Rhodium-catalyzed Synthesis of Indenols by Regioselective Coupling of Alkynes with Ortho-carbonylated Arylboronic Acids

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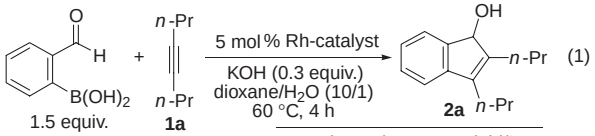
A rhodium/diene-catalyzed regioselective synthesis of indenols has been developed through the coupling of alkynes with ortho-carbonylated arylboronic acids. These reactions proceed under mild conditions in uniformly high yield and regioselectivity. The reaction has also been applied to its asymmetric variant by the use of chiral diene ligands to achieve high enantioselectivity.

Indenols are an important family of compounds due to their utility as synthetic intermediates in organic chemistry.[1] In addition, there have been several reports on the biological activity of indenol-containing organic molecules.[2] As a consequence, the development of efficient methods for the synthesis of indenols, particularly catalytic enantioselective ones, is a significant objective. Typical synthetic approaches to these compounds are, however, based on the use of a preformed indan structure with a manipulation of its oxidation state.[3] In contrast, only a few methods have provided a catalytic synthesis of indenols in a convergent manner,[4,5] and unfortunately, none of these have been applied to the asymmetric variants so far.[6]

For the development of a new convergent method for indenol synthesis, we initiated a program focusing on the coupling of alkynes with ortho-carbonylated arylboronic acids under rhodium catalysis.[7] Herein we describe that a rhodium/diene catalyst is uniquely effective for a regioselective coupling of these components under mild conditions, and that the employment of chiral diene ligands leads to the realization of carbon–carbon bond-forming catalytic asymmetric synthesis of indenols in relatively high enantioselectivity.

As a starting point, we chose to examine a reaction of 4-octyne (**1a**) with 2-formylphenylboronic acid (1.5 equiv.) in the presence of 5 mol % rhodium catalyst at 60 °C (Eq 1). Although Rh/phosphine complexes are known to catalyze a reaction of internal alkynes with arylboronic acids,[8] the use of phosphine ligands in this reaction failed to produce the desired indenol (**2a**). In contrast, the reaction proceeded smoothly in the presence of $[Rh(OH)(cod)]_2$ as a catalyst, furnishing the targeted indenol (**2a**) in 92% yield.



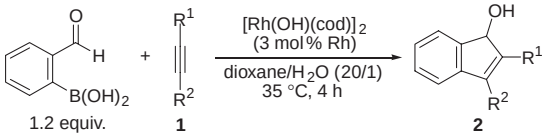
(1)

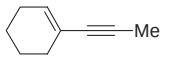
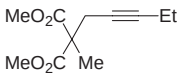
Rh-catalyst	Yield/%
$RhCl(PPh_3)_3$	0
$[RhCl((R)\text{-binap})]_2$	<5
$[Rh(OH)(cod)]_2$[a]	92

[a]No KOH was added.

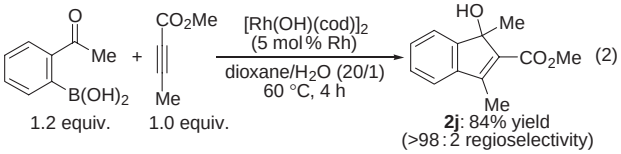
After some investigations, we found that the reaction also proceeds with 3 mol % catalyst loading at 35 °C by using 1.2 equiv. of 2-formylphenylboronic acid to give indenol **2a** in 81% yield (Table 1, Entry 1). Under these conditions, a variety of internal alkynes can be coupled with 2-formylphenylboronic acid to afford the corresponding indenols in high yield as shown in Table 1 (78–94% yield).[9] When unsymmetrical alkynes are used, they generally exhibit high regioselectivity in the product formation. For example, aryl or alkenyl groups can be well-distinguished from alkyl groups (methyl, primary alkyl, and secondary alkyl) in the ratio of ≥90:10 (Entries 3–6). Furthermore, high regioselectivity is also achieved even when two substituents on the alkyne are both primary alkyl groups as long as one is sufficiently bulkier than the other (>98:2; Entry 7). Esters and silyl groups on the alkyne are good handles as well to induce high regioselectivity in these coupling reactions (82:18–>98:2; Entries 8 and 9). With respect to the arylboronic acid, 2-acetylphenylboronic acid can also be employed under similar conditions to give a corresponding indenol with high efficiency as well (84% yield; Eq 2).

Table 1. Rhodium-catalyzed regioselective synthesis of indenols

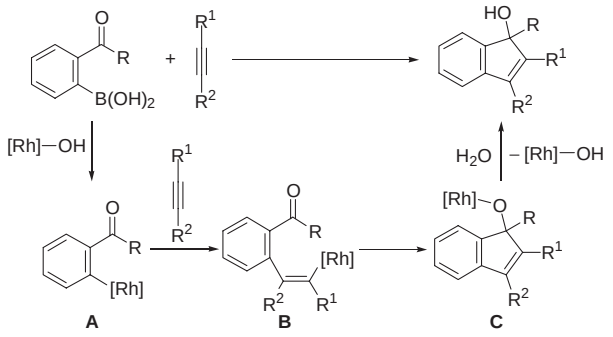


Entry	$R^1—≡—R^2$		Yield/%[a]	
1	*n*-Pr—≡—*n*-Pr	(**1a**)	81	
2[b]	Ph—≡—Ph	(**1b**)	83	
3	Ph—≡—Me	(**1c**)	92	(95:5)
4[b]	Ph—≡—*n*-Bu	(**1d**)	78	(95:5)
5[b]	Ph—≡—Cy	(**1e**)	82[c]	(90:10)
6		(**1f**)	81	(95:5)
7		(**1g**)	88	(>98:2)
8	MeO_2C—≡—Me	(**1h**)	87	(>98:2)
9[d]	Me_3Si—≡—Me	(**1i**)	94	(82:18)

[a]Isolated yield (combined yield of regio isomers unless otherwise noted). Numbers in parentheses describe the regioselectivity. [b]The reaction was conducted at 60 °C. [c]Isolated yield of the major regio isomer. [d]2.4 equiv. of 2-formylphenylboronic acid was used.



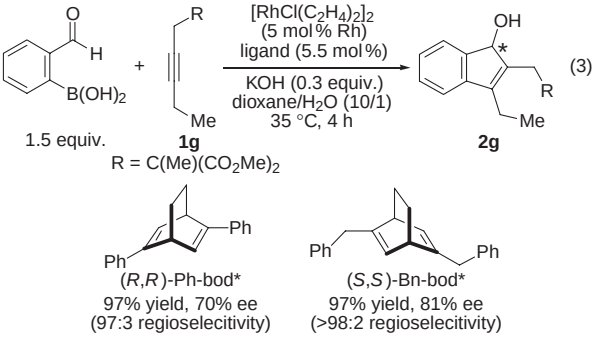
(2)



Scheme 1. Proposed catalytic cycle of the rhodium-catalyzed coupling of alkynes with ortho-carbonylated arylboronic acids.

These coupling reactions presumably go through a catalytic cycle illustrated in Scheme 1. Thus, transmetallation of an arylboronic acid to the hydroxorhodium catalyst forms arylrhodium species **A**. An alkyne inserts into this carbon–rhodium bond to generate alkenylrhodium intermediate **B**. Insertion of the carbonyl group at the ortho-position results in the formation of an alkoxorhodium species with a five-membered carbocycle (**C**). Hydrolysis of this intermediate produces the desired indenol and regenerates the hydroxorhodium species.

Because the second carbon–carbon bond formation of this process (i.e., **B** → **C**) creates a stereogenic center, the use of a proper chiral ligand might be able to show a good control on the stereochemical outcome. In this regard, because Rh/phosphine complexes do not catalyze these reactions as described in Eq 1, the use of chiral phosphine ligands is not promising for the development of an asymmetric variant. We therefore decided to employ chiral diene ligands on the basis of the high efficiency of Rh/cod catalyst as demonstrated in Table 1. For example, in the reaction of alkyne **1g** with 2-formylphenylboronic acid, the use of (*R*,*R*)-Ph-bod*, a C_2-symmetric chiral diene ligand developed in our group,[10,11] regioselecitvely furnished indenol **2g** in 97% yield with 70% ee (Eq 3). By changing the ligand to (*S*,*S*)-Bn-bod*,[10,12] the enantioselectivity is improved to 81% ee with excellent yield and regioselectivity.



In summary, we have developed a rhodium-catalyzed regioselective synthesis of indenols through the coupling of alkynes with ortho-carbonylated arylboronic acids. These reactions proceed under mild conditions in uniformly high yield and regioselectivity. The reaction has also been applied to its asymmetric variant by using chiral diene ligands, achieving high enantioselectivity. Future studies will explore further expansion of the scope of this and related processes.

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