ORGANIC LETTERS

2013
Vol. 15, No. 5
1148–1151

Enantioselective Rh-Catalyzed Domino Transformations of Alkynylcyclohexadienones with Organoboron Reagents

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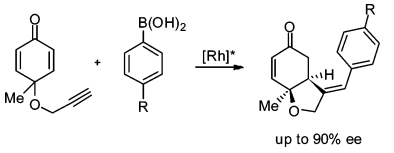
Received February 6, 2013

ABSTRACT



A new enantioselective rhodium-catalyzed domino reaction is described that gives access to fused heterocycles by desymmetrization of alkyne-tethered cyclohexadienones. Two new C−C bonds and two stereocenters are formed in one step with good enantioselectivity. In contrast to prior reports, it was found that a vinylidene is not involved in the product formation but that *syn*-addition of the rhodium-aryl species onto the alkyne takes place.

The formation of multiple C−C bonds in transition-metal-catalyzed domino reactions is an attractive means to construct complex structures starting from relatively simple starting materials.[1] In the past decade, the addition of arylboronic acids to unsaturated organic functional groups has proven to be a useful synthetic tool for C−C bond formation.[2] In particular, the addition of Rh(I)−aryl complexes to alkynes, also referred to as hydroarylation, has found widespread application.[3]

Rh-catalyzed hydroarylation proceeds via transmetalation of the catalyst with the boronic acid. Subsequent *syn*-addition onto an alkyne results in 1,2-carborhodation and can occur in two orientations with rhodium ending up on either C-atom of the triple bond (Scheme 1). Depending on the respective flanking groups, moderate to excellent regioselectivities can be obtained with internal alkynes. Hayashi and our group were early contributors,[3a,4] and since then hydroarylations have been investigated extensively. For terminal alkynes another catalytic pathway has been proposed.[5] Formal 1,1-carborhodation via formation of an intermediate vinylidene and subsequent α-migration would give the 1,1-addition product.[6]

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Negishi, E.-i.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393. (c) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908. (d) Boyer, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7346–7349. (e) Liu, H.; El-Salfiti, M.; Chai, D. I.; Auffret, J.; Lautens, M. *Org. Lett.* **2012**, *14*, 3648–3651.

(2) (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (c) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093–2105.

(3) (a) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918–9919. (b) Arcadi, A.; Aschi, M.; Chiarini, M.; Ferrara, G.; Marinelli, F. *Adv. Synth. Catal.* **2010**, *352*, 493–498. (c) Tsui, G. C.; Lautens, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8938–8941. (d) Panteleev, J.; Zhang, L.; Lautens, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9089–9092.

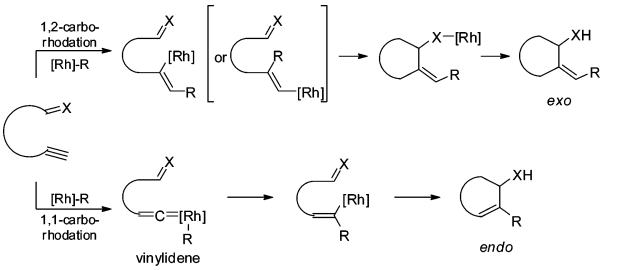
(4) (a) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123–125. (b) Lautens, M.; Yoshida, M. *J. Org. Chem.* **2003**, *68*, 762–769.

(5) Chen, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 15598–15599.

(6) Prior to their work, rhodium vinylidene intermediates were only observed in stoichiometric systems by using Rh(I)−phosphine complexes: (a) Wolf, J.; Werner, H.; Serhadli, O.; Ziegler, M. L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 414–416. (b) Wiedemann, R.; Steinert, P.; Schäfer, M.; Werner, H. *J. Am. Chem. Soc.* **1993**, *115*, 9864–9865. But several examples in catalytic processes have been published, proposing vinylidene intermediates when using phosphine ligands on rhodium: (c) Kim, H.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 6336–6337. (d) Fukumoto, Y.; Asai, H.; Shimizu, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 13792–13793. (e) Fukumoto, Y.; Kawahara, T.; Kanazawa, Y.; Chatani, N. *Adv. Synth. Catal.* **2009**, *351*, 2315–2318. (f) Mizuno, A.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 8318–8320. (g) Joo, J. M.; Yuan, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 14818–14819. (h) Joo, J. M.; David, R. A.; Yuan, Y.; Lee, C. *Org. Lett.* **2010**, *12*, 5704–5707. Additionally, Rh(cod)−vinylidene complexes have been suggested as intermediates: (i) Moran, G.; Green, M.; Orpen, A. G. *J. Organomet. Chem.* **1983**, *250*, C15–C20. (j) Komatsu, H.; Suzuki, Y.; Yamazaki, H. *Chem. Lett.* **2001**, 998–999.

10.1021/ol400363f
Published on Web 02/20/2013

Scheme 1. Carborhodation Pathways and Products Resulting from Subsequent Intramolecular Cyclization[5]

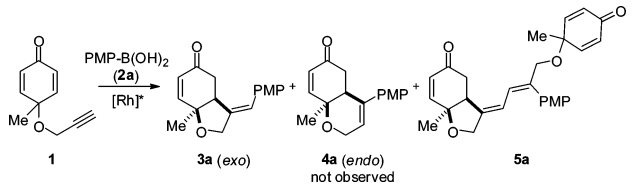


After addition of Rh(I)-aryl to the alkyne, the resulting Rh(I) species can undergo cyclization onto an internal functional group in a domino fashion.[2c,7] In the case of 1,2-carbometalation, the emerging ring bears an *endo*-cyclic double bond, while after 1,1-carbometalation an *exo*-cyclic double bond is formed (Scheme 1).

With cyclohexadienone as an internal functional group, a desymmetrization of this structural motif can be achieved. Since cyclohexadienones can be easily derived from phenols, it only takes a few steps to generate complexity from simple and commercially available starting materials.[8,9]

We now report the domino transformation of boronic acids with a cyclohexadienone-tethered alkyne **1** which can be easily obtained from *p*-cresol and propargyl alcohol in moderate yields. This scaffold has been used before in desymmetrization reactions,[9] and applying it to the desired reaction allows for the formation of a fused heterocycle, two C−C bonds, and two stereocenters. Application of reaction conditions similar to those reported by Lee et al. ($[Rh(cod)Cl]_2$, 1.1 equiv of *p*-methoxy phenylboronic acid (**2a**), 1.5 equiv of Et_3N, MeOH) led to the formation of product **3a** in 46% yield (Scheme 2). In addition, 37% of a side product **5a** was isolated. 2D-NMR, MS, and also deuterium labeling did not help to clarify the structure of the isolated product **3a**, but finally, we were able to obtain

Scheme 2. Domino Reactions of Alkyne **1** with Boronic Acid **2a** (PMP = *p*-methoxy phenyl)

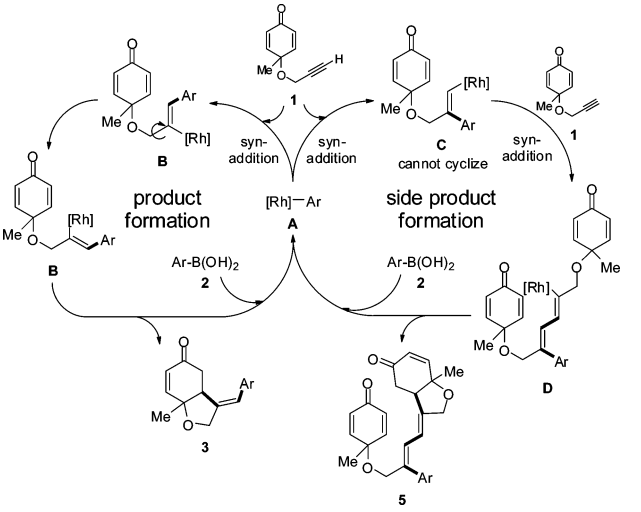


(7) (a) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482–7483. (b) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217–224.

(8) (a) Studer, A.; Schleth, F. *Synlett* **2005**, *20*, 3033–3041. (b) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552–2553. (c) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056–4057. (d) Takizawa, S.; Nguyen, T. M.-N.; Grossmann, A.; Enders, D.; Sasai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5423–5426.

(9) Tello-Aburto, R.; Harned, A. M. *Org. Lett.* **2009**, *11*, 3998–4000.

Scheme 3. Proposed Catalytic Cycle



the X-ray structure of the 4-Br-derivative **3b**, which proved the formation of a five-membered ring (Figure 1). The ^1H NMR spectrum of **5a** showed that it contains not only 1 equiv of the boronic acid **2a** but also 2 equiv of the starting alkyne **1** with one of the cyclohexadienone systems intact.

The formation of both **3a** and **5a** can be explained by *syn*-addition of the [Rh]−aryl complex **A** onto the alkyne **1** (Scheme 3). When the aryl group adds to the terminal carbon of the starting alkyne **1** [Rh]-complex, **B** is generated. Upon cyclization, **B** forms **3** with a five-membered ring and an *exo*-cyclic double bond (see product formation).

Addition of the aryl group to the internal carbon of the starting alkyne **1** leads to [Rh]-complex **C**, which cannot cyclize onto the cyclohexadienone moiety and instead reacts with another alkyne **1**. *syn*-Addition of the [Rh] complex **C** takes place with opposite regioselectivity, and the alkyl residue ends up at the terminal carbon. The resulting rhodium-complex **D** can undergo cyclization onto the cyclohexadienone moiety, which yields the side product **5** and reforms the catalyst **A**.

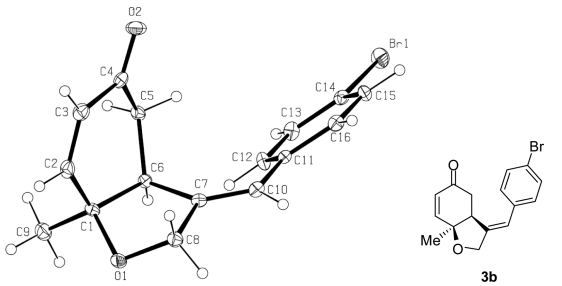
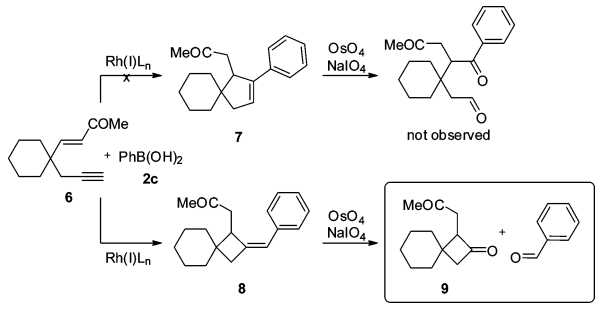


Figure 1. Crystal structure of **3b**.

Due to the similarity between Lee's and our work, the question arises which mechanism is operative with their

substrate. The absence of a vinylidene intermediate under similar conditions has already been observed and reported by other groups,[10] who also exclusively obtained *exo*-cyclic double bonds. We therefore repeated the cyclization reaction with compound **6** as reported by Lee et al (Scheme 4).

Scheme 4. Domino Reaction of **6**[5] and Oxidative Cleavage



Since standard analytical techniques (e.g., 2D-NMR) cannot explicitly rule out either of the possible products **7** or **8**, an oxidative cleavage was performed. Instead of a single product containing an aldehyde and ketone, we isolated two products, one of which was benzaldehyde and the other had an IR-stretch at 1767 cm^{-1} and a ^{13}C NMR signal at 209.2 ppm which indicate the formation of cyclobutanone **9**, whose molecular mass was also confirmed by MS. These results support that, instead of vinylidene formation, a *syn*-addition forms the interesting and unexpected strained four-membered ring **8** with an *exo*-cyclic double bond.[11]

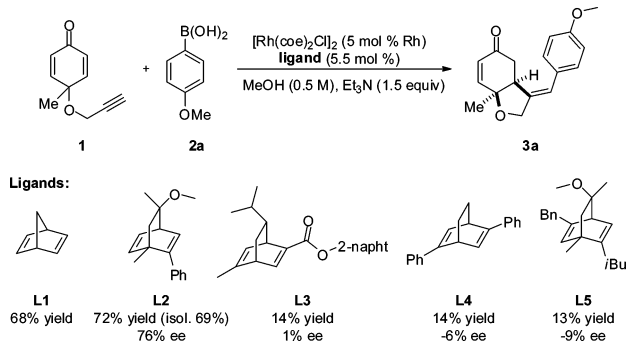


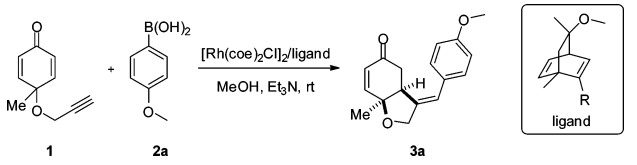
Figure 2. Ligand optimization.

In order to achieve an enantioselective variant, a catalyst optimization with different precursors and ligands was performed.[12] It was found that the amount of side product strongly depends on the ligand with $[Rh(cod)Cl]_2$, giving 37% of **5a** along with 46% of **3a**. The precursor $[Rh(coe)_2Cl]_2$ did not catalyze the reaction well on its own, but when norbornadiene (**L1**) was added, 68% of **3a** and 28% **5a** were observed in the crude ^1H NMR.

Chiral and achiral phosphine ligands were found to be inefficient and mainly led to decomposition of the starting material, which is in agreement with previous findings.[5,13] We next tested several chiral diene ligands (see Figure 2). Using **L2** gave 19% of **5a** and predominantly the desired product **3a** in 72% yield with 76% ee. Other types of chiral diene ligands **L3**–**L5** in combination with $[Rh(coe)_2Cl]_2$ were not efficient in catalyzing the title reaction, requiring significantly longer reaction times and giving low to no ee. The absolute stereochemistry of the products was determined by an X-ray structure of the 4-Br-derivative **3b** (Figure 1).

A thorough optimization of the conditions with regard to the amount of catalyst, ligand, base, solvent, and boronic acid as well as the temperature and the kind of base and solvent was undertaken, but did not lead to an improvement in yield or ee.[12] Instead, modification of the phenyl substituent on the diene ligand proved to have a significant effect on the ee, and a number of different diene ligands was synthesized[12] and tested (Table 1).

Table 1. Ligand Screening[a]



entry	R =	yield [%][b]	ee [%][c]
1	C_6H_5 (**L2**)	72	76
2	2-Me-C_6H_4 (**L6**)	13	22
3	4-Me-C_6H_4 (**L7**)	72	75
4	3-MeO-C_6H_4 (**L8**)	67	79
5	4-MeO-C_6H_4 (**L9**)	75	76
6	3,4-di-MeO-C_6H_3 (**L10**)	76	84
7	3,4,5-tri-MeO-C_6H_2 (**L11**)	66	83
8	4-NO_2-C_6H_4 (**L12**)	60	55
9	4-CF_3-C_6H_4 (**L13**)	62	64
10	2-CF_3-C_6H_4 (**L14**)	15	10
11	4–F-C_6H_4 (**L15**)	67	75
12	1-naphthyl (**L16**)	20	30
13	2-naphthyl (**L17**)	75	75

[a] Reaction conditions: see Table 1. [b] Yields determined by ^1H NMR of the crude mixture. [c] The ee was determined by chiral HPLC.

Substitution of the phenyl group in the 2-position (entries 2, 10, and 12) leads to a decrease of activity and selectivity. This result and the fact that diene ligands with more than one substituent on the alkenes gave poor results (see Figure 2) are interesting because, in contrast to previous findings, increasing the steric bulk of the ligand is highly detrimental to the enantioselectivity.[14,15] Electron-donating

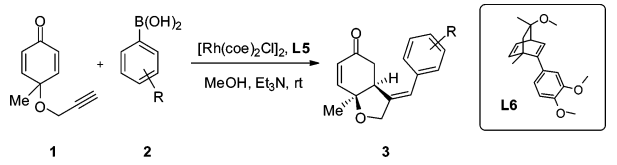
(10) (a) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2007**, *9*, 5075–5077. (b) Artok, L.; Kuş, M.; Urer, B. N.; Türkmen, G.; Aksin-Artok, Ö. *Org. Biomol. Chem.* **2010**, *2010*, 2060–2067.

(11) Chen, Y.; Lee, C. *J. Am. Chem. Soc.* **2012**, *134*, 20564–20564.

(12) For a more detailed discussion, see Supporting Information.

(13) Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3909–3912.

Table 2. Boronic Acid Scope[a]



entry	boronic acid R=	product	yield [%][b]	ee [%][c]
1	H (**2c**)	**3c**	69	85
2	2-MeO (**2d**)	**3d**	67	88
3	4-MeO (**2a**)	**3a**	67	84
4	2,6-di-MeO (**2e**)[d]	**3e**	67	88
5	4-Me (**2f**)	**3f**	71	88
6	2-Br (**2g**)	**3g**	58	82
7	4-Br (**2b**)	**3b**	62	64
8	2-Cl (**2h**)[e]	**3h**	58	82
9	4-Cl (**2i**)	**3i**	74	71
10	4-CF_3 (**2j**)	**3j**	52	62
11	4-CO_2Me (**2k**)	**3k**	62	79
12	4-CN (**2l**)[f]	**3l**	49	66
13	4-OH (**2m**)	**3m**	59	86
14	4-CHO (**2n**)	**3n**	71	78

[a] Reaction conditions: $[Rh(coe)_2Cl]_2$ (5 mol % Rh), **L5** (5.5 mol %), alkyne **1** (1 equiv), arylboronic acid **2** (1.1 equiv), Et_3N (1.5 equiv), methanol (0.5 M), rt, 30–120 min. [b] Isolated yields. [c] The ee was determined by chiral HPLC. [d] Time: 180 min. [e] Time: 240 min. [f] Time: 7 h.

groups in the 3- or 4-position were found to improve the performance, and the best ligand for the title reaction is the 3,4-dimethoxy-phenyl derivative **L10**, which gives a 76% NMR-yield of **3a** in 84% ee. In all cases the amount of side product is in the range of 10–15%. With the optimized reaction conditions in hand, the reaction scope with regard to the substitution pattern on the boronic acids was investigated using the 3,4-dimethoxy-substituted ligand **L6** (Table 2).

The reaction shows a high functional group tolerance, and electron-neutral or -rich boronic acids work well, while electron-poor boronic acids give slightly lower yields. Electron-rich (cf. entries 3 and 7, Table 2) and sterically hindered boronic acids (entries 6 and 7) result in higher ee-values than electron-poor and sterically less demanding boronic acids. With 1-naphthylboronic acid **2o** the corresponding product **3o** is obtained with only a 36% yield but a 90% ee, while the sterically less demanding 2-naphthyl-substituted cyclization product **3p** is obtained in 71% yield and 84% ee (Figure 3). Heteroaromatic boronic acids such as 3-furylboronic acid (**2q**), 3-thiopheneboronic acid (**2r**), or the benzofused derivatives **2s** and **2t** yield the corresponding products in moderate yields and high ee's (Figure 3, **3o**–**3t**). Under the standard reaction conditions, 3- and 4-pyridylboronic acids and alkylboronic acids did not react.

Lastly, the cyclohexadienone was modified near the alkyne. Preliminary experiments showed that the 3-methoxyphenyl-

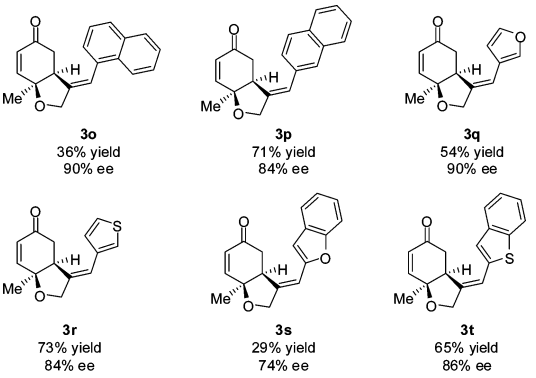


Figure 3. Boronic acid scope.

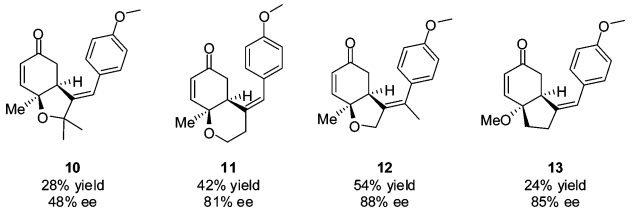


Figure 4. Alkyne scope.

substituted ligand **L8** worked best.[12] The products **10**–**13** were obtained in moderate yields and with moderate to good ee's (Figure 4).

In conclusion, we developed a new enantioselective Rh-catalyzed domino reaction that gives access to fused heterocycles by desymmetrization of alkyne-tethered cyclohexadienones. In this process two new C–C bonds and two new stereocenters are formed with good enantioselectivities. We have evidence that an alkylidene is not involved in the product formation but that the rhodium-aryl species reacts via a *syn*-addition with the alkyne.

Acknowledgment. We thank Merck, the Natural Science and Engineering Research Council (NSERC) for an Industrial Research Chair, and the University of Toronto for financial support. We also thank Dr. Alan Lough (X-ray analysis), Dr. Darcy Burns (2D NMR-analyses), and Dr. Harald Weinstabl from the University of Toronto for fruitful discussions. J.K. thanks the Deutsche Forschungsgemeinschaft (DFG) for a postdoctoral fellowship. S.G.N. thanks NSERC for a postgraduate scholarship.

Supporting Information Available. Experimental procedures, spectroscopic and analytical data for starting materials and products, copies of NMR spectra, and X-ray data for compound **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(14) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669–7672.

(15) Darses and Fillion found that the presence of *ortho*-substituents on the aryl ring of the diene ligand is essential to obtain high enantioselectivities in Rh-catalyzed 1,4-addition reactions: Reference 14; Mahoney, S. J.; Dumas, A. M.; Fillion, E. *Org. Lett.* **2009**, *11*, 5346–5349.