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Multicomponent-Multicatalyst Reactions (MC)^{2}R: Efficient Dibenzazepine Synthesis

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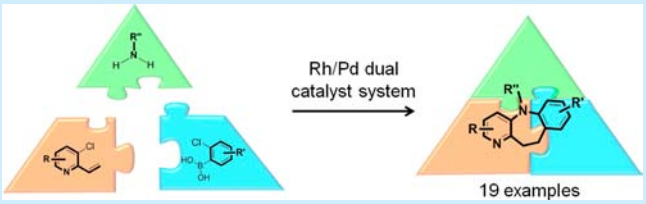
Supporting Information

ABSTRACT: A Rh^I/Pd^0 catalyst system was applied to the multicomponent synthesis of aza-dibenzazepines from vinylpyridines, arylboronic acids, and amines in a domino process with no intermediate isolation or purification.



In recent years, significant efforts have been made toward developing new concepts in catalysis that more closely mimic enzymatic systems where multiple catalysts each execute a transformation selectively. While progress has been made toward developing combinations of organocatalysts[1] or biocatalysts[2] with transition-metal catalysts, the use of two or more transition metals in domino sequences is less studied as orthogonal reactivity and time resolution are necessary.[3−5] We recently reported the synthesis of aza-dibenzoxepines using a two catalyst-two component domino reaction.[4k] As the analogous dibenzazepine motif is prevalent in many pharmaceutically relevant molecules,[6] and few *de novo* syntheses exist,[7] we were interested in applying our methodology to the synthesis of these interesting structures. However, the attempted synthesis using *ortho*-aminophenylboronic acids with our previously developed method failed to give the desired product (Scheme 1). We speculated that a strategy using two aryl halides followed by formation of the azepine ring with two Pd^0-catalyzed C−N bond formations with an external amine might circumvent this problem.

Not only would this allow further complexity to be added to the desired product in a highly modular fashion, but also would expand the field of multicatalyst-multicomponent reactions ((MC)^{2}R). Inclusion of three components in a multimetal catalyzed domino process would increase the complexity of this strategy as the three Rh^I- and Pd^0-catalyzed transformations must operate independently under the same reaction conditions without one catalyst interfering with the others. Furthermore, as the *ortho*-aminophenylboronic acid does not react with **1**, the order of the reaction sequence is critical for success, as the C−N bond must be formed after the other couplings. We speculated that the C−N bond would form first on the pyridyl ring, followed by the intramolecular amination. Herein, we report the successful application of Rh^I/Pd^0-catalysis in a multicomponent, domino reaction to access aza-dibenzazepines. To the best of our knowledge, this is the first example of a three catalyst-three component domino reaction.[8,9]

Scheme 1. Proposed Catalytic Steps

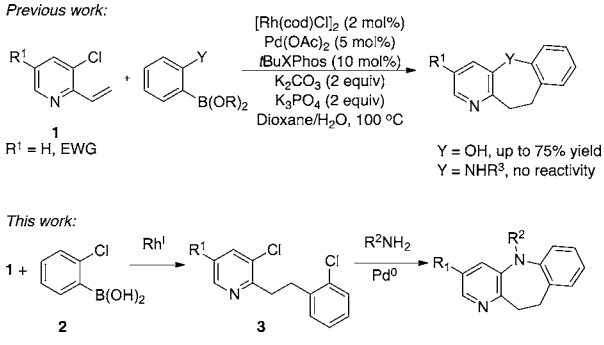
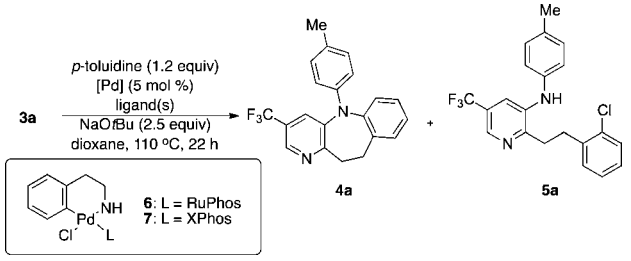


Table 1. Optimization of Pd^0-Catalyzed Amination



entry	[Pd]	ligand(s)	**4a** (%)[a]	**5a** (%)[a]
1	$Pd(OAc)_2$	RuPhos (5 mol %)	19	41
2	$Pd(OAc)_2$	RuPhos (10mol %)	73	–
3	$Pd(OAc)_2$	BrettPhos (10 mol %)	–	31
4	$Pd(OAc)_2$	RuPhos (5 mol %) XPhos (5 mol %)	89	–
5	**6**	XPhos (5 mol %)	88	–
6	**7**	RuPhos (5 mol %)	73	–

[a]Determined by ^{1}H NMR spectroscopy using *p*-nitroacetophenone as an internal standard.

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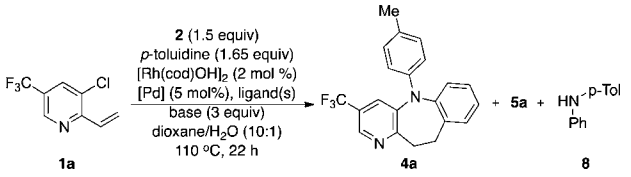
Table 2. Optimization of Domino Process



entry	[Pd]	ligand(s) (5 mol %)[a]	base	4a (%)[b]	5a (%)[b]
1	$Pd(OAc)_2$	RuPhos	NaO*t*Bu	57	15
		XPhos			
2	$Pd(OAc)_2$	RuPhos[c]	K_2CO	52	11
3	**6**	XPhos	K_2CO_3	71 (67)	–
4	**6**	–	K_2CO_3	46	52
5	**6**	RuPhos	K_2CO_3	54	34
6	**6**	XPhos	K_2CO_3	56[d]	

[a]5 mol % of each ligand is added to the reaction so that the Pd/L ratio is 1:2. [b]Determined by ^1H NMR spectroscopy using *p*-nitroacetophenone as an internal standard. Isolated yields in parentheses. [c]10 mol % RuPhos was used. [d]Reaction was performed on a 1 mmol scale. Isolated yield.

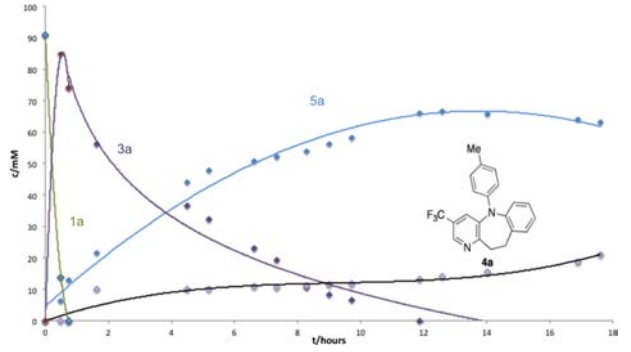
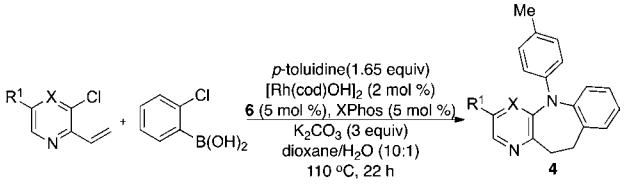


Figure 1. *In situ* monitoring of the reaction of **1a**, **2**, and *p*-toluidine. Conditions: **6** (5 mol %), XPhos (5 mol %), K_2CO_3 (3 equiv), dioxane-d_8/D_2O (10:1, 0.909 M), 95−110 °C, 400 MHz.[14]

Table 3. Scope of Domino Process (1)

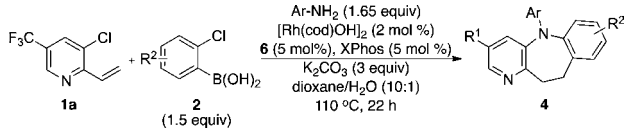


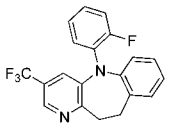
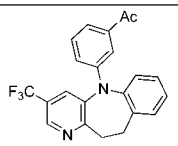
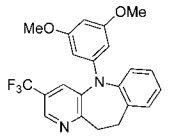
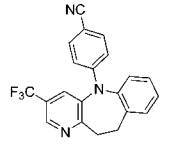
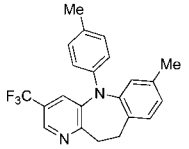
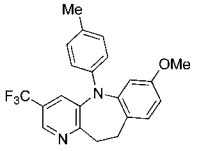
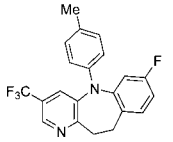
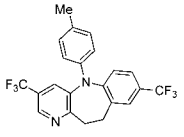
entry	product	R^1	X	yield (%)[a]
1	**4a**	CF_3	CH	67
2	**4b**	CN	CH	49
3	**4c**	H	CH	41[b]
4	**4d**	H	N	53

[a]Isolated yields. [b]Isolated using a one-pot procedure: **1c**, **2**, $[Rh(cod)OH]_2$, and K_2CO_3 were stirred at 110 °C in dioxane/H_2O for 30 min until **1c** was fully consumed, and then *p*-toluidine, **6**, and XPhos were added to the reaction and stirring resumed at 110 °C for 16 h.

Studies showed that the Rh^I-catalyzed arylation reaction with *ortho*-halogenated arylboronic acids can occur in high yields in a short reaction time.[10] This encouraging result indicates that a time-resolved reaction sequence would be possible. A study of the Pd^0-catalyzed amination steps was then conducted using **3a** (R^1=CF_3). Using $Pd(OAc)_2$ and an equimolar amount of RuPhos (which has been shown to be effective for C−N bond formations between 2° amines and aryl chlorides),[11] we found that formation of the dibenzazepine ring was incomplete, giving predominantly intermediate **5a**, where the amine reacted only with the more electronically favored pyridyl chloride (Table 1,

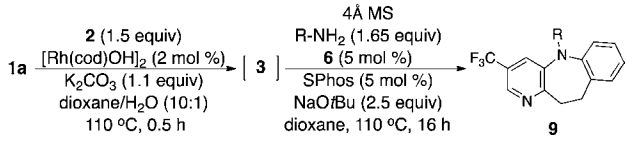
Table 4. Scope of Domino Reaction (2)

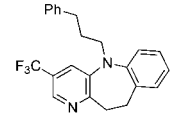
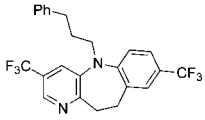
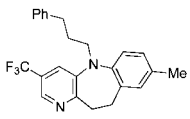
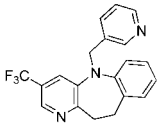
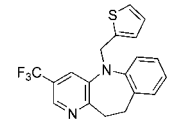
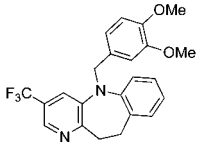
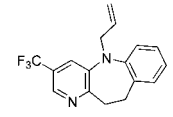


Product	Yield (%)[a]	Product	Yield (%)[a]
4e 	69	**4f** 	76
4g 	45	**4h** 	59
4i 	82	**4j** 	74
4k 	82	**4l** 	52

[a]Isolated yields.

Table 5. Reaction Scope with Aliphatic Amines



Product	Yield (%)[a]	Product	Yield (%)[a]
9a 	60	**9b** 	68
9c 	27[b]	**9d** 	68
9e 	56	**9f** 	64
9g 	50		

[a]Isolated yields. [b]Isolated as an inseparable mixture of **9c** and monoaminated product.

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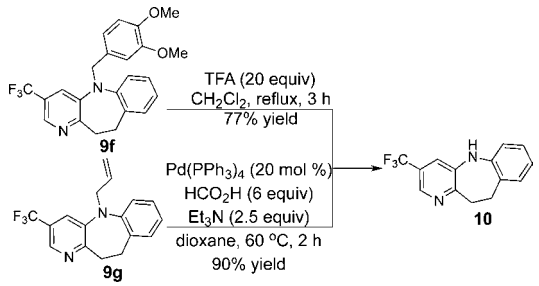
Scheme 2. Deprotection of 9f and 9g



entry 1). Adding an excess of ligand partially resolved this problem, giving a 73% yield of the desired product (entry 2). Based on reports from Buchwald and co-workers,[12] we also examined multiligand based palladium catalysts, as C−N coupling with both 1° and 2° amines is required in our sequence. We found that using a 1:1 ratio of RuPhos and XPhos gave us the best results, yielding 89% of the desired dibenzazepine product (entry 4).

We next looked into the compatibility of the three catalyst systems in a domino process. When all three starting materials were combined with the catalyst systems, we were able to form the desired aza-dibenzazepine product **4a** as the major product, with intermediate **5a** and the amination/protodeboronation byproduct **8** produced in minor amounts. By using Buchwald's precatalyst **6** as the palladium source,[12] we were able to produce **4a** in good yield while also simplifying the reaction setup (Table 2, entry 3). Further studies show that, without the addition of XPhos, product yields were significantly lower (entries 4−5). This suggests that both palladium complexes are critical for optimal results. The domino process was performed on a 1 mmol scale, giving a yield of 56% (entry 6).

A study of the reaction by ^{1}H NMR spectroscopy (Figure 1) showed that the vinylpyridine substrate **1a** is first rapidly consumed to give arylation product **3a**. The dihalogenated intermediate is then converted more slowly to form both the amination intermediate **5a** and the final cyclized product **4a**. This study indicates that the domino reaction occurs in a time-resolved fashion, where the first catalytic cycle creates the product that is fed into the next catalytic cycle. The intermolecular C−N bond formation on the pyridyl chloride occurs faster than the intramolecular amination, and no intermolecular C−N bond forms on the phenyl chloride. While the reaction did not reach completion within the same time as that under standard reaction conditions, heating for another 24 h showed full conversion to the product **4a**.[13]

With the optimized conditions in hand, we examined the scope of the (MC)^{2}R. Electron-poor vinylpyridines work best and gave the desired products in good yields (Table 3, entries 1−2). When the vinylpyridine is not sufficiently electrophilic, the arylated product, **5**, and unidentified byproducts were observed in the domino process.

When there are no substituents on the vinylpyridine, the aza-dibenzazepine product can be accessed in a sequential, one-pot procedure (entry 3).[15] Other *N*-heterocycles can also be used, such as vinylpyrazines (entry 4) in good yields.

The electronically biased vinylpyridine **1a** was used to further explore the reaction scope of the domino process (Table 4) due to its higher reactivity.

Ortho-, *meta*-, and *para*-substituents are tolerated on the aniline partner, giving moderate to good yields (**4e**−**h**). Functional groups such as ketones (**4f**) and nitriles (**4h**) are also compatible, and electron-poor anilines are generally higher yielding. Substituents on the arylboronic acids are also permitted at the 4- (**4i**−**j**) and 5-position (**4k**−**l**), but 6-substituted arylboronic acids lead to only trace amounts of the arylation product.

For aliphatic amines, the reaction was best run in a sequential, one-pot fashion.[16] Full conversion of the Rh^I-catalyzed step can generally be observed within 30 min, after which the Pd^0 catalyst, additional base, and amine can be added to the reaction vessel.[17,18] Increasing the electron density of aryl chloride **2** leads to decreasing yields of the cyclized product **9** (Table 5, entries **9a**−**9c**). Notably, heterocycles such as pyridines (**9d**) and thiophenes (**9e**) can be incorporated. Protected amines such as 2,4-dimethoxy-benzyl (**9f**) and allyl (**9g**) amines are also compatible, which can then be deprotected readily to provide the secondary amine **10** (Scheme 2).

In summary, we successfully implemented a Rh^I/Pd^0-catalyzed multicomponent reaction methodology in a domino process to access *N*-aryl aza-dibenzazepines in good yields. This method was further adapted into a pot-economical protocol in order to generate *N*-alkyl aza-dibenzazepines in moderate to good yields. These convergent processes can allow the rapid creation of complex and structurally diverse compound libraries from simple starting materials. These processes also exemplify that multiple transition-metal complexes can operate independently in one pot, completing several bond-forming steps without any intermediate workup or purifications. Further studies to extend this (MC)^{2}R concept are ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) While we have only two metals, the two phosphine ligands each bind to palladium to form two catalytic systems, as evident from the differences in product yields when both RuPhos and XPhos are used versus only RuPhos.

(9) For examples of a three-catalyst/two-component reaction, see: (a) Komon, Z. J. A.; Diamond, G. M.; Leclerc, M. K.; Murphy, V.; Okazaki, M.; Bazan, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 15280. (b) Huff, C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18122.

(10) Typical reaction conditions for Rh^{I}-catalyzed arylation: Vinylpyridine, *o*-chloroboronic acid (1.2 equiv), $[Rh(cod)OH]_2$ (2 mol%), K_2CO_3 (2 equiv), dioxane/H_2O (10:1), 110 °C, 2 h. Yields are between 81% and 91%.

(11) (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686. (b) Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5766.

(12) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914.

(13) The reaction mixture in the NMR tube shows two distinct solvent phases from lack of stirring, which explains why the reaction is not complete in the same time as in the conventional setup.

(14) We were unable to obtain spectral data at 110 °C due to poor shimming. Initial studies at 95 °C showed no formation of product **4a**; thus, Scheme 3 refers to data obtained from running the reaction in a sealed NMR tube at 110 °C, with cooling to 95 °C to collect data.

(15) With electron-rich substituents such as morpholine, the Pd^0-catalyzed C−N bond formation does not occur.

(16) Attempts to extend the domino "all-in-one" methodology to aliphatic amines using the optimized conditions led to primarily the monoaminated intermediate. The origin of the problem is likely the need for water in the first step and the need for a strong base such as NaO*t*Bu in the second.

(17) Optimization studies showed that using precatalyst **6** (5 mol%) and SPhos (5 mol%) gave better results for the aliphatic amines than with XPhos used for the aromatic amines. See Supporting Information for further details.

(18) Isolated yields for product **9a** were 60% with 4 Å MS versus 48% without.