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Rh-Catalyzed Domino Addition–Enolate Arylation: Generation of 3-Substituted Oxindoles via a Rh(III) Intermediate

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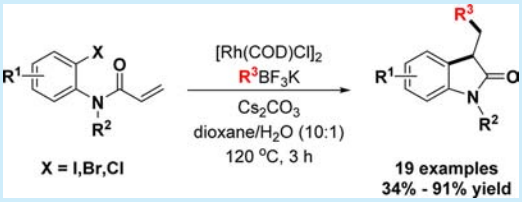
Supporting Information

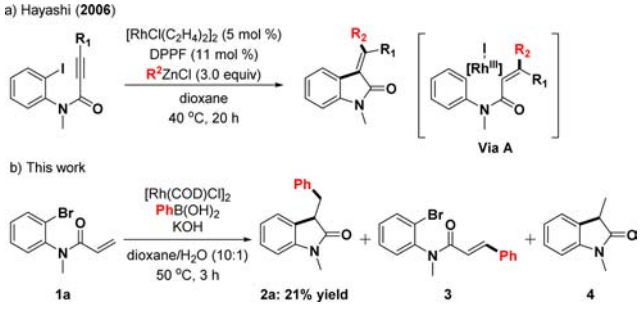
ABSTRACT: A Rh-catalyzed domino conjugate addition–arylation sequence via a Rh(III) intermediate is reported. This process involving a proposed intramolecular oxidative addition of a rhodium enolate was utilized to achieve the synthesis of 3-substituted oxindole derivatives in moderate to excellent yields.



Transition metal catalyzed α-arylation has attracted considerable attention due to its versatility and utility in the synthesis of many medicinal targets.[1] A myriad of catalytic variants have been developed since Semmelhack's seminal report in 1973.[2] Transition metal catalysts including palladium, copper, and nickel are most widely used, and of these, palladium catalysts have been most thoroughly studied.[3] A major drawback of current methods resides in the use of strong bases in the generation of enolate nucleophiles and, combined with the use of transition metals that are prone to facile oxidative addition, can limit functional group tolerance. In addition, current methods often suffer from poor selectivity toward monoarylation, leading to decreased yields.[4] To circumvent these problems, we sought to develop an alternative α-arylation strategy with a broader scope and applicability.

In 2006, Hayashi reported a Rh-catalyzed cascade conjugate addition–α-arylation sequence to ynamides using aryl-zinc species (Scheme 1).[5] Therein, a novel intramolecular oxidative addition of a Rh(I) allenolate was proposed, generating rhodacycle **A** en route to methylene oxindoles (Scheme 1a). We hypothesized that through the use of more readily available boronic acids and *o*-bromoaniline derived acrylamides, we could access Rh(I) enolate species. This would allow efficient and catalytic access to diverse oxindole derivatives that exhibit numerous biological activities.[6]

Scheme 1. Oxindole Synthesis via Rh-Catalyzed Domino Conjugate Addition–Arylation



Although oxidative addition of Rh(I) is well documented,[7] only a limited number of examples involve oxidative addition into a carbon–halogen bond under mild conditions. In recent years, Chatani[8] and Cramer[9] have demonstrated the utility of Rh-catalyzed cascade processes involving oxidative addition of Rh(I) species to access diverse building blocks.

Furthermore, the use of boron reagents provides a simple way to incorporate diverse carbon-based functional groups. In addition, organoboron reagents, in comparison to organozinc reagents, are more compatible with protic solvents and are more easily accessible.

To test this approach, **1a** was treated with $[Rh(COD)Cl]_2$ (2.5 mol %), $PhB(OH)_2$ (1.5 equiv), and KOH (3 equiv) in a dioxane/water (10:1) solution at 50 °C. After 3 h, **2a** was isolated in 21% yield from a mixture with **3** and **4**, resulting from β-hydride elimination via the Rh(I)-catalyzed Heck-type process.[10] Attempts to suppress these byproducts using substrates such as **3** led to complex mixtures.

A series of optimization reactions were carried out in order to improve the yield of **2a**. The $[Rh(COD)Cl]_2$ catalyst was found to be superior compared to other dimeric rhodium species (Table 1, entry 2). Increasing the temperature to 110 °C provided a moderate increase in yield (entry 3). The use of bidentate phosphine ligands such as (±)-BINAP significantly increased the yield of **2a** to 64% (entry 4). Switching to Cs_2CO_3 further promoted the reaction and eliminated the need for a phosphine ligand (entry 5). Switching to the trifluoroborate salt showed a further increase in yield (entry 7). Finally, our optimized conditions were achieved by elevating the temperature to 120 °C and decreasing the catalyst loading to 1.25 mol %, providing an isolated yield of 84% (entry 9).

With the optimized conditions in hand, we examined the scope of the reaction (Scheme 2). To probe the oxidative

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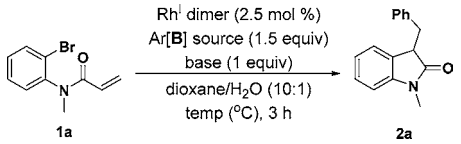
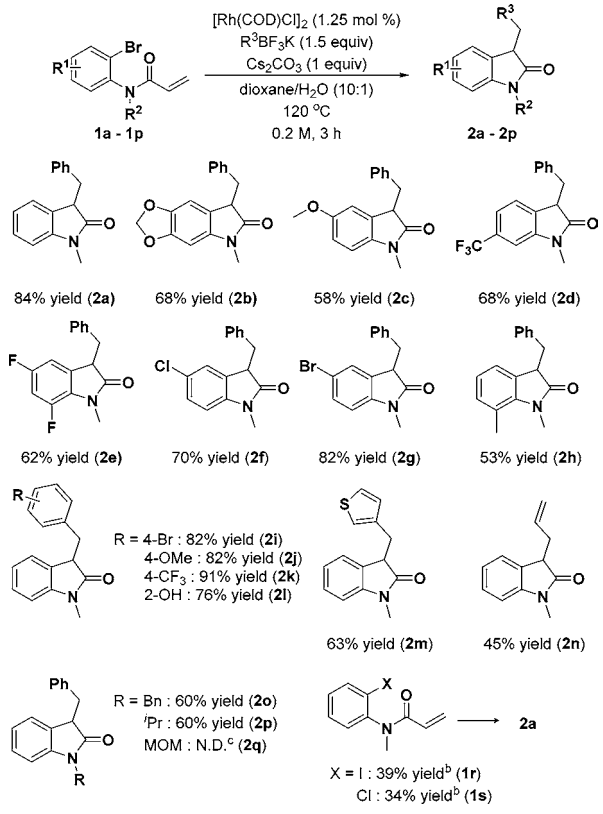
Table 1. Rh-Catalyzed Domino Conjugate Addition−Arylation: Optimization of Reaction Parameters[a]



entry	Rh[I] dimer	Ar[B] source	base	temp (°C)	ligand	yield[b,d] **1b** (%)
1	$[Rh(COD)Cl]_2$	$PhB(OH)_2$	KOH[c]	50	–	35
2	$[Rh(COD)OH]_2$	$PhB(OH)_2$	KOH	50	–	21
3	$[Rh(COD)Cl]_2$	$PhB(OH)_2$	KOH	110	–	40
4	$[Rh(COD)Cl]_2$	$PhB(OH)_2$	KOH	110	BINAP	64
5	$[Rh(COD)Cl]_2$	$PhB(OH)_2$	Cs_2CO_3	110	–	74
6	$[Rh(COD)Cl]_2$	$PhBF_3K$	Cs_2CO_3	110	–	78
7	$[Rh(COD)Cl]_2$	$PhBF_3K$	Cs_2CO_3	110	BINAP	74
8	$[Rh(COD)Cl]_2$ (1.25 mol %)	$PhBF_3K$	Cs_2CO_3	110	–	84
9	$[Rh(COD)Cl]_2$ (1.25 mol %)	$PhBF_3K$	Cs_2CO_3	120	–	89 (84)

[a]See the Supporting Information for reaction details. [b]Yields were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c]3 equiv of base were used. [d]Yield in parentheses represents isolated yields.

Scheme 2. Rh-Catalyzed Domino Conjugate Addition−Arylation: Reaction Scope[a]



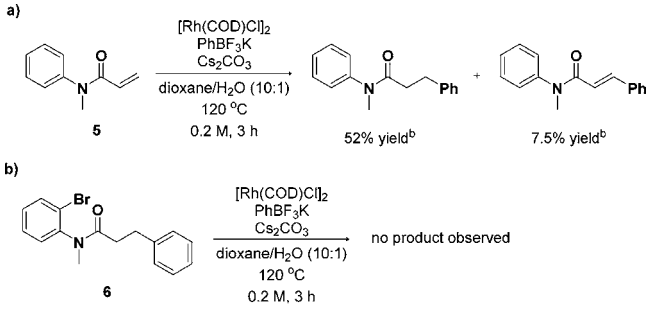
[a]See the Supporting Information for reaction details. [b]NMR yield; yields were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c]Inseparable from byproducts; see Scheme 5 for details.

addition process of the Rh-enolate, the electronics of the aryl ring were varied. Electron-rich as well as electron-deficient substrates gave moderate yields (**2a−2e**). Dihalogenated acrylamides (**2f**, **2g**) are tolerated with high fidelity to produce halogenated oxindoles with no formation of Rh-catalyzed Suzuki coupled products.[11]

A diverse array of boronic acids can be incorporated (**2i−2l**). Electron-rich as well as electron-deficient boronic acids produced the desired oxindoles in excellent yields. Heteroaromatic (**2m**) and aliphatic (**2n**) boronic acids also gave moderate yields. Different protecting groups on the nitrogen can be used (**2o**, **2p**), except for the −Boc group and the free N−H amide which failed to undergo the desired transformation. Lastly, the presence of a methyl group next to the bromide impedes the reaction, and replacing the bromide with an iodide (**1r**) or a chloride (**1s**) lowers the yield.

To gain a better understanding of the reaction mechanism, a number of control experiments were conducted (Scheme 3).

Scheme 3. Control Experiments[a]



[a]See the Supporting Information for reaction details. [b]Isolated yield.

The first control experiment with a substrate lacking the ortho bromo group (Scheme 3a) demonstrates that the halide is necessary to achieve the ring formation. Additionally, subjecting the product from conjugate addition-protonation (**6**) under the optimized conditions does not generate the enolate, illustrating that both the conjugate addition and the oxidative addition process have to occur sequentially without hydrolysis of the rhodium enolate (**B**). Based on these observations we propose the following catalytic cycle (Scheme 4).

We speculate the Rh(I) species undergoes transmetalation with the boronic acid to produce Rh−Ar species that subsequently carborhodation onto **1a** to produce intermediate **B**. Intermediate **B** can undergo either oxidative addition to produce intermediate **C** or β-hydride eliminate to produce intermediate **3**. Intermediate **C** will reductively eliminate to furnish the desired oxindole and regenerate the active catalyst.

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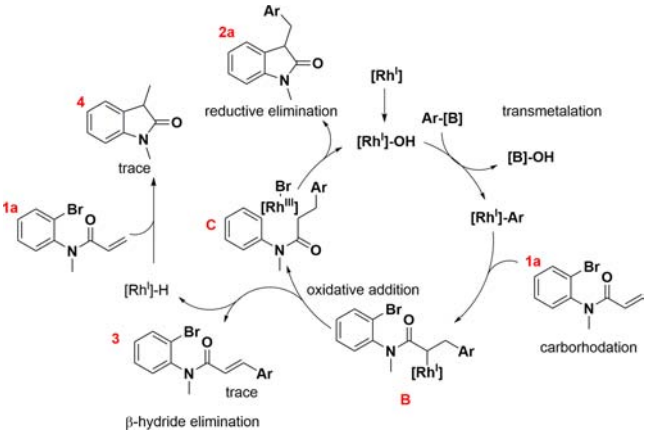
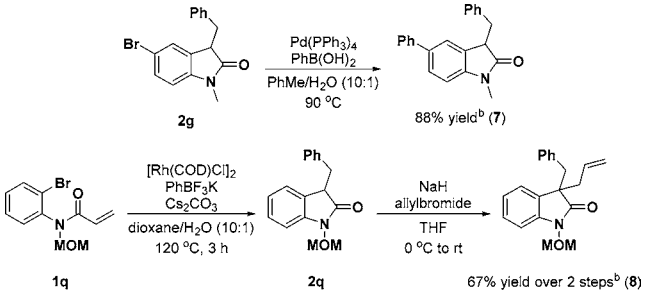
Scheme 4. Proposed Catalytic Cycle



On the other hand, production of intermediate **3** will produce the Rh−H species which may undergo hydrolysis to regenerate the active catalyst, Rh−OH, or it may consume either of the two substrates **1a** or **3** leading to **4** or **2a**, respectively. Trace amounts of compounds **3** and **4** are observed in the reaction mixture in a combined yield of <5%.

Further product derivatization experiments were performed to demonstrate the synthetic utility of the oxindoles (Scheme 5). A Suzuki reaction of the aryl bromide **2g** was accomplished

Scheme 5. Derivatization of Oxindole Products[a]



[a]See the Supporting Information for reaction details. [b]Isolated yield.

to produce the phenylated oxindole **7** in 88% yield. −MOM protected acrylamide (**1s**) underwent a stepwise cyclization and allylation to form oxindole **8** in 67% yield over two steps.

In conclusion, we developed an alternative method for the rhodium-catalyzed domino conjugate addition−arylation sequence to furnish various 3-substituted oxindole derivatives. Further studies will be carried out to expand the scope and versatility of these types of cascade reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01737.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected examples of application of α-arylation in total syntheses, see: (a) Carril, M.; SanMartin, R.; Churruca, F.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2005**, *7*, 4787. (b) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631. (c) Honda, T.; Sakamaki, Y. *Tetrahedron Lett.* **2005**, *46*, 6823.

(2) Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, *14*, 4519.

(3) (a) Hamann, B.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (b) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (c) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (d) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740. For selected reviews on α-arylation, see: (e) Prim, D.; Marque, S.; Gaucher, A.; Campagne, J.-M. *Org. React.* **2012**, *76*, 49. (f) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

(4) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345.

(5) (a) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799. For selected reviews on Rh(I)-catalyzed conjugate addition, see: (b) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (d) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(6) Liu, X.-L.; Pan, B.-W.; Zhang, W.-H.; Yang, C.; Yang, J.; Shi, Y.; Feng, T.-T.; Zhou, Y.; Yuan, W.-C. *Org. Biomol. Chem.* **2015**, *13*, 601.

(7) (a) Morimoto, T.; Yamasaki, K.; Hirano, A.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K.; Harada, Y.; Fukumoto, Y.; Chatani, N.; Nishioka, T. *Org. Lett.* **2009**, *11*, 1777. (b) Fujioka, M.; Morimoto, T.; Tsumagari, T.; Tanimoto, H.; Nishiyama, Y.; Kakiuchi, K. *J. Org. Chem.* **2012**, *77*, 2911.

(8) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766.

(9) Souillart, L.; Cramer, N. *Chem. Sci.* **2014**, *5*, 837.

(10) Lautens, M.; Mancuso, J.; Grover, H. *Synthesis* **2004**, *12*, 2006.

(11) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229.

(12) For a selected review on the utility of trifluoroborate salts, see: Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

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