Rhodium-catalysed cyclisation reaction of allenynes with arylboronic acids†

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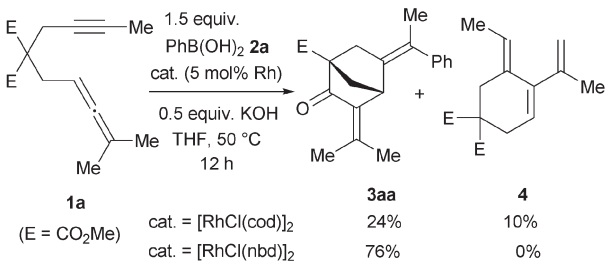
Allenynes having malonate-based tethers reacted with arylboronic acids in the presence of a rhodium(I) catalyst to sequentially form three carbon–carbon bonds, and arylated bicyclic skeletons were constructed in a stereoselective manner.

Recently, the rhodium-catalysed cyclisation reaction with organoboron reagents has been demonstrated to be a powerful method for the synthesis of carbocyclic compounds.[1] An organorhodium(I) species, generated through transmetalation between rhodium(I) and boron, can undergo multiple carborhodation steps onto acceptor compounds bearing two and more functional groups to form cyclic skeletons.[2] An alkyne moiety provides an expedient entry point for incorporation of an organorhodium(I) species in the molecule, which then adds intramolecularly to another functional group.[3] We have previously described the rhodium-catalysed cyclisation reaction of 1,6-enynes with arylboronic acids to form arylated bicyclic compounds with a stereodefined exocyclic double bond.[4]

Allenyl compounds present a versatile platform for synthetic manipulations due to their unique structure and high reactivity.[5] In pursuit of a new reaction involving multiple carborhodation steps, we became interested in affecting an arylative cyclisation reaction using allenynes,[6] which have been employed in other types of cyclisation reactions.[7] In this paper is described a new cyclisation reaction of allenynes with arylboronic acids.

When allenyne (**1a**, 1.0 equiv.) was treated with phenylboronic acid (**2a**, 1.5 equiv.) in the presence of $[RhCl(cod)]_2$ (5 mol% Rh, cod = cycloocta-1,5-diene) and KOH (0.5 equiv.) in THF at 50 °C for 12 h, bicyclo[2.2.1]heptan-2-one **3aa** was obtained in 24% yield together with the starting material **1a** (28%) and the cycloisomerisation product **4** (10%)[8] (Scheme 1). The (*Z*)-configuration of the exocyclic double bond of **3aa** was determined by an NOE study. Remarkably, the use of $[RhCl(nbd)]_2$ (5 mol% Rh, nbd = norborna-2,5-diene) as the catalyst suppressed the formation of **4** and the yield of **3aa** increased to 76%.

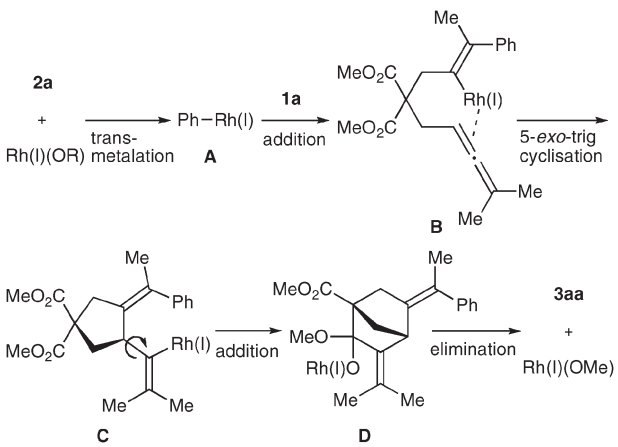
We speculate the possible reaction pathway as depicted in Scheme 2 for the production of **3aa** starting from **1a** and **2a**, although we have no experimental evidence for the intermediate species. Initially, phenylrhodium(I) species **A** is generated by the transmetalation between rhodium(I) and **2a**.[9] Then,



Scheme 1 Reaction of allenyne **1a** with phenylboronic acid (**2a**).

regioselective 1,2-addition of **A** across the carbon–carbon triple bond of **1a** occurs to form the alkenylrhodium(I) intermediate **B**.[10] From here, **B** undergoes intramolecular carborhodation onto the allene moiety in a 5-*exo* mode to give (cyclopentylvinyl)rhodium(I) intermediate **C**. Finally, intramolecular acylation of **C** with the methoxycarbonyl group on the tether *via* addition–elimination affords **3aa** regenerating the catalytically active (methoxo)rhodium(I) species.

The results obtained with various combinations of allenynes **1** and arylboronic acids **2** are summarised in Table 1.‡ Both electron-donating and -withdrawing arylboronic acids **2b–2f** were suitably reactive (Entries 1–5). Even sterically hindered *o*-tolylboronic acid (**2g**) participated in the cyclisation reaction with **1a** (Entry 6). The reaction of allenynes **1b–1d** having primary and secondary alkyl groups at the alkyne termini afforded the corresponding products **3ba–3da** in yields ranging from 61% to 93% (Entries 8–10). Allenynes **1e** and **1f** having a di-substituted allene terminus were also converted to the corresponding products **3ea** and **3fa**, albeit in lower yields than that of **1a** (Entries 11 and 12). On the other hand, the



Scheme 2 A plausible mechanism for the catalysed cyclisation reaction.

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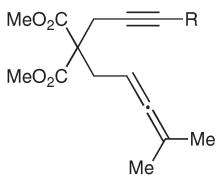
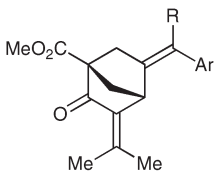
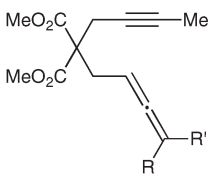
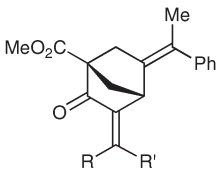
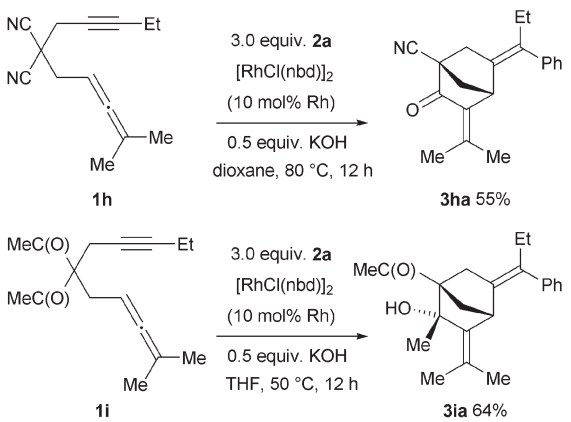
Table 1 Rh(I)-catalysed cyclisation reaction of **1** with **2**[a]

Entry	Substrate	$ArB(OH)_2$	Product	Yield (%)[b]
				
1	**1a** R = Me	**2b** 4-Br-C_6H_4	**3ab**	70
2	**1a** R = Me	**2c** 3-Br-C_6H_4	**3ac**	62
3	**1a** R = Me	**2d** 3-Cl-C_6H_4	**3ad**	65
4	**1a** R = Me	**2e** 3-MeO-C_6H_4	**3ae**	73
5	**1a** R = Me	**2f** 3-MeO_2C-C_6H_4	**3af**	61
6	**1a** R = Me	**2g** 2-Me-C_6H_4	**3ag**	61
7	**1a** R = Me	**2h** 3-Thienyl	**3ah**	46
8	**1b** R = Et	**2a** Ph	**3ba**	87
9	**1c** R = CH_2OMe	**2a** Ph	**3ca**	61
10	**1d** R = *i*-Pr	**2a** Ph	**3da**	93[c]
				
11	**1e** R,R′ = -$(CH_2)_5$-	**2a** Ph	**3ea**	71
12	**1f** R,R′ = Me, Ph	**2a** Ph	**3fa**	36
13	**1g** R,R′ = Me, H	**2a** Ph	**3ga**	—

[a] Conditions: **1** (0.1 mmol), **2** (0.15 mmol), $[RhCl(nbd)]_2$ (2.5 μmol, 5 mol%), KOH (50 μmol) in THF (1.5 mL) at 50 °C for 12 h under Ar. [b] Isolated yield unless otherwise noted. [c] ^1H NMR yield using $CHBr_2CHBr_2$ as an internal standard.

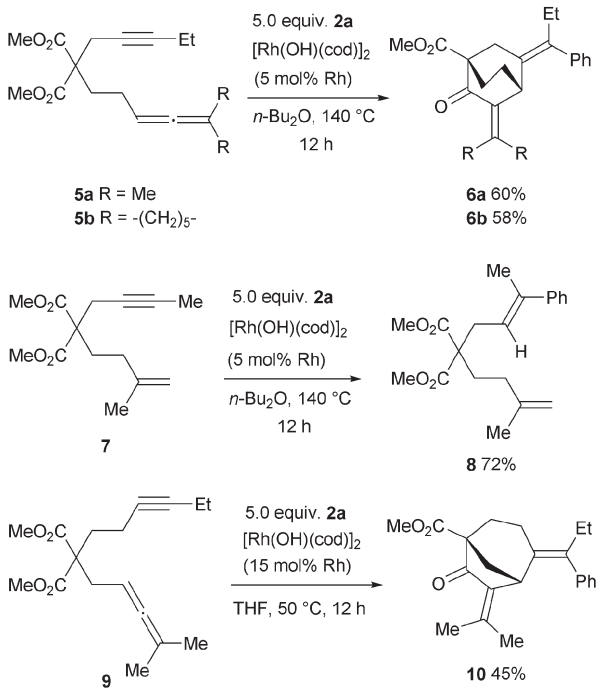
allenyne **1g** with a mono-substituted allene terminus gave a complex mixture, and none of the desired product **3ga** was obtained (Entry 13).

Interestingly, allenynes **1h** and **1i** possessing malononitrile and acetylacetone tethers underwent an analogous cyclisation reaction to afford the bicyclic products **3ha** and **3ia** through intramolecular addition onto the cyano and ketocarbonyl groups [eqn (1)].



(1)

Next, we examined the possibility of a cyclisation reaction in a 6-*exo* mode using allenynes equipped with a tether longer by one carbon (Scheme 3). The allenynes **5a** and **5b** were found to



Scheme 3 Reaction of substrates having a four-carbon tether with **2a**.

be considerably less reactive than **1a**. When **5a** and **5b** were treated with **2a** (5.0 equiv.) in the presence of $[Rh(OH)(cod)]_2$ (5 mol% Rh) under more forcing conditions, intramolecular carborhodation onto the allene moiety occurred in a 6-*exo* mode, and bicyclo[2.2.2]octan-2-ones **6a** and **6b** were obtained in 60% and 58% yields, respectively. In contrast, 1,7-enyne **7** failed to cyclise in a 6-*exo* mode, instead afforded the 1,2-adduct **8** by protonolysis as the major product (72%). Thus, the allenyl groups of **5a** and **5b** were more reactive than the isopropenyl group of **7**. In the reaction of allenyne **9** having a four-carbon tether, bicyclo[3.2.1]octan-6-one **10** was produced in 45% yield.

In summary, we have developed a new rhodium-catalysed cyclisation reaction of allenynes with arylboronic acids, which provides a unique access to bicyclic compounds that were otherwise difficult to form. The reaction also demonstrates that the allene moiety serves as the acceptor of the *in situ* generated organorhodium(I) species in a cascade reaction.[11]

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Notes and references

‡ General procedure: To an oven-dried flask was added $[RhCl(nbd)]_2$ (1.3 mg, 2.7 μmol, 5 mol% Rh), KOH (3.0 mg, 53 μmol), organoboronic acid **2** (0.15 mmol, 1.5 equiv.) and a solution of allenyne **1** (0.10 mmol, 1.0 equiv.) in dry THF (1.5 mL). The reaction mixture was stirred at 50 °C for 12 h under an argon atmosphere, and then quenched with addition of water (2.0 mL). The resulting aqueous solution was extracted with ethyl acetate (4 × 10 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by

preparative thin-layer chromatography (hexane–ethyl acetate = 10 : 1 or 5 : 1) to give the corresponding bicyclic compounds **3**.

1 For a review, T. Miura and M. Murakami, *Chem. Commun*., 2007, 217.

2 For representative examples, see: (*a*) M. Lautens and J. Mancuso, *Org. Lett*., 2002, **4**, 2105; (*b*) D. F. Cauble, J. D. Gipson and M. J. Krische, *J. Am. Chem. Soc*., 2003, **125**, 1110; (*c*) M. Lautens and J. Mancuso, *J. Org. Chem*., 2004, **69**, 3478; (*d*) N.-W. Tseng, J. Mancuso and M. Lautens, *J. Am. Chem. Soc*., 2006, **128**, 5338; (*e*) T. Miura, T. Harumashi and M. Murakami, *Org. Lett*., 2007, **9**, 741.

3 For representative examples, see: [aldehyde] (*a*) R. Shintani, K. Okamoto, Y. Otomaru, K. Ueyama and T. Hayashi, *J. Am. Chem. Soc*., 2005, **127**, 54; [ketone] (*b*) T. Miura, M. Shimada and M. Murakami, *Tetrahedron*, 2007, **63**, 6131; [nitrile] (*c*) T. Miura, H. Nakazawa and M. Murakami, *Chem. Commun*., 2005, 2855; [isocyanate] (*d*) T. Miura, Y. Takahashi and M. Murakami, *Org. Lett*., 2007, **9**, 5075; [electron-deficient alkene] (*e*) M. Lautens and T. Marquardt, *J. Org. Chem*., 2004, **69**, 4607; (*f*) Y. Chen and C. Lee, *J. Am. Chem. Soc*., 2006, **128**, 15598; [alkene] (*g*) M. Shimada, T. Harumashi, T. Miura and M. Murakami, *Chem.–Asian J*., 2008, **3**, 1035; [alkyne] (*h*) T. Miura, M. Yamauchi and M. Murakami, *Synlett*, 2007, 2029; [halide] (*i*) Y. Harada, J. Nakanishi, H. Fujihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc*., 2007, **129**, 5766.

4 T. Miura, T. Sasaki, H. Nakazawa and M. Murakami, *J. Am. Chem. Soc*., 2005, **127**, 1390.

5 *Modern Allene Chemistry*, ed. N. Krause and A. S. K. Hashmi, Wiley-VCH, Weinheim, 2004.

6 For the palladium-catalysed reaction, see: A. K. Gupta, C. Y. Rhim and C. H. Oh, *Tetrahedron Lett*., 2005, **46**, 2247.

7 For recent examples, see: (*a*) C. V. Bray, S. Dérien, P. H. Dixneuf and M. Murakami, *Synlett*, 2008, 193; (*b*) O. Buisine, V. Gandon, L. Fensterbank, C. Aubert and M. Malacria, *Synlett*, 2008, 751; (*c*) K. M. Brummond, D. Chen, T. O. Painter, S. Mao and D. D. Seifried, *Synlett*, 2008, 759; (*d*) C. H. Oh and A. Kim, *Synlett*, 2008, 777; (*e*) T. Hirose, N. Miyakoshi and C. Mukai, *J. Org. Chem*., 2008, **73**, 1061; (*f*) P. H. Cheong, P. Morganelli, M. R. Luzung, K. N. Houk and F. D. Toste, *J. Am. Chem. Soc*., 2008, **130**, 4517. See references therein for other examples.

8 For previous reports on cycloisomerisation forming **4**, see: (*a*) K. M. Brummond, H. Chen, P. Sill and L. You, *J. Am. Chem. Soc*., 2002, **124**, 15186; (*b*) T. Shibata, Y. Takesue, S. Kadowaki and K. Takagi, *Synlett*, 2003, 268.

9 P. Zhao, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc*., 2007, **129**, 1876.

10 (*a*) T. Hayashi, K. Inoue, N. Taniguchi and M. Ogasawara, *J. Am. Chem. Soc*., 2001, **123**, 9918; (*b*) M. Lautens and M. Yoshida, *Org. Lett*., 2002, **4**, 123; (*c*) M. Murakami and H. Igawa, *Helv. Chim. Acta*, 2002, **85**, 4182; (*d*) E. Genin, V. Michelet and J.-P. Genêt, *J. Organomet. Chem*., 2004, **689**, 3820.

11 For intermolecular addition of organorhodium(I) species to allenes, see: T. Nishimura, S. Hirabayashi, Y. Yasuhara and T. Hayashi, *J. Am. Chem. Soc*., 2006, **128**, 2556.