino catalysis · heterocycles · multicatalytic reactions

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[8] Optimization studies of the rhodium-catalyzed arylation show that some decomposition of *ortho*-halogenated aryl-alkynes occurs under the reaction conditions. This behavior accounts for the remainder of the mass balance of the reaction.

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[10] For formation of $[Rh(binap)OH]_2$, see: T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052 – 5058.

[11] For the use of Pd/binap in C–N/C–O coupling, see: a) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333 – 10334; b) S. Shekhar, P. Ryberg, J. F. Hartwig, J. S. Mathew, D. G. Blackmond, E. R. Strieter, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 3584 – 3591.

[12] For the use of Pd/X-Phos in Suzuki reactions, see: T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685 – 4696.

[13] See the Supporting Information for ^{31}P NMR spectra; in addition, in situ hydrogenation of the cod ligand with H_2 did not yield any observable Rh/X-Phos complexation.

[14] Reactions were carried out after premixing the Rh/binap and the Pd/X-Phos catalyst solutions separately for 15 min at 50 °C.

[15] L. M. Alcazar-Roman, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 12905 – 12906.

[16] See the Supporting Information.

