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Multi-Catalytic Reactions

Rh/Pd Catalysis with Chiral and Achiral Ligands: Domino Synthesis of Aza-Dihydrodibenzoxepines**

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Domino catalysis is an ideal strategy in the synthesis of heterocyclic scaffolds, as multiple bonds can be formed under a single set of reaction conditions. Beyond the rapid generation of molecular complexity, time and cost efficiencies resulting from the lack of purification of intermediates make such methods attractive. To this end, various permutations of domino metal-, organo-, and bio-catalyzed methods have been developed,[1] including several recent examples in which transition metals act in tandem to provide a single product.[2] In addition, methods featuring a single metal and mixtures of chiral and achiral ligands have been described, wherein both ligands are essential to achieve good yields and selectivities owing to the formation of a ligand–metal heterocomplex.[3]

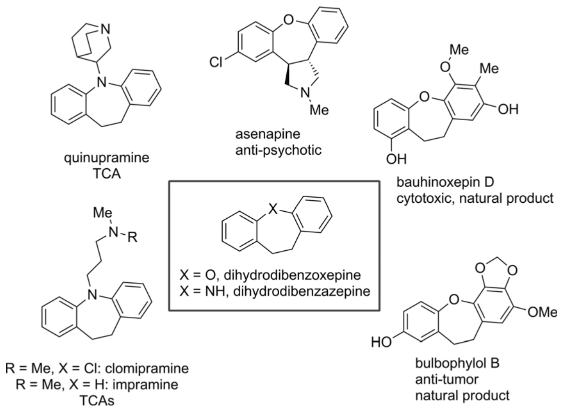
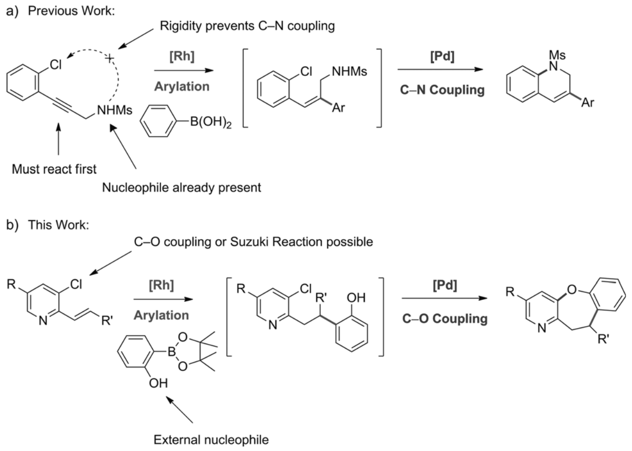


Figure 1. Biologically active dihydro-dibenzoxepines and dibenzazepines. TCA = tricyclic antidepressant.

The dihydro-dibenzoxepine and -dibenzazepine motifs are often found in biologically active compounds (Figure 1).[4] Previous work by our group and others has shown that vinyl pyridines react with phenylboronic acids under Rh catalysis to furnish formal hydroarylation products.[5] We envisioned combining these conditions with Pd-catalyzed C–O coupling[6] to generate functionalized aza-dihydrodibenzoxepines; modification of the starting materials to include an acceptor (halogen) on the pyridine and a donor (hydroxy group) on the boronic acid would allow us to furnish the motif, a scaffold of potential biological importance[7] (Scheme 1 b).

In our previous domino synthesis of dihydroquinolines through the Rh-catalyzed hydroarylation and Pd-catalyzed C–N coupling of aryl alkynyl chlorides,[2h] structural rigidity precluded the occurrence of the Pd-catalyzed C–N coupling before the Rh-catalyzed arylation. Herein, the time-resolved domino reaction of 3-chloro-2-vinylpyridines with 2-hydroxyphenylboronic esters is described, yielding the desired aza-dihydrodibenzoxepines, despite the possibility of side-products arising from unwanted bond-formation sequences (Scheme 1).



Scheme 1. Design of reactions utilizing domino catalysis. Ms = methanesulfonyl.

Initial optimization[8] of reaction parameters illustrated that [{Rh(cod)OH}$_2$]/dppp and Pd(OAc)$_2$/*t*BuX-Phos catalyst systems led to the desired aza-dihydrodibenzoxepine **4a** in good yield over a two-step domino process (Table 1, entry 1). NMR analysis of the crude reaction mixture revealed two major by-products in addition to **4a**: phenol, resulting from deborylation of the boronic ester under the reaction conditions, and an arylated intermediate wherein the pyridyl chloride had been replaced by a hydroxy group,[9,10] a catalytic dead end for the C–O coupling step. Although detected in a ToF MS of the crude reaction mixture, no Suzuki product was ever isolated or detected by NMR analysis, thus suggesting that $<5\%$ was formed.

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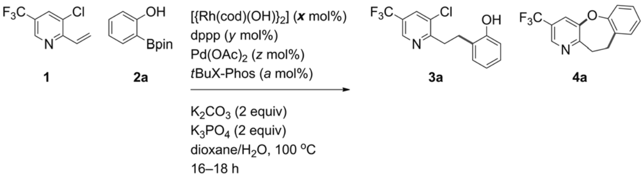
Table 1: Preliminary results in a domino reaction towards **3a** and **4a**.[a]



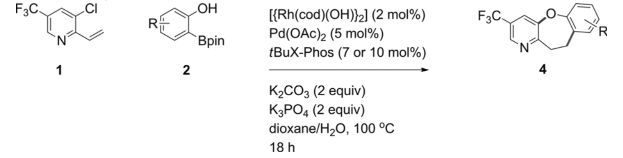
Entry	Rh dimer [mol %]	dppp [mol %]	Pd [mol %]	*t*BuX-Phos [mol %]	**3a**[b] [%]	**4a**[b] [%]
1	2	4	5	10	0	64
2	2	0	5	10	0	67[c]
3	2	0	0	10	83	0
4[d]	2	0	0	0	86	0
5[d]	0	0	5	10	10	0
6[e]	2	0	5	10	65	11

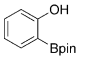
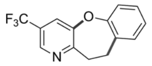
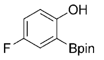
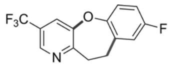
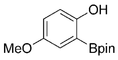
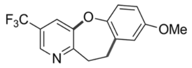
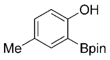
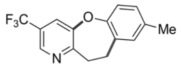
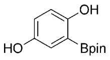
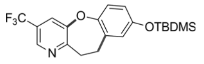
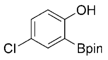
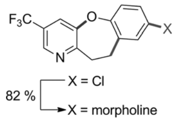
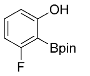
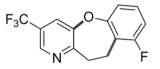
[a] For reaction conditions, see the Supporting Information. [b] Yields determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Yield of isolated product. [d] Reaction performed at room temperature for 10 min. [e] Reaction performed at room temperature for 18 h. OAc = acetate, cod = 1,5-cyclooctadiene, dppp = 1,3-bis(diphenylphosphanyl)propane, *t*BuX-Phos = 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl.

Further study demonstrated that the phosphine ligand (dppp) was unnecessary for the promotion of arylation,[11] whereas Pd was required for the C–O coupling step (Table 1, entries 2 and 3). Subjecting the starting materials to the Rh-catalyzed arylation conditions illustrated that a prolonged reaction time or a high reaction temperature was not necessary: the arylation reaction was complete within minutes at room temperature (entry 4). When the starting materials were instead subjected to the Pd-catalyzed C–O coupling conditions at room temperature, only 10 % of the arylation product (**3a**) was observed (entry 5).[12] When all domino components were present at room temperature, full conversion to **3a** was observed by TLC within ten minutes, thus supporting the preferential reaction of starting materials through Rh-catalyzed arylation. Prolonged reaction at room temperature gave only 11 % of **4a**, which indicates that higher temperatures are necessary for the C–O coupling to proceed (entry 6). Although the full conversion of **3a** into **4a** was possible at lower temperatures, we favored a method that used higher temperatures, as the conditions were more general when used with a diverse range of starting materials (Tables 2 and 3). Our optimized method gave 67 % of **4a** over a two-step, domino process.

We next examined the effect of substituents on the boronic ester (Table 2), and found that both electron-withdrawing and electron-donating groups were tolerated. For two examples that only proceeded in moderate yield in the domino reaction (entries 6 and 7), we compared the yields obtained over a two-step process involving chromatographic purification between steps; in the case of fluoro-substituted **4f** and chloro-substituted **4g**, an improvement in yield was observed when following the two-step process; this is presumably due to difficulty in purification of the domino reaction mixtures. The formation of chloro-substituted aza-dihydrodibenzoxepine **4f** suggests preferential insertion into the pyridinyl chloride,[13] which leaves the remaining aryl chloride for further functionalization: for example, C–N coupling[14] gave a morpholine-substituted aza-dihydrodibenoxepine in good yield, thus highlighting the utility of our products. Our method also tolerated a free hydroxy group, giving silyl ether **4e** after protection to facilitate purification.

Table 2: Scope of boronic esters in the domino reaction.[a]



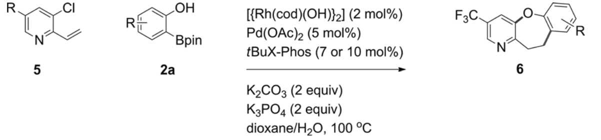
Entry	Boronic ester	Product	Yield [%][b]
1	 **2a**	 **4a**	67
2	 **2b**	 **4b**	60
3	 **2c**	 **4c**	59
4	 **2d**	 **4d**	58[c]
5	 **2e**	 **4e**	46[d]
6	 **2f**	 **4f**	39 (48)
7	 **2g**	 **4g**	33 (52)

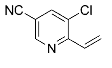
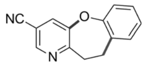
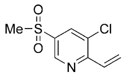
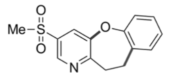
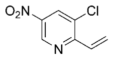
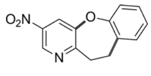
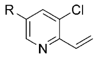
[a] Reaction conditions: vinyl pyridine (1 equiv), [{Rh(cod)(OH)}$_2$] (2 mol %), Pd(OAc)$_2$ (5 mol %), *t*BuX-Phos (7 or 10 mol %), K$_2$CO$_3$ (2 equiv), K$_3$PO$_4$ (2 equiv) and boronic ester (2 equiv) in dioxane/water (10:1), stirred at room temperature for 10 min, then heated to 100 °C for 18 h. Yields in parentheses correspond to those obtained in a two-step process, with chromatographic purification of the intermediate. [b] Yield of isolated product. [c] Reaction performed using [Pd$_2$dba$_3$] (2.5 mol %) as the Pd source. [d] Free hydroxy group protected as the silyl ether for isolation purposes, yield shown is over 2 steps. Pin = pinacolyl, TBDMS = *tert*-butyldimethylsilyl.

We then determined that pyridine electronics were crucial to the observed domino reactivity (Table 3): whereas vinyl pyridines featuring a cyano, methanesulfonyl, or nitro group (**5a**–**5c**) gave the desired aza-dihydrodibenzoxepine products (**6a**–**6c**) in good yields with none of the arylated intermediates detected, vinyl pyridines featuring a methyl, morpholino, or no substituent did not react as smoothly, giving mixtures of an arylated intermediate and aza-dihydrodibenzoxepine. To extend our method to these examples, a stepwise procedure was developed (entry 4), producing **6d**–**6f** in good yield over two steps.

Recently, Lam and co-workers reported an asymmetric variant of our Rh-catalyzed arylation[15] using β-substituted

Table 3: Scope of substituted vinyl pyridines in the domino reaction.[a]

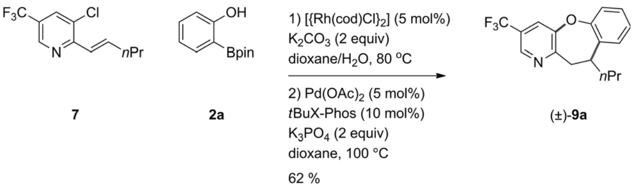


Entry	Method	Pyridine	Product	Yield [%][b]
1	domino	 **5a**	 **6a**	61
2	domino	 **5b**	 **6b**	56
3	domino	 **5c**	 **6c**	50
4	stepwise	 R = H, **5d** R = morpholino, **5e** R = methyl, **5f**	**6d** **6e** **6f**	75 71 61

[a] For reaction conditions, see Table 2 (entries 1–3), and the Supporting Information (entry 4). [b] Yield of isolated products.

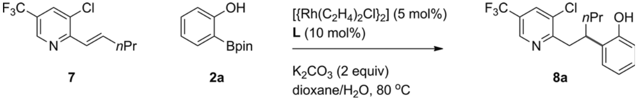
alkenyl-arenes and -heteroarenes, and chiral diene ligands. Successful arylation of vinyl pyridines required activation by an electron-deficient substituent.[16] As our Rh-catalyzed conditions were effective in the arylation of vinyl pyridines with similar electronics, we envisioned a route towards chiral aza-dihydrodibenzoxepines. At the outset, we tested this extension to our method in a two-step racemic process; subjecting **7** to the Rh-catalyzed arylation followed by the Pd-catalyzed C−O coupling gave our desired product in an overall yield of 62 % (Scheme 2).

We then screened several chiral ligands that have displayed excellent reactivity and enantioselectivity in conjugate additions of boronic acids (Table 4), as reported by the groups of Carreira (**L1**–**2**), Chan and Li (P-Phos), Genet (**L3**), Hayashi (**L4**), Lam (**L5**–**6**), and Korenaga and Sakai (Cl-MeO-BiPhep).[16–17] Although good enantiomeric induction was observed with many of the ligands tested, optimal results were obtained using the dibenzylamide diene (Table 4, entry 7, **L5**) developed by Lam and co-workers.



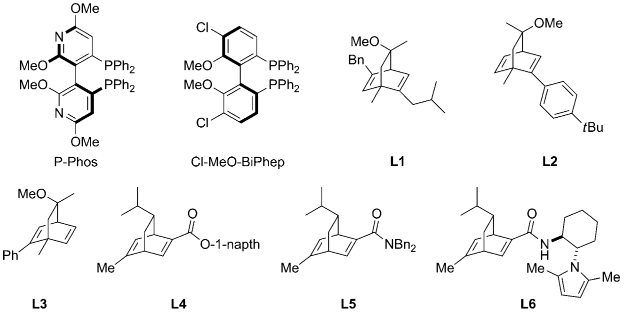
Scheme 2. Two-step process towards **9a**.

Table 4: Ligand screening for asymmetric Rh-catalyzed arylation.[a]



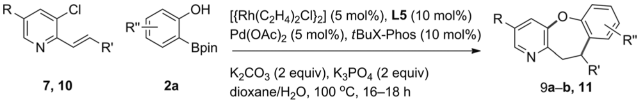
Entry	Ligand	Yield of **8a** [%][b]	*ee* [%][c]
1	P-Phos	59	90
2	Cl-OMe-BiPhep	55	88
3[d]	**L1**	35	80
4	**L2**	73[e]	70
5[d]	**L3**	64	76
6	**L4**	41	90
7	**L5**	72[e]	95
8	**L6**	14	n.d.

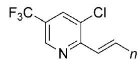
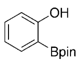
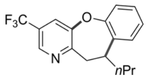
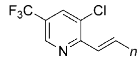
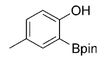
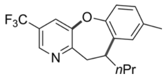
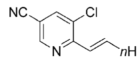
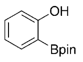
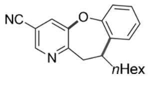
[a] Reaction conditions: vinyl pyridine (1 equiv), [{Rh(C_2H_4)Cl}$_2$] (5 mol %), **L** (10 mol %), K_2CO_3 (2 equiv), in dioxane/water (10:1), heated to 80 °C. Unreacted starting material observed in all cases: 16 % of **7** recovered in entry 4; 17 % of **7** recovered in entry 7. [b] Yields determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] *ee* values determined by HPLC analysis on a chiral stationary phase. [d] Alkenyl pyridine had an *n*-hexyl substituent [e] Yield of isolated products. Bn = benzyl, n.d. = not determined.



When we applied **L5** in a domino transformation, we were pleased to isolate our desired product in satisfactory yield with no loss in *ee* (Table 5, entry 1).[18] To the best of our knowledge, this is the first example of an asymmetric multicomponent, multi-metal reaction with both a chiral diene and an achiral phosphine ligand present in one pot. A

Table 5: Enantioselective domino reaction.[a]



Entry	Pyridine	Boronic ester	Product	Yield [%][b]	*ee* [%][c]
1	 **7**	 **2a**	 **9a**	56	95
2	 **7**	 **2d**	 **9b**	62	95
3	 **10**	 **2a**	 **11**	56	92

[a] Reaction conditions: vinyl pyridine (1 equiv), boronic ester (2 equiv or 4 equiv), [{Rh(C_2H_4)Cl}$_2$] (5 mol %), and **L5** (10 mol %) dissolved in dioxane at room temperature, transferred to a solution of Pd(OAc)$_2$ (5 mol %), *t*BuX-Phos (10 mol %), K_2CO_3 (2 equiv), and K_3PO_4 (2 equiv) in dioxane/water (10:1), then heated to 100 °C. [b] Yield of isolated products. [c] *ee* values determined by HPLC analysis on a chiral stationary phase.

preliminary scope study suggests that varying the substituents on the pyridine and on the boronic ester is possible, with similar yields and *ee* values to **9a** (Table 5, entries 2 and 3).

In conclusion, we have developed a domino process leading to aza-dihydrodibenzoxepines by combining a Rh-catalyzed arylation and a Pd-catalyzed C–O coupling in one pot. Domino reactivity was discovered to depend on the electronics of the vinyl pyridine, with electron-poor vinyl pyridines producing optimal conversion into the desired products. A two-step process was developed for those substrates that did not proceed to full conversion under domino conditions. Finally, we have developed an asymmetric variant of this reaction, the first example of an enantioenriched product formed in the presence of two transition metals and a chiral and achiral ligand in the same pot. Ongoing work in our laboratory on the further application of such domino reactivity will be reported in due course.

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Keywords: chemoselectivity · domino catalysis · enantioselectivity · heterocycles · multi-catalytic reactions

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