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Cyclization Reaction of Cyano-Substituted Unsaturated Esters Prompted by Conjugate Addition of Organoborons

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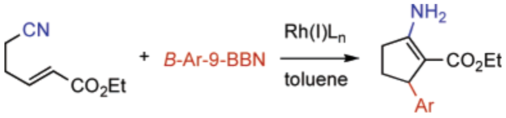
ABSTRACT



Unsaturated esters possessing a pendent cyano moiety react with *B*-Ar-9-BBNs in the presence of a rhodium(I) catalyst to give the five- and six-membered *β*-enamino esters in good yield. An (oxa-*π*-allyl)rhodium(I) intermediate, formed by initial conjugate addition of an Ar-rhodium(I) species, undergoes a facile intramolecular addition to the cyano group to construct the carbocyclic skeletons.

Cascade-type reactions, in which carbocyclic rings are constructed through multiple carbometalation steps, provide powerful methods for the synthesis of structurally complex molecules in an efficient and atom-economical manner.[1] Molecules that possess two different unsaturated functionalities onto which organometallic species can add are particularly attractive substrates for cascade reactions. The more reactive functionality provides the entry point for incorporation of a reactive carbon−metal linkage by way of initial intermolecular carbometalation. This triggers the second carbometalation onto the less reactive functionality in an intramolecular way to construct a carbocyclic skeleton. For example, Krische and co-workers developed a copper-catalyzed cyclization reaction of cyano-substituted unsaturated ketones with organozinc reagents, in which an intermediate zinc enolate added to a cyano group intramolecularly.[2,3] We have recently developed a rhodium-catalyzed cyclization reaction of cyano-substituted alkynes with arylboronic acids.[4] The initial intermolecular carborhodation onto the alkyne moiety gives rise to a reactive alkenylrhodium(I) intermediate, which then adds to the cyano moiety in a 5-exo mode. Thus, cyano groups can act as a secondary electrophile that accepts the alkenylrhodium(I) intermediate in an intramolecular way, even though they are much less reactive in intermolecular cases.[5] We then examined the use of an unsaturated ester functionality as the entry point to see if a resulting (oxa-π-allyl)rhodium(I) intermediate could be trapped by a cyano group placed at an appropriate position in the molecule.[6] We describe herein the rhodium-catalyzed cyclization reaction of cyano-substituted unsaturated esters prompted by the conjugate addition of arylboron reagents. Notably, this reaction enables, in a single manipulation, the

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[1] Reviews: (a) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (b) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65. (c) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217.

[2] Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528.

[3] For the addition of Zn enolates to nitliles, see: Blaise, E. E. *C. R. Hebd. Seances Acad. Sci.* **1901**, *132*, 478.

[4] (a) Miura, T.; Nakazawa, H.; Murakami, M. *Chem. Commun.* **2005**, 2855. (b) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339.

[5] (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. (b) Ueura, K.; Miyamura, S.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2006**, *691*, 2821.

[6] For Rh-catalyzed conjugate addition/electrophilic trapping reaction, see: (a) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331. (b) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (c) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984. (d) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110. (e) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421. (f) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874.

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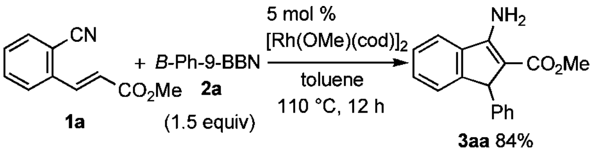
synthesis of five- and six-membered β-enamino esters, which are valuable and versatile building blocks in organic synthesis.[7]

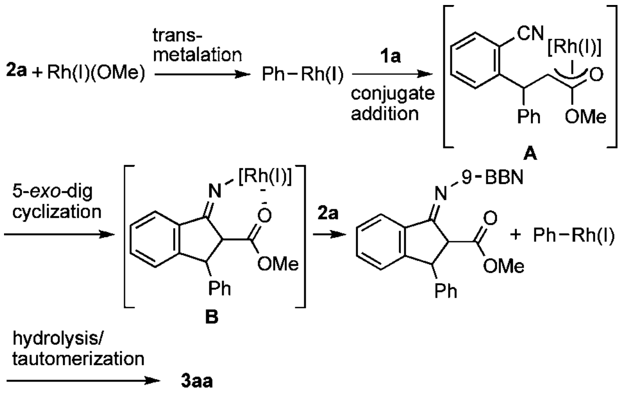
Cyano-substituted unsaturated ester **1a** was treated with phenylboronic acid (3.0 equiv) in the presence of $[Rh(OH)(cod)]_2$ (5 mol % of Rh) in dioxane at 100 °C for 3 h. The five-membered β-enamino ester **3aa** was obtained in 72% yield together with the noncyclized 1,4-adduct (10%), which results from protonation of the intermediate (oxa-π-allyl)rhodium(I) (**A** in Scheme 1). Thus, when *B*-Ph-9-BBN (**2a**, 1.5 equiv, *B*-Ph-9-BBN = 9-phenyl-9-borabicyclo[3.3.1]nonane)[8] and $[Rh(OMe)(cod)]_2$ (10 mol % of Rh) were used in toluene,[6c] the formation of the noncyclized 1,4-adduct was suppressed and the yield of **3aa** increased to 84% (eq 1).



(1)

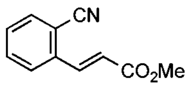
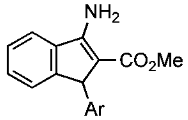
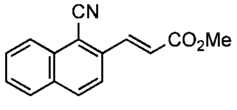
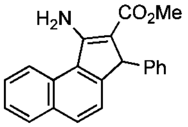
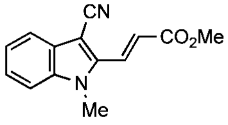
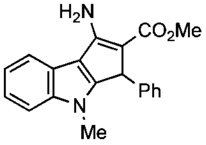
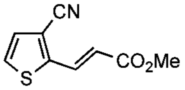
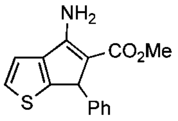
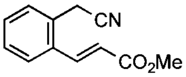
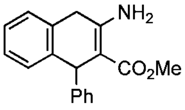
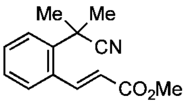
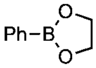
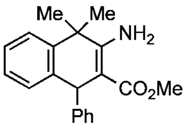
The mechanism shown in Scheme 1 may account for the production of **3aa** starting from **1a** and **2a**. Initially, a phenylrhodium(I) species is generated by the transmetalation of methoxorhodium(I) with **2a**. Then, conjugate addition of the phenylrhodium(I) species to **1a** occurs to afford the (oxa-π-allyl)rhodium(I) intermediate **A**. The intermediate **A** undergoes intramolecular nucleophilic addition to the pendent cyano moiety, forming the *N*-rhodium(I) imine **B**.[9] Subsequent transmetalation of **B** with **2a** produces the *N*-boryl imine species and regenerates the phenylrhodium(I) catalyst. Finally, the *N*-boryl imine undergoes hydrolysis/tautomerization to afford the observed product **3aa**.

Scheme 1



The results of the reaction of other cyano-substituted unsaturated esters **1a**−**f** with *B*-Ar-9-BBNs **2a**−**c** are summarized in Table 1.[10]

Table 1. Rh(I)-Catalyzed Reaction of Cyano-Substituted Unsaturated Ester **1** with *B*-Ar-9-BBN **2**[a]

entry	substrate	*B*-Ar-9-BBN	product	yield (%)[b]
				
1	**1a**	**2b** Ar = 4-MeO-C_6H_4	**3ab**	87
2	**1a**	**2c** Ar = 4-Cl-C_6H_4	**3ac**	88
3	 **1b**	**2a**	 **3ba**	88[c]
4	 **1c**	**2a**	 **3ca**	72
5	 **1d**	**2a**	 **3da**	76
6	 **1e**	**2a**	 **3ea**	81
7	 **1f**	 **2a'**	 **3fa**	80[d]

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $[Rh(OMe)(cod)]_2$ (15 μmol) in toluene (3 mL) at 110 °C for 8−17 h under N_2. [b] Isolated yield after chromatography. [c] **2a** (0.45 mmol). [d] Reaction conditions: **1** (0.2 mmol), 2-phenyl[1,3,2]dioxaborolane (**2a′**, 0.4 mmol), $[Rh(OMe)(cod)]_2$ (10 μmol), H_2O (0.04 mmol) in dioxane (2 mL) at 100 °C for 11 h under N_2.

Both electron-donating and -withdrawing *B*-Ar-9-BBNs, **2b** and **2c**, were suitably reactive (entries 1 and 2). Reactions of various unsaturated esters **1b**−**d** afforded the five-membered products **3ba**−**3da** in yields ranging from 72% to 88% (entries 3−5). Even unsaturated esters **1e** and **1f** possessing a tether longer by one carbon reacted well, giving the six-membered ring products **3ea** and **3fa** in good yield (entries 6 and 7). In the case of unsaturated ester **1f**, the use

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[7] Fustero, S.; García de la Torre, M.; Jofré, V.; Carlón, R. P.; Navarro, A.; Fuentes, A. S.; Carrió, J. S. *J. Org. Chem.* **1998**, *63*, 8825.

[8] Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1974**, *73*, 1.

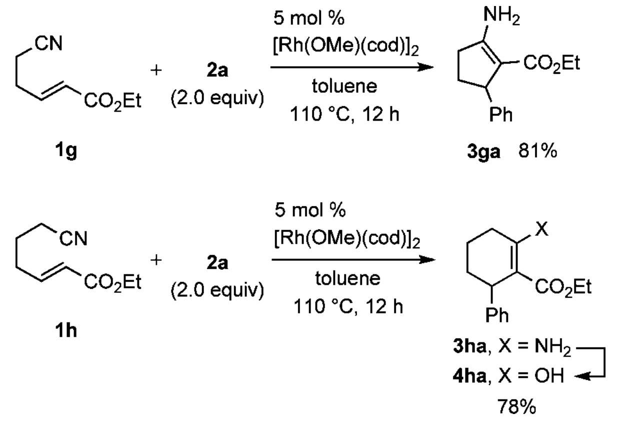
[9] Another reaction pathway involving transmetalation of **A** with **2a** to generate a boron enolate cannot be excluded, as suggested by one of the reviewers, to whom the authors are grateful.

[10] **General procedure:** To an oven-dried, N_2-purged flask was added substrate **1** (0.3 mmol, 1.0 equiv), $[Rh(OMe)(cod)]_2$ (15 μmol, 10 mol % of Rh), and a solution of *B*-Ar-9-BBN **2** (0.6 mmol, 2.0 equiv) in toluene (3.0 mL). The resulting reaction mixture was stirred for 8−17 h at 110 °C. After the reaction mixture was cooled, water (5−10 mL) was added, and the aqueous layer was extracted with ethyl acetate (15 mL × 5). 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 (dichloromethane) to give the product **3**. The second chromatography (hexane/ethyl acetate) was carried out in some cases to remove small amounts of impurities.

of 2-phenyl[1,3,2]dioxaborolane (**2a′**) was preferred for the ease of isolation of the product **3fa**.

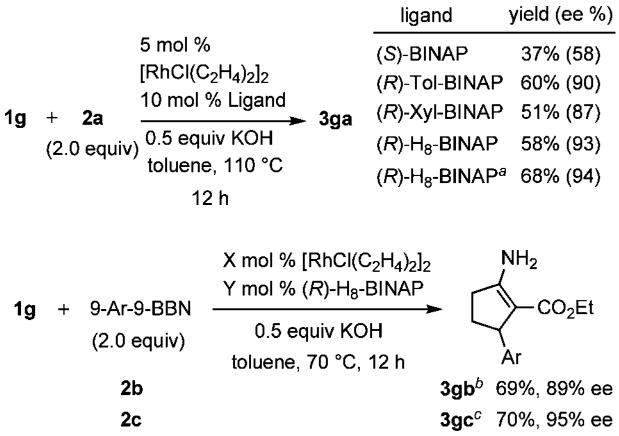
The reaction also proceeded with linear cyano-substituted unsaturated esters (Scheme 2). The five-membered product **3ga** was obtained in 81% yield from **1g**. In the case of the linear unsaturated ester **1h**, the initial product **3ha** was so readily hydrolyzed during purification that β-enol ester **4ha** was isolated in 78% yield after acidic hydrolysis.

Scheme 2



The asymmetric version was studied using **1g** (Scheme 3).[11,12] Among the BINAP-type chiral phosphine ligands examined, (*R*)-H_8-BINAP[13] gave the best result (68% chemical yield and 94% enantiomeric excess at 70 °C). Similarly, **2b** and **2c** afforded the cyclized products **3gb** and **3gc** in 89% and 95% enantiomeric excess, respectively.

Scheme 3

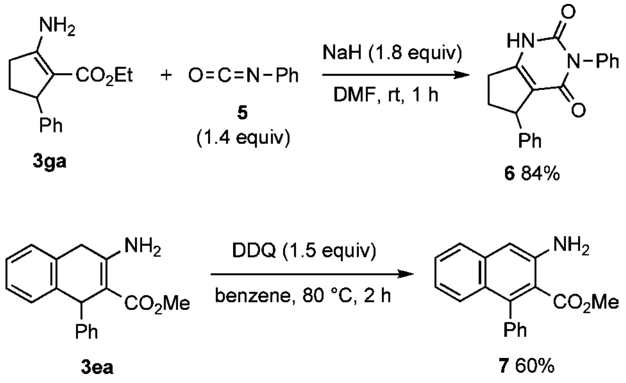


ligand	yield (ee %)
(*S*)-BINAP	37% (58)
(*R*)-Tol-BINAP	60% (90)
(*R*)-Xyl-BINAP	51% (87)
(*R*)-H_8-BINAP	58% (93)
(*R*)-H_8-BINAP[a]	68% (94)

[a] 70 °C. [b] X = 7.5, Y = 15. [c] X = 5.0, Y = 10.

Conversion of the obtained β-enamino esters to synthetically useful compounds is exemplified in Scheme 4. Treatment of the five-membered β-enamino ester **3ga** with phenyl isocyanate (**5**) afforded the uracil derivative **6** in 84% yield.[14] DDQ oxidation of the six-membered β-enamino ester **3ea** gave the β-naphthylamine derivative **7** in 60% yield.[15]

Scheme 4



In summary, we have developed a new cascade reaction triggered by the rhodium-catalyzed conjugate addition of organoboron species, allowing the formation of five- and six-membered β-enamino esters from cyano-substituted unsaturated esters in a single manipulation. This reaction demonstrates that cyano groups can act as electrophilic acceptors of (oxa-π-allyl)rhodium(I) intermediates.

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Supporting Information Available: Reaction procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] For a review on catalytic asymmetric cascade transformations triggered by conjugate additions, see: Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354.

[12] For a review on Rh-catalyzed asymmetric conjugate addition, see: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

[13] Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283.

[14] Fustero, S.; Piera, J.; Sanz-Cervera, J. F.; Catalán, S.; Ramírez de Arellano, C. *Org. Lett.* **2004**, *6*, 1417.

[15] Di Raddo, P.; Harvey, R. G. *Tetrahedron Lett.* **1988**, *29*, 3885.