Multicatalytic Reactions

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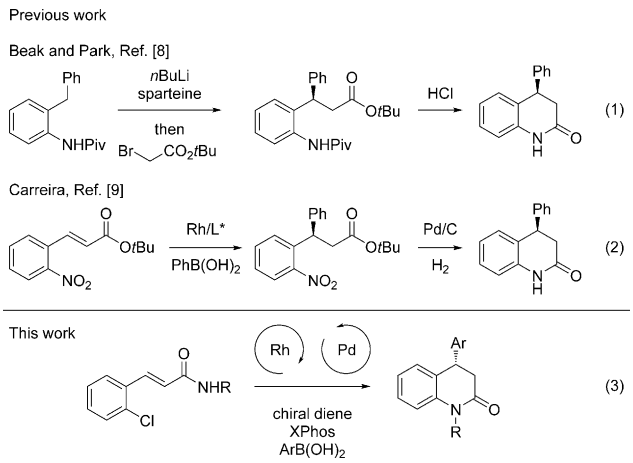
Sequential Rhodium/Palladium Catalysis: Enantioselective Formation of Dihydroquinolinones in the Presence of Achiral and Chiral Ligands**

*Lei Zhang, Zafar Qureshi, Lorenzo Sonaglia, and Mark Lautens**

Abstract: *Compatible combinations of achiral and chiral ligands can be used in rhodium/palladium catalysis to achieve highly enantioselective domino reactions. The difference in rates of catalysis and minimal effects of ligand interference confer control in the domino sequence. The "all-in-one" 1,4-conjugate arylation and C–N cross-coupling through sequential Rh/Pd catalysis provides access to enantioenriched dihydroquinolinone building blocks.*

The use of more than one metal catalyst in a single reaction vessel is a recent and promising area of research. An important advantage of multimetal catalysis is the ability to promote various modes of catalysis that cannot be achieved with a single catalyst. For example, bimetallic catalysis and cooperative dual metal catalysis are modes of catalysis that lead to transformations involving catalyst–catalyst interactions.[1–3] An alternative mode involves domino or sequential catalysis.[4] However, examples of multiligand domino catalysis remain rare.[4k–o] As metal catalysis is highly dependent on ligands to confer specific reactivity, multiligand systems enable transformations that can empower the domino mode of catalysis. In this mode, independent catalytic cycles operate with differing rates such that undesired catalytic pathways are suppressed to afford a controlled reaction sequence, conferring time resolution.[5] In addition, the ligands should not interfere[6] with subsequent steps so that combinations of ligands can be tolerated and each ligand binds to a specific metal to obtain highly reactive metal–ligand complexes. The ligand may bind selectively or nonselectively, but in either case a single reactive complex does the desired transformation. This allows similar ligands (two or more phosphines) or different ligands (diene and phosphine) to be mixed in the same vessel.

Taking advantage of the orthogonal ligand association, we have recently demonstrated a number of ligand-dependent Rh/Pd-catalyzed domino reactions,[4l–o] including the use of a chiral and achiral ligand to access chiral dihydrodibenzoxepines[4m] with high enantioselectivity, though with modest yields and limited scope. Now we report the use of the highly compatible Rh/Pd catalyst system with a different ligand combination to access dihydroquinolinones in a direct and expedient manner, affording high yields and enantioselectivities. Molecules of this class of heterocycles exhibit important biological activities.[7] Current methods to access chiral C4-substituted dihydroquinolinones include the work of Beak and Park,[8] through an asymmetric (−)-spartiene mediated deprotonation [Eq. (1), Scheme 1], and that of Carreira,[9]



Scheme 1. Domino Rh/Pd catalysis strategy for the enantioselective synthesis of dihydroquinolinones.

through a Rh-catalyzed asymmetric conjugate arylation of a cinnamate [Eq. (2)]. Our "all-in-one" method involves a Rh-catalyzed asymmetric conjugate arylation to an acrylamide followed by a Pd-catalyzed amidation of the pendant aryl chloride [Eq. (3)]. These starting acrylamides can be readily accessed in a reliable and straightforward manner, thereby affording a broad substrate scope. Furthermore, these chiral heterocyclic products are known to be functionalized into various tetrahydroquinoline derivatives.

Our initial study on the conjugate addition of phenylboronic acid to acrylamide **1a** with a Rh^{I} catalyst and a phosphine ligand such as binap (Table 1, entry 1) did not give the desired product. Full recovery of the starting acrylamide was observed. The halogen substituent seemed to have a profound effect by hindering the reaction when

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

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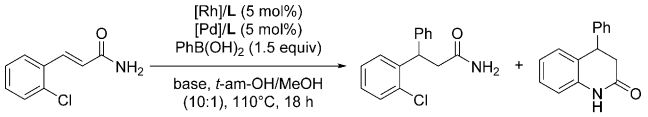
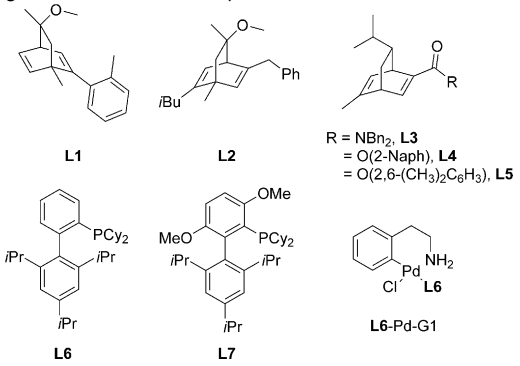
Table 1: Reaction Optimization.[a]



1a 2a 3a

Entry	Rh/**L**	Pd/**L**	Base	Yield [%][c] **2a**/**3a**	*ee* [%] (**3a**)
1	$[Rh(cod)Cl]_2$/binap	–	K_3PO_4	0/–	–
2	$[Rh(cod)Cl]_2$	–	K_3PO_4	99/–	–
3	$[Rh(cod)Cl]_2$	$[Pd(allyl)Cl]_2$/**L6**	K_3PO_4	0/99	–
4	$[Rh(C_2H_4)_2Cl]_2$/**L1**	$[Pd(allyl)Cl]_2$/**L6**	K_3PO_4	0/76	0
5	$[Rh(C_2H_4)_2Cl]_2$/**L2**	$[Pd(allyl)Cl]_2$/**L6**	K_3PO_4	22/0	–
6	$[Rh(C_2H_4)_2Cl]_2$/**L3**	$[Pd(allyl)Cl]_2$/**L6**	K_3PO_4	0/16	0
7	$[Rh(C_2H_4)_2Cl]_2$/**L4**	$[Pd(allyl)Cl]_2$/**L6**	K_3PO_4	0/24	95
8[b,c]	$[Rh(\mathbf{L4})_2Cl]_2$	**L6**-Pd-G1	KOH	0/63	95
9[c]	$[Rh(\mathbf{L5})_2Cl]_2$	**L6**-Pd-G1	KOH	0/68	95
10[d]	$[Rh(\mathbf{L5})_2Cl]_2$	**L6**-Pd-G1	KOH	0/89	95

[a] Representative reaction conditions: [Rh], [Pd], and respective ligands were added to a 2-dram vial under Ar atmosphere and subsequently **1a**, phenylboronic acid, and base (2.2 equiv) were added. The solvent was added to the vial, and the mixture was stirred for 5 min at room temperature prior to heating at 110 °C for 18 h. Yields were determined by ^{1}H NMR spectroscopy. [b] 8 mol% [Rh] was used. [c] 3.5 equiv KOH was used. [d] 2.5 equiv phenylboronic acid was used. Yields of isolated products are given. *t*-am-OH = 2-methyl-2-butanol.



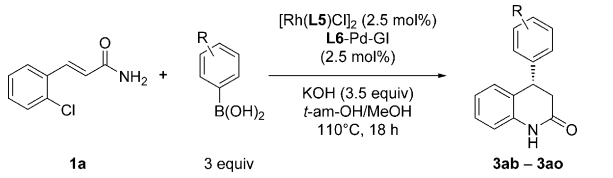
phosphine ligands were used.[4n] However, excellent reactivity was observed once binap was omitted, and the reaction reached completion within 30 min (Table 1, entry 2). The conjugate addition delivers an amide that can participate in a Buchwald–Hartwig amidation, which was readily achieved with a Pd catalyst and the biaryl phosphine ligand XPhos (**L6**) over a period of 16 h.

Because of the minimal interference of **L6** with Rh in the conjugate addition, the combination of **L6**, Pd, and Rh can be used concurrently, accessing the dihydroquinolinone in a highly efficient manner in a single operation (Table 1, entry 3). The time resolution of the reaction sequence renders high control over undesired reaction pathways. In particular, the fast consumption of the phenylboronic acid minimized the Pd-catalyzed Suzuki–Miyaura cross-coupling of **1a**.[10] As cyclooctadiene was a suitable ligand for Rh in the dual catalysis, we sought to develop the enantioselective Rh-catalyzed conjugate arylation using chiral diene ligands. The abundance of diene ligands in Rh^I catalysis and the predominant use of phosphine ligands in Pd^0 catalysis offer orthogonality in ligand association and minimize the ligand–metal–ligand interference. Consequently we screened a number of diene ligands in this dual metal catalysis. The use of diene ligands developed by Genet,[11] Carreira,[9] and Lam[12] (Table 1, entries 4–6) did not afford the desired reactivity. **L1** and **L3** did not confer enantioselectivity and the reaction stalled at the intermediate **2a** with the use of **L2**. However, the use of ligand **L4** developed by Hayashi[13] afforded the desired product in 24% yield with an excellent *ee* value of 95% (Table 1, entry 7). Significant improvement in the yield was observed as the Rh/**L4** loading was increased to 8 mol% and KOH was used as base (Table 1, entry 8). The use of the Buchwald palladacycle **L6**-Pd-G1 as the amidation catalyst further simplified the reaction protocol. We realized that the use of KOH and MeOH in the reaction conditions may hydrolyze the naphthyl ester on the diene ligand **L4**, thereby stifling the conjugate arylation. Substitution of the naphthyl to a mesityl group would withstand the hydrolytic conditions. Consequently, the use of Rh/**L5** in lowered catalytic loadings (5 mol%) still conferred a suitable yield and an excellent *ee* value (Table 1, entry 9). An increase in the equivalents of the arylboronic acid gave an excellent yield of 89% with 95% *ee*, exemplifying the efficiency of the time-resolved domino-catalysis sequence. To verify that the catalysts in the domino sequence indeed operate in an independent manner, we performed the individual steps separately. The Rh-catalyzed conjugate addition was highly enantioselective, and no erosion of optical purity was observed in the subsequent Pd-catalyzed amidation.[14] Comparing the optical rotation of the product to the literature,[8,9] we were able to assign the absolute configuration of the carbon atom bearing the phenyl group as (*S*).

To explore the reaction scope of the developed Rh/Pd domino catalysis, we examined a variety of arylboronic acids (Table 2). In general, the number of equivalents of the substituted arylboronic acids was increased to three to achieve consistent and improved yields. The reaction exhibited good to high yields and enantioselectivity. While electron-rich (Table 2, entries 3–8) and electron-poor (entries 12–14) arylboronic acids are tolerated in the reaction, substitution at the 3 position resulted in poorer reactivity (Table 2, entries 4 and 13). Functionalized nucleophiles such as thioether and fluorine-containing arylboronic acids (Table 2, entries 6, 11, 12, and 14–16) can be readily employed.

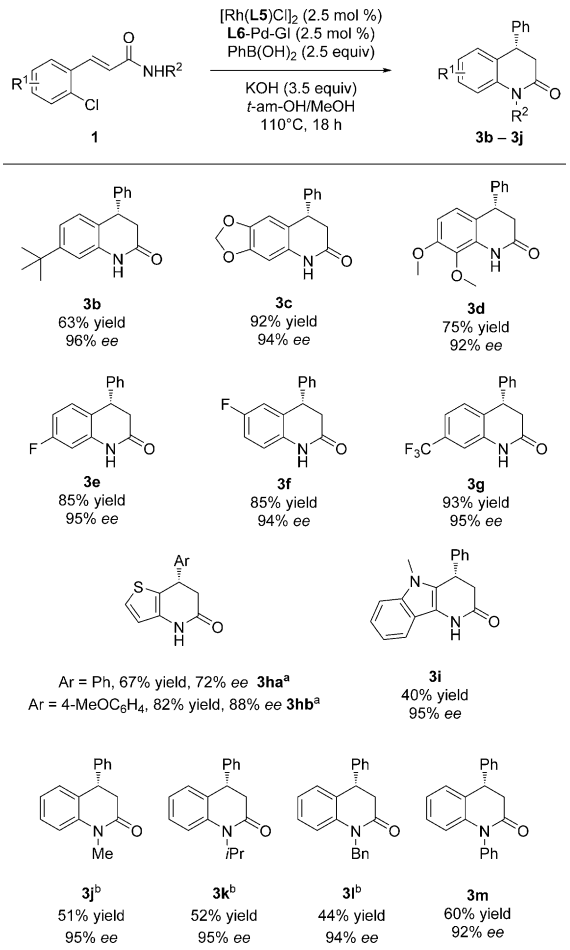
The reaction also tolerated substituents on the acrylamides (Scheme 2). A variety of these acrylamides can be accessed reliably in a straightforward manner (see the Supporting Information). Both electron-donating (**3b**–**3d**) and electron-withdrawing (**3e**–**3g**) groups (R^1) on the arylacrylamide had a favourable effect, and high yields and enantioselectivities were achieved. Heterocyclic lactam derivatives can also be accessed with thiophenyl and indolyl acrylamides with an increased Rh loading (**3g**–**3i**). While the observed deterioration in the enantioselectivity of the con-

Table 2: Reaction scope of arylboronic acids.[a]



Entry	R	Product	Yield [%]	*ee* [%]
1	3-Me	**3ab**	89	94
2	4-Me	**3ac**	88	98
3	4-*t*Bu	**3ad**	76	96
4	3-OMe	**3ae**	56	92
5	4-OMe	**3af**	80	96
6	3,4-$(OMe)_2$	**3ag**	80	95
7	3,4,5-$(OMe)_3$	**3ah**	78	94
8	4-Ph	**3ai**	70	92
9	2-naphthyl	**3aj**	75	95
10	4-SMe	**3ak**	72	96
11	4-Ac	**3al**	48	92
12	4-F	**3am**	61	94
13	3-CF_3	**3an**	46	82
14	4-CF_3	**3ao**	82	75

[a] Reaction conducted on 0.2 mmol scale; see the Supporting Information for reaction details.



Scheme 2. Reaction scope of arylacrylamides. Reaction conducted on 0.2 mmol scale. [a] [Rh(**L5**)Cl]$_2$ (4 mol%, 8 mol% [Rh]) and 3 equiv of arylboronic acid was used. [b] [Pd(allyl)Cl]$_2$ (3 mol%) and **L7** (6 mol%) was used instead of **L6**-Pd-GI.

jugate addition for the thiophenyl acrylamide **3ha** may be an effect of the proximal sulfur atom, the use of an electron-rich arylboronic acid can result in good yield and enantioselectivity (**3hb**). The indolyl acrylamide (**3i**) also exhibited poorer reactivity at the conjugate addition step, and the formation of by-products was noted. Nevertheless the "all-in-one" process can give a modest yield with a high enantioselectivity.

N-Substituted acrylamides also can participate in the reaction (**3k**–**3m**). While N-phenyl-substituted products (**3m**) can be accessed with **L6**, substrates with other N substituents (**3j**–**l**), including alkyl, react less readily. Switching the Pd catalyst and the ligand to [Pd(allyl)Cl]$_2$ and **L7** (Brettphos), modest yields were achieved while the high enantioselectivity was retained. The ability to pair the Rh-catalyzed conjugate addition with a number of Buchwald–Hartwig catalysts and ligands to tailor specific reactivity demonstrates the flexibility of the "two-catalyst" strategy.

Further functionalization of the useful quinolinone scaffolds have already been demonstrated, including Friedel–Crafts reaction,[15a] amination,[15b] and alkylation.[8] For example, Beak established an efficient synthesis of 3,4-disubstituted tetrahydroquinolines in a stereoselective manner in two steps.[8]

In summary, we have developed a versatile "two-catalyst-two-ligand" system, in which one ligand is chiral and the other is achiral, that enables the direct and efficient access to chiral dihydroquinolinone scaffolds in a single step. Selecting ligands that demonstrate orthogonal catalyst association behavior and the faster rate of the Rh-catalyzed enantioselective conjugate addition versus Pd-catalyzed amidation confer time resolution that gives a high degree of control on the sequence of reactivity.

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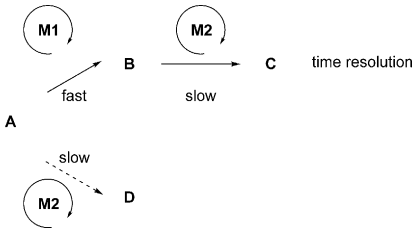
[5] Time resolution can be viewed as the result of differing reaction rates of two competing concurrent catalytic processes.



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