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Catalytic Asymmetric Synthesis with Rh–Diene Complexes: 1,4-Addition of Arylboronic Acids to Unsaturated Esters

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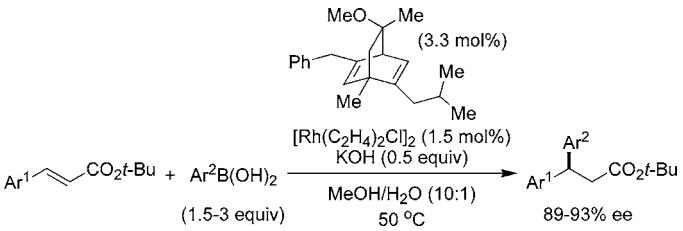
ABSTRACT



A general route to enantioenriched *tert*-butyl 3,3-diarylpropanoates is presented. These useful building blocks are prepared via an asymmetric rhodium-catalyzed conjugate addition of arylboronic acids to unsaturated *tert*-butyl esters in the presence of chiral dienes as ligands. The addition of both electron-poor and electron-rich boronic acids proceeds smoothly with various enoates in 63–90% yield with high enantioselectivites (89–94% ee).

The stereoselective preparation of compounds bearing diarylmethine stereocenters is challenging, particularly when only minor electronic or steric effects differentiate the two aryl groups. This structural motif is present in a number of notable pharmaceuticals (for example, tolterodine and sertraline)[1] and natural products;[2] however, methods for the stereoselective synthesis of these stereocenters is limited.[3] An attractive approach to these compounds involves the Rh-catalyzed conjugate addition of aryl boronic acid nucleophiles to electron-deficient acceptors, because these processes are generally insensitive to the electronic properties of the nucleophile.[4] Chiral dienes have recently been applied as ligands for late-transition metals (i.e., Ir, Rh) for asymmetric reactions of preparative importance.[5,6] In particular, the combination of metal−diene complexes and arylboronic acids has been successfully applied in a number of transformations.[7] We have recently reported the catalytic, asymmetric conjugate addition of arylboronic acids to a wide range of electron-acceptors including enals,[8] enones, enamides, and coumarins (Figure 1).[9,10]

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(7) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (c) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54.

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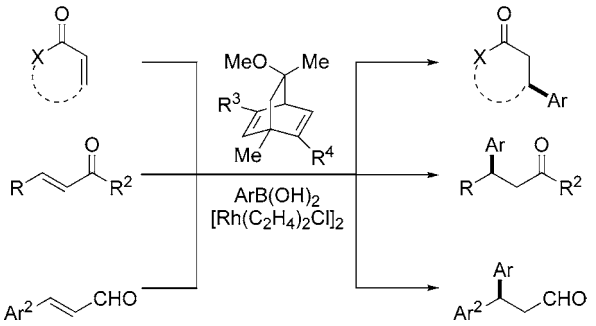


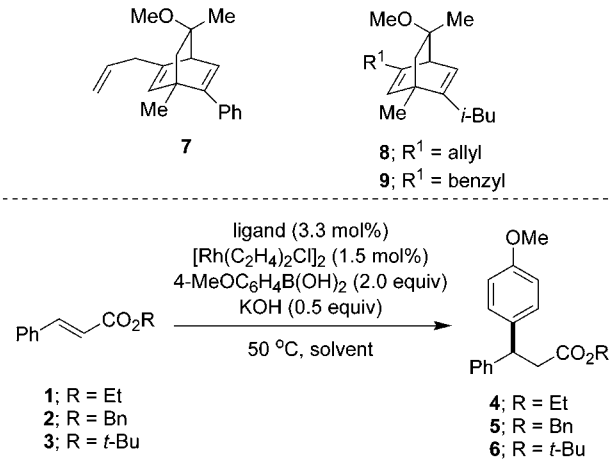
Figure 1.

The use of cinnamic acid esters[11] as acceptors is advantageous for a number of reasons: the wide variety of unsaturated acids that are commercially available, and the increased stability of the esters, which thus make them easily handled starting materials. Of additional importance in pursuing this study was the fact that conjugate additions of arylboronic acids to cinnamate ester acceptors in the presence of metal−diene complexes were lacking in precedence.

We examined the Rh-catalyzed reaction of ethyl cinnamate with 4-methoxybenzeneboronic acid in the presence of diene ligand **7** using the conditions developed for the conjugate addition of arylboronic acids to enones.[10] As expected, the reactivity of the esters was considerably attenuated compared to that of the corresponding enals (18 h vs 75 min reaction time).[8] We were able to isolate the desired 3,3-diarylpropanoate in 72% yield, albeit in only 19% ee (Table 1, entry 1). The enantioselectivity was improved to 65% ee using the isobutyl substituted ligand *ent*-**8** (entry 2). Increasing the size of the ester (R = Bn) provided a small increase in enantioselectivity to 71% ee. The combination of benzyl-substituted ligand **9** and benzyl ester **2** provided **5** in substantially improved enantioselectivity (entry 4, 89% ee). Under optimal conditions, *tert*-butyl cinnamate **3**[12] was converted to diarylpropanoate **6** in the presence of the Rh(I)·**9** complex (3 mol % Rh) in excellent yield and enantioselectivity (entry 6, 85% yield, 93% ee).

While examining the scope of the Rh-catalyzed conjugate addition reaction to *tert*-butyl cinnamate **3**, we observed that both electron-rich (Table 2, entry 1) and electron-poor boronic acids (entries 2 and 3) afforded the desired adducts in 69−85% yield and 92−93% ee. By switching the aryl acceptor and donor, we could easily prepare both enantiomers of a given product (cf. entries 1 and 4) using a single enantiomer of ligand **9**.[13] In addition, a wide variety of substituted cinnamate esters could be used as acceptors in

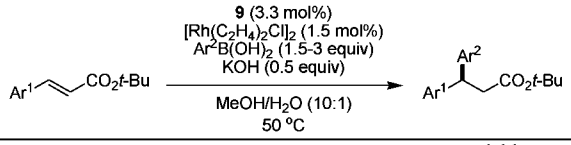
Table 1. Ligand Screening and Reaction Optimization

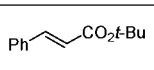
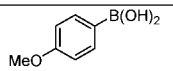
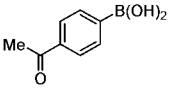
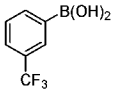
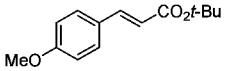
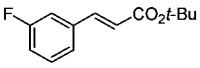
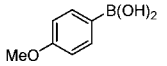
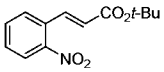
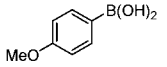


entry	ester	ligand	solvent	yield (%)[a]	ee (%)[b]
1	**1**	**7**	dioxane/H_2O (10:1)	72	19
2	**1**	*ent*-**8**	dioxane/H_2O (10:1)	99	−65
3	**2**	**8**	dioxane/H_2O (10:1)	85	71
4	**3**	**8**	dioxane/H_2O (10:1)	72	89
5	**3**	**9**	dioxane/H_2O (10:1)	89	92
6	**3**	**9**	MeOH/H_2O (10:1)[c]	85	93

[a] Isolated yield after chromatography. [b] Determined by chiral HPLC (see Supporting Information for details). [c] Reaction time = 75 min.

Table 2. Conjugate Addition Reactions Catalyzed by Rh(I)·**9**



entry	ester	$Ar^2B(OH)_2$	yield (%)[a]	ee (%)[b,c]
1			85	93
2			76	92
3			69	92
4		$PhB(OH)_2$	95	91
5		$PhB(OH)_2$	95	94[d]
6			93	93
7		$PhB(OH)_2$	78	92
8			84	92

[a] Isolated yield after chromatography. [b] Determined by chiral HPLC. [c] Assigned on the basis of our previous work (ref 9). [d] This value was estimated because the signals could not be completely resolved in the chiral HPLC.

(8) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, In Press.

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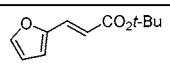
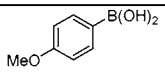
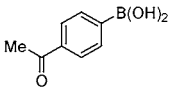
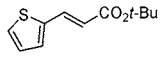
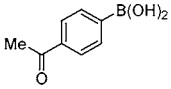
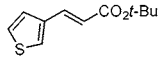
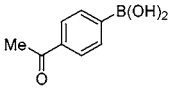
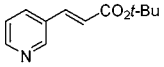
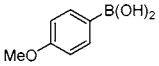
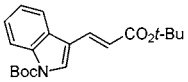
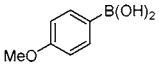
Table 3. Conjugate Addition Reactions Catalyzed by Rh(I)·**9** to Heterocylic Acceptors

entry	ester	$Ar^2B(OH)_2$	yield (%)[a]	ee (%)[b,c]
1			62	92
2			68	91
3[d]			65	91
4[d]			68	89
5[d]			70	93
6[d]			90	94

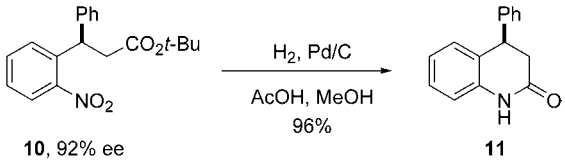
[a] Isolated yield after chromatography. [b] Determined by chiral HPLC. [c] Assigned on the basis of our previous work (ref 9). [d] The solvent for these reactions was 1,4-dioxane.

the conjugate addition reaction. Aromatics substituted with electron-donating (entry 4) and electron-withdrawing groups (entries 5−8) provided the 3,3-diarylpropanoates in 78−95% yield and 92−94% ee. In particular, the nitro-substituted cinnamate (entries 7 and 8) were good substrates for this conjugate addition reaction, whereas the corresponding aldehydes afforded mostly decomposition. It is noteworthy that the enantioselectivity of these reactions is independent of substitution on the donor or acceptor, providing the desired products within a narrow window of enantioselectivities (91−94% ee).

We also examined a number of heterocyclic acceptors to broaden the scope of the conjugate addition reaction while generating functionalized products. In all cases, the heterocycle-substituted enoates reacted more slowly than the cinnamate derivatives, often requiring reaction times of 12−18 h (Table 3). In some cases, it was advantageous to carry out the reactions in 1,4-dioxane in place of MeOH (entries 3−6). Furyl-substituted acceptors reacted with both electron-rich and -poor boronic acids to give the desired adducts in 62−68% yield and 91−92% ee (entries 1−2). Both regioisomeric thienyl-substituted acceptors afforded adducts in 65−68% yield and 89−91% ee (entries 3 and 4). We were pleased to observe that the pyridyl-substituted enoate was smoothly converted to the 1,4-addition product in 70% yield and 93% ee (entry 5). In our previous study, the corresponding enal did not afford the 1,4-addition product. Finally, the indolyl-substituted enoate provided the conjugate addition product in excellent yield and enantioselectivity (entry 6, 90%, 94% ee).

To extend the utility of this methodology, we decided to take advantage of the functional groups present in the conjugate addition products for subsequent synthetic elaboration. In particular, the adduct of phenylboronic acid and *o*-NO_2-substituted cinnamate ester provided the opportunity to prepare optically enriched dihydroquinolin-2-ones from the 1,4-adducts.[14] Thus, subjection of **10** (Table 2, entry 7) to hydrogenation (H_2, Pd/C in MeOH) cleanly afforded the amino ester, which could be converted to the desired lactam **11** by treatment with AcOH in THF (Scheme 1). A one-step protocol involving hydrogenation of **10** in the presence of 1 equiv of AcOH afforded a mixture of aniline and lactam and continued stirring under argon furnished **11** in 96% yield.[15]

Scheme 1. Conversion to Dihydroquinolin-2-one



10, 92% ee **11**

In summary, we have successfully demonstrated the functional utility of chiral Rh−diene complexes in the preparation of 3,3-diarylpropanoates in 76−95% yield and 91−94% ee. The Rh-catalyzed addition of arylboronic acids was also used to prepare 3-aryl-3-heteroaryl-propanoates in 62−90% yield and 89−94% ee. This process is attractive because of the ready availability of the starting materials (esters and boronic acids) and its success with a wide variety of donors and acceptors. In addition, we have established the applicability of this reaction as exemplified by the simple, one-pot synthesis of optically enriched dihydroquinolin-2-one **11**.

Acknowledgment. This research is supported by a Swiss National Science Foundation Grant and by the ETHZ. J.-F.P. is grateful to the National Sciences and Engineering

(10) Subsequently, Hayashi and co-workers reported the Rh·phosphine complex catalyzed addition of arylboronic acids to coumarins. See: Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285.

(11) (a) Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 1651. (b) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, R. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (c) Song, Z. J.; Zhao, M.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J. J.; Dolling, U. H.; Reider, P. J.; Okada, S.; Kato, Y.; Mano, E. *J. Org. Chem.* **1999**, *64*, 9658. (d) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. (e) Navarre, L.; Pucheault, M.; Darses, S.; Genêt, J.-P. *Tetrahedron Lett.* **2005**, *46*, 4247.

(12) For the facile preparation of *tert*-butyl esters using Boc_2O and DMAP, see: Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.-i.; Mizuno, Y.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, 1063.

(13) At the current level of development, *o*-heteroatom-substituted arylboronic acids (such as *o*-nitrophenylboronic acid) cannot be employed in the reaction. Thus, for adducts requiring such substitution, it is best to have the *o*-substituted acceptor reaction partner as described herein.

(14) (a) Higuchi, R. I.; Edwards, J. P.; Caferro, R. R.; Ringgenberg, J. D.; Kong, J. W.; Hamann, L. G.; Arienti, K. L.; Marschke, K. B.; Davis, R. L.; Farmer, L. J.; Jones, T. K. *Biorg. Med. Chem. Lett.* **1999**, *9*, 1335. (b) Angibaud, P. R.; Venet, M. G.; Filliers, W.; Broeckx, R.; Ligny, Y. A.; Muller, P.; Poncelet, V. S.; End, D. W. *Eur. J. Org. Chem.* **2004**, 479.

(15) The hydrogenation was accelerated in the presence of AcOH (ca. 2 h compared to 24 h).

Research Council of Canada (NSERC) for a postdoctoral fellowship.

Supporting Information Available: General experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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