Asymmetric Catalysis

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Rhodium-Catalyzed Asymmetric Synthesis of Spirocarbocycles: Arylboron Reagents as Surrogates of 1,2-Dimetalloarenes**

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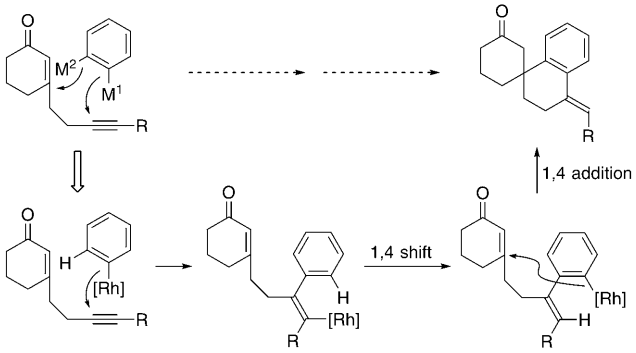
Enantiopure spirocycles that possess a quaternary spirocarbon stereocenter[1] represent an important class of compounds as they can be found in various useful organic molecules, such as natural products,[2] biologically active compounds,[3] and effective chiral ligands for asymmetric catalysis.[4] Construction of such spirocycles using transition-metal-catalyzed asymmetric carbon–carbon bond-forming reactions are highly desirable in view of the efficiency of the process.[5] In this context, sequential addition of 1,2-dimetalloarenes to 2-cycloalken-1-ones that are tethered at the 3-position to another electrophilic substituent, such as an alkyne, could rapidly afford spirocarbocycles in a convergent manner, as illustrated in Scheme 1; however, the preparation

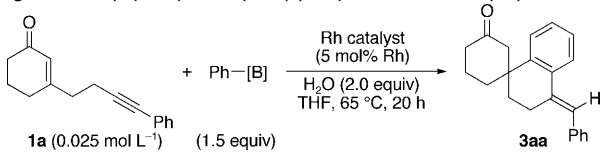


Scheme 1. Strategy for the convergent synthesis of spirocarbocycles.

and successful use of 1,2-dimetalloarenes is not always trivial.[6] To circumvent the potential difficulty of this convergent strategy, we anticipated that an arylrhodation–1,4-rhodium-migration sequence could be used as a surrogate, which is a known process in the context of the addition of arylboron reagents to internal alkynes under rhodium catalysis.[7,8]

To implement the aforementioned strategy, we chose 3-(4-phenyl-3-butyn-1-yl)-2-cyclohexen-1-one (**1a**) as a model substrate and conducted a reaction with phenylboronic acid in the presence of [{Rh(OH)(cod)}$_2$] (5 mol% Rh) in aqueous tetrahydrofuran at 65 °C.[9] Under these conditions, substrate **1a** was fully consumed and the desired spirocycle **3aa** was successfully obtained in 60% yield (Table 1, entry 1). The use

Table 1: Rhodium-catalyzed addition–cyclization of phenylboron reagents to 3-(4-phenyl-3-butyn-1-yl)-2-cyclohexen-1-one (**1a**).



Entry	[Rh] catalyst	Ph-[B]	Yield [%][a]
1	[{Rh(OH)(cod)}$_2$]	PhB(OH)$_2$	60
2[b]	[{Rh(OH)(cod)}$_2$]	PhB(OR)$_2$[c]	33
3	[{RhCl(cod)}$_2$]	Ph$_4$BNa	73
4	[{RhCl(binap)}$_2$]	Ph$_4$BNa	< 5[d]

[a] Yield of isolated product. [b] The reaction was conducted in the absence of H_2O. [c] (OR)$_2$ = $OCH_2CMe_2CH_2O$. [d] Determined by ^{1}H NMR analysis of the crude material. cod = 1,5-cyclooctadiene, binap = 1,1′-binaphthalene-2,2′-diylbis(diphenylphosphine).

of phenylboronic acid neopentylglycol ester under anhydrous conditions resulted in lower yield of **3aa** (33% yield; Table 1, entry 2). In contrast, sodium tetraphenylborate (**2a**),[10] which was reported by Murakami and co-workers as an effective nucleophile in a related transformation,[7b] was found to be a better nucleophile, and gave **3aa** in 73% yield under the catalysis of [{RhCl(cod)}$_2$] in aqueous tetrahydrofuran (Table 1, entry 3). It is worth noting that the reaction using **2a** did not proceed effectively with a rhodium–bis(phosphine) complex as the catalyst (Table 1, entry 4).

Using sodium tetraphenylborate in the presence of [{RhCl(cod)}$_2$] catalyst, aryl, alkenyl, and alkyl substituents were all tolerated on the alkyne group of 3-(2-alkynylethyl)-2-cyclohexen-1-ones **1** to give the corresponding spirocycles **3** (60–74% yield; Table 2, entries 1–5); 2-cyclopenten-1-one derivative **1f** was also employed with similar efficiency (77% yield; Table 2, entry 6).[11] With regard to the nucleophilic component, (hetero)aryl-substituted tetraarylborates were effectively incorporated in the reaction (62–77% yield; Table 2, entries 7–13), and the use of 3-substituted tetraarylborates led to the regioselective formation of a spirocycle at the less-hindered position (selectivity ≥ 11:1; Table 2, entries 10–12).

When sodium tetrakis(pentadeuteriophenyl)borate (**[D$_{20}$]-2a**) was used as the nucleophile in the reactions with **1a** and **1f**, the products obtained (**3aa** and **3fa**, respectively)

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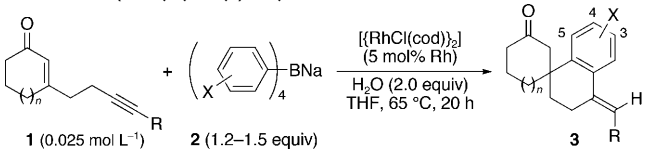
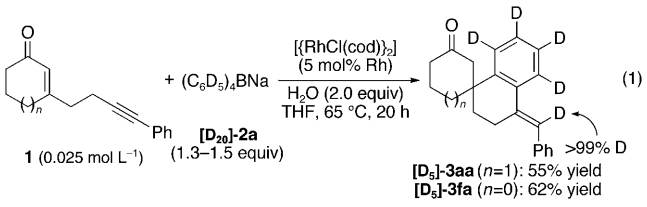
Table 2: Rhodium-catalyzed addition–cyclization of sodium tetraarylborates **2** to 3-(2-alkynylethyl)-2-cycloalken-1-ones **1**.



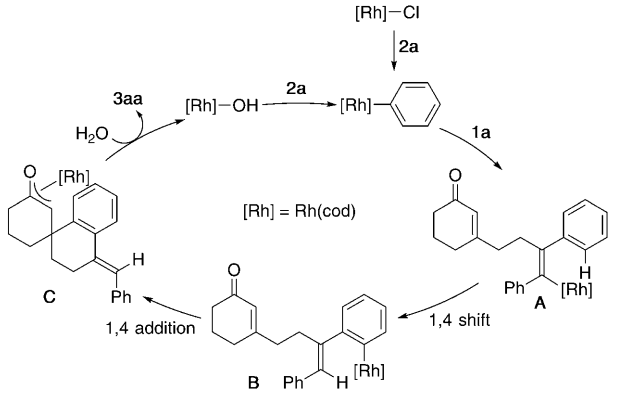
Entry	**1** (*n*; R)	**2** (X)	Product	Yield [%][a]
1	**1a** (1; Ph)	**2a** (H)	**3aa**	73
2	**1b** (1; 4-FC_6H_4)	**2a**	**3ba**	70
3	**1c** (1; 2-naphthyl)	**2a**	**3ca**	74
4	**1d** (1; 1-cyclohexenyl)	**2a**	**3da**	60
5	**1e** (1; $CH_2CMe_2(OMe)$)	**2a**	**3ea**	64
6	**1f** (0; Ph)	**2a**	**3fa**	77
7	**1f**	**2b** (4-Me)	**3fb**	69
8[b]	**1f**	**2c** (4-Cl)	**3fc**	77
9	**1f**	**2d** (4-F)	**3fd**	72
10	**1f**	**2e** (3-OMe)	**3fe**	64[c]
11	**1f**	**2f** (3-Me)	**3ff**	62[d]
12[e]	**1f**	**2g** (3-Cl)	**3fg**	70[f]
13	**1f**	**2h**[g]	**3fh**	68[h]

[a] Yield of isolated product. [b] 35 hours, 7 mol% of catalyst. [c] Regioselectivity 3-MeO/5-MeO = 11:1. [d] Regioselectivity: 3-Me/5-Me > 99:1. [e] 45 hours, 8 mol% of catalyst. [f] Regioselectivity: 3-Cl/5-Cl = 23:1. [g] **2h**: sodium tetrakis(3-thienyl)borate. [h] Regioselectivity: 2,3-fused/3,4-fused = 3:1.

showed quantitative deuteration at the olefin carbon, as shown in Equation (1).[12] On the basis of these results, we



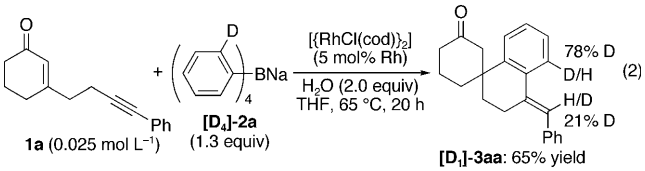
have proposed a catalytic cycle for the reaction between **1a** and **2a** (Scheme 2).[7,13] Thus, a phenylrhodium species, which is initially generated by the transmetalation of a phenyl group from **2a** onto the chlororhodium species, undergoes insertion



Scheme 2. Proposed catalytic cycle for the rhodium-catalyzed addition–cyclization of **2a** to **1a**.

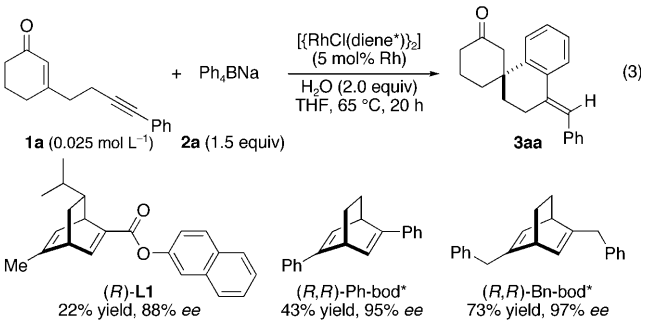
of the alkyne group of **1a** to give alkenylrhodium intermediate **A**.[14] Successive 1,4-rhodium migration gives arylrhodium species **B**, which then reacts with the tethered enone moiety, leading to oxa-π-allylrhodium intermediate **C**. Hydrolysis of this intermediate releases product **3aa** along with a hydroxorhodium complex, the transmetalation of which with **2a** regenerates the phenylrhodium species to complete the cycle.

We also conducted the reaction of **1a** with sodium tetrakis(2-deuteriophenyl)borate (**[D4]-2a**) and found that product **3aa** contained 21% deuteration at the olefin carbon atom and 78% deuterium remained at the aromatic carbon atom [Eq. (2)]. This result indicates that a primary kinetic



isotope effect ($k_H/k_D = 3.7$) is observed in the 1,4-rhodium migration step (**A**→**B**; Scheme 2), and that this step could be the turnover-limiting step of the catalytic cycle.

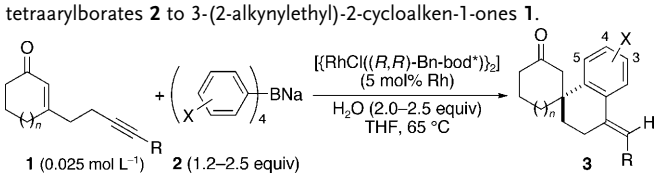
Because the step from **B** to **C** in Scheme 2 creates a quaternary carbon stereocenter,[15,16] and the present reaction is effectively catalyzed by a rhodium–diene complex, we began to explore the development of its asymmetric variant using chiral diene ligands.[17–19] As shown in Equation (3), the use of (*R*)-**L1**[15c,20] as the ligand in the reaction of **1a** with **2a**



gave product **3aa** in only 22% yield, although the enantioselectivity was relatively high (88% *ee*). By changing the ligand to (*R*,*R*)-Ph-bod*,[21] **3aa** was obtained in somewhat higher yield and *ee* value (43% yield, 95% *ee*), and further improvement was observed using (*R*,*R*)-Bn-bod*,[21] and gave **3aa** in 73% yield with 97% *ee*.

Under the conditions with (*R*,*R*)-Bn-bod* as the ligand, several 3-(2-alkynylethyl)-2-cycloalken-1-ones **1** efficiently reacted with sodium tetraphenylborate (**2a**) and gave the corresponding spirocycles **3** with excellent enantioselectivity (70–76% yield, 95–97% *ee*; Table 3, entries 1–4). As well as **2a**, some other aryl nucleophiles were also successfully employed, constructing quaternary spirocarbon stereocenters with high enantiomeric excess values (55–75% yield, 91–96% *ee*; Table 3, entries 5–8). The olefin portion of product

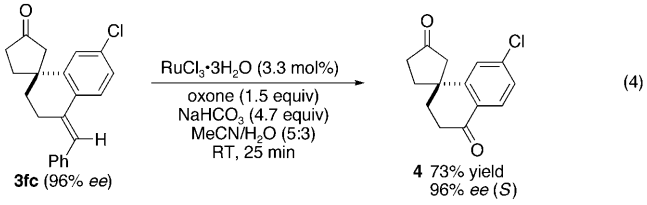
Table 3: Rhodium-catalyzed asymmetric addition–cyclization of sodium tetraarylborates **2** to 3-(2-alkynylethyl)-2-cycloalken-1-ones **1**.



Entry	1	2	t [h]	Product	Yield [%][a]	ee [%][b]
1	**1a**	**2a**	20	**3aa**	73	97
2	**1b**	**2a**	20	**3ba**	72	97
3	**1c**	**2a**	20	**3ca**	70	97
4	**1f**	**2a**	20	**3fa**	76	95
5	**1f**	**2b**	45	**3fb**	72	94
6	**1f**	**2c**	45	**3fc**	71	96
7	**1f**	**2d**	45	**3fd**	75	96
8	**1f**	**2f**	45	**3ff**	55[c]	91

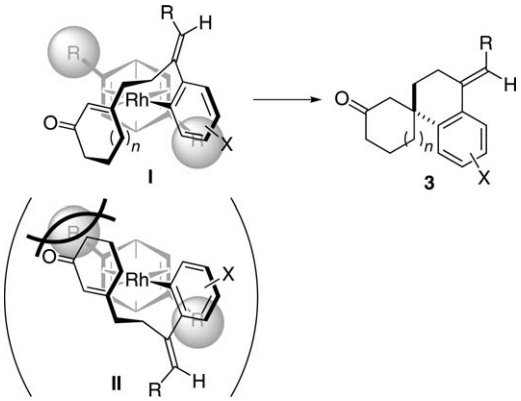
[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase with hexane/2-propanol. [c] Regioselectivity: 3-Me/5-Me > 99:1.

3fc readily underwent oxidative cleavage with oxone under ruthenium catalysis[22] and gave spirocyclic diketone **4** with retention of enantiomeric purity, as illustrated in Equation (4). The absolute configuration of diketone **4** was determined to be *S* by X-ray crystallographic analysis.[23]



(4)

On the basis of the absolute configuration of **4**, the stereochemical course of the present asymmetric catalysis with rhodium–(*R*,*R*)-Bn-bod* can be explained as shown in Scheme 3. Thus, during the step from **B** to **C** (Scheme 2) two possible intermediates, **I** and **II**, could undergo insertion of the enone; intermediate **I** is preferred to **II** as it would avoid the unfavorable steric interaction between the carbonyl moiety of the enone and the benzyl group on the olefin of (*R*,*R*)-Bn-bod*; this mechanism would lead to the selective formation of spirocycle **3** with the observed absolute configuration.



Scheme 3. Proposed stereochemical pathway for the formation of spirocycle **3**, catalyzed by Rh/(*R*,*R*)-Bn-bod*.

In summary, we have developed the addition of sodium tetraarylborates to alkyne-tethered 2-cycloalken-1-ones, catalyzed by a rhodium–diene complex, for the convergent synthesis of spirocarbocycles. These tetraarylborates function as surrogates of 1,2-dimetalloarenes, sequentially forming two new carbon–carbon bonds through the catalytic process. We have also developed an effective asymmetric variant of the present catalysis by employing a chiral diene ligand to create quaternary spirocarbon stereocenters with high enantiomeric purity.

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[11] The use of alkene-tethered enone 3-(4-phenyl-3-buten-1-yl)-2-cyclohexen-1-one as a substrate results in a messy reaction with approximately 40% recovery of the substrate.

[12] $k_H/k_D = 1.04$ was observed when the reaction of **1a** was conducted with an equimolar mixture of **2a** and **[D$_{20}$]-2a**.

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[23] CCDC 764834 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

