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Rhodium-Catalyzed Conjugate Addition–Enantioselective Protonation: The Synthesis of α,α′-Dibenzyl Esters

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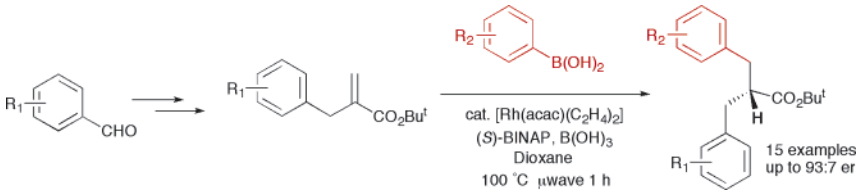
ABSTRACT



α-Benzyl acrylates, which are conveniently prepared from the corresponding aldehydes, can be employed as substrates in a tandem rhodium-catalyzed conjugate addition–enantioselective protonation protocol to afford enantiomerically enriched α,α′-dibenzyl esters. The synergistic effect of enantiopure ligand and proton source was rapidly optimized with use of a microwave reactor.

Tandem catalytic reactions including enantioselective processes have emerged as important methods for the formation of new chemical bonds in an efficient manner.[1] Within this context, the stereoselective construction of C−C bonds with the rhodium-catalyzed 1,4-addition of organometallics can generate a reactive π-allylrhodium intermediate for further C−C bond-forming reactions.[2,3] An interesting and challenging variant of this type of process is the asymmetric arylation of activated alkenes or allenes via enantioselective protonation.[4,5] This approach entails the selective protonation of a chiral π-allylrhodium intermediate formed by the reaction of a 1,1′-disubstituted substrate and an arylrhodium species (Figure 1). In this circumstance, the combined effect of the chiral rhodium complex, the nature of the organometallic, and the structure of the proton source dictate the overall enantioselectivity.[6]

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(1) (a) Pelissier, H. *Tetrahedron* **2006**, *62*, 2143−2173. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619−1665. (c) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1−21 and references cited therein.

(2) For reviews see: (a) Hayashi, T. *Synlett* **2001**, 879−887. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196. (d) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313−4327. (e) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13−21.

(3) (a) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984−10985. (b) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 1901−1905. (c) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110−1111. (d) Bocknack, B. M.; Wang, L. C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421−5424.

(4) (a) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083−4085. (b) Chapman, C. J.; Wadsworth, K. J.; Frost, C. G. *J. Organomet. Chem.* **2003**, *680*, 206−211. (c) Moss, R. J.; Wadsworth, K. J.; Chapman, C. J.; Frost, C. G. *Chem. Commun.* **2004**, 1984−1985. (d) Navarre, L.; Darses, S.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719−723. (e) Sibi, M. P.; Tadamidani, H.; Patil, K. *Org. Lett.* **2005**, *7*, 2571−2573. (f) Hargrave, J. D.; Herbert, J.; Bish, G.; Frost, C. G. *Org. Biomol. Chem.* **2006**, *4*, 3235−3241. (g) Hargrave, J. D.; Bish, G.; Frost, C. G. *Chem. Commun.* **2006**, 4389−4391.

(5) Nishimura, T.; Hirabayashi, S.; Yasuhara, Y.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 2556−2557.

(6) For a review on the enantioselective protonation of enolates, see: Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1−24.

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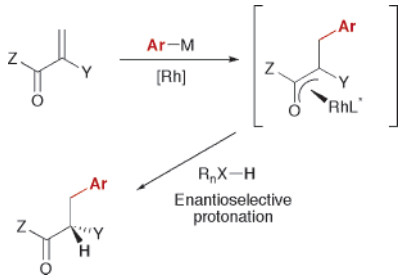
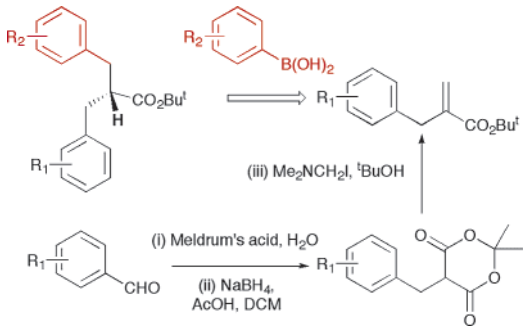


Figure 1. Rhodium-catalyzed conjugate addition−enantioselective protonation strategy.

Given that the enantioselective protonation occurs via the rhodium complex *after* the carbon−carbon bond-forming step, this allows us to explore the construction of chiral molecules with only subtle differences in their structural features. Herein, we document the synthetic utility of this method in a versatile catalytic, asymmetric synthesis of α,α′-dibenzyl esters as shown in Scheme 1. At the outset it was

Scheme 1. The Catalytic, Asymmetric Synthesis of α,α′-Dibenzyl Esters

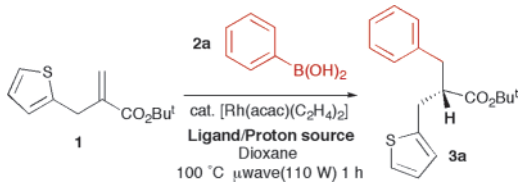


decided to employ a *tert*-butyl ester based on a precedent for higher enantioselectivities in related additions and its ease of deprotection.[4e] The requisite α-substituted *tert*-butyl acrylates were straightforward to prepare via a Mannich-type process employing a variant of the method reported by Tsukamoto et al.[7]

Thus, an initial Knoevengal condensation of aldehyde and Meldrum's acid was followed by reduction with sodium borohydride according to the procedure of Bigi et al.[8] The 5-monosubstituted Meldrum's acid derivatives were then treated with Eschenmoser's iodide salt in the presence of *tert*-butanol to afford the α-substituted *tert*-butyl acrylates in excellent isolated yield.[9]

Our initial investigation focused on the addition of phenylboronic acid (**2a**) to the thiophene-substituted *tert*-butyl acrylate **1** in dioxane as solvent with variation of the enantiopure ligand and proton source (selected examples are shown in Table 1). For ease of operation and rapid evaluation, the rhodium-catalyzed addition was performed in capped tubes under microwave irradiation (CEM Discover model 045704 system at 100 °C for 1 h).[10] It should be noted that the reactions proceeded in similar yields and enantioselectivities by heating in an oil bath or heating block at 110 °C for 18−24 h. In line with previous rhodium-catalyzed 1,4-additions on α-substituted acrylates, higher enantioselectivities were observed when employing BINAP and related analogues.[4] The use of water as proton source afforded the product with modest enantioselectivity (Table 1, entry 5). The combination of BINAP and 2-methoxyphenol (Table 1, entry 6) as previously reported by Genet et al. (for α-amino acids[4d]), or DIFLUORPHOS and phthalimide (Table

Table 1. Rhodium-Catalyzed Conjugate Addition-Enantioselective Protonation; Optimization of Ligand and Proton Source[a]



entry	ligand[i]	proton source	yield[b] (%)	er[c] (**3a**:*ent*-**3a**)
1[d]	(*R*,*R*)-Me-DUPHOS	H_2O	91	49:51
2[d]	(*R*)-PROPHOS	H_2O	24	35:65
3[d]	(*S*,*S*)-CHIRAPHOS	H_2O	42	67:33
4	(*R*)-DIFLUORPHOS	phthalimide	49	22:78
5[d]	(*S*)-BINAP	H_2O	63	79:21
6	(*S*)-BINAP	2-methoxyphenol	54	80:20
7	(*S*)-BINAP	phthalimide	57	81:19
8	(*S*)-BINAP	(*R*)-BINOL	47	85:15
9	(*S*)-BINAP	(*S*)-BINOL	48	85:15
10	(*S*)-BINAP	(*rac*)-BINOL	45	85:15
11[e]	(*S*)-BINAP	(*rac*)-BINOL	55	85:15
12	(*S*)-BINAP	$B(OH)_3$	65	90:10
13[f]	(*S*)-BINAP	$B(OH)_3$	78	90:10
14[g]	(*S*)-BINAP	$B(OH)_3$	84	90:10
15[g]	(*R*,*R*,*R*)-diene[h]	$B(OH)_3$	76	24:76
16[g]	(*S*)-tol-BINAP	$B(OH)_3$	54	84:16
17[g]	(*S*)-SYNPHOS	$B(OH)_3$	71	86:14
18[g]	(*S*)-Xyl-BINAP	$B(OH)_3$	69	81:19

[a] Reaction conditions: **1** (1.0 equiv), phenylboronic acid **2a** (4.0 equiv), [Rh(acac)$(C_2H_4)_2$] (4 mol %), dioxane, proton source (1.0 equiv), microwave reactor (110 W, 100 °C). [b] Isolated yields. [c] Determined by HPLC analysis with use of a Chiralcel OD-H column. [d] Dioxane:H_2O (10:1). [e] With $B(OH)_3$ (1.0 equiv). [f] $B(OH)_3$ (3.0 equiv). [g] $B(OH)_3$ (4.0 equiv). [h] (1*R*,4*R*,8*R*)-5-Benzyl-8-methoxy-1,8-dimethyl-2-(2′-methylpropyl)-bicyclo[2.2.2]octa-2,5-diene. [i] See Figure 2.

(7) Hin, B.; Majer, P.; Tsukamoto, T. *J. Org. Chem.* **2002**, *67*, 7365−7368.

(8) (a) Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203−5205. (b) Maggi, R.; Bigi, F.; Carloni, S.; Mazzacani, A.; Sartori, G. *Green Chem.* **2001**, *3*, 173−174.

(9) See the Supporting Information for full details.

(10) For selected accounts of the use of microwaves in organic synthesis see: (a) Adam, D. *Nature* **2003**, *421*, 571−572. (b) Loupy, A. In *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002. (c) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284. (d) Caddick, S. *Tetrahedron* **1995**, *51*, 10403−10432.

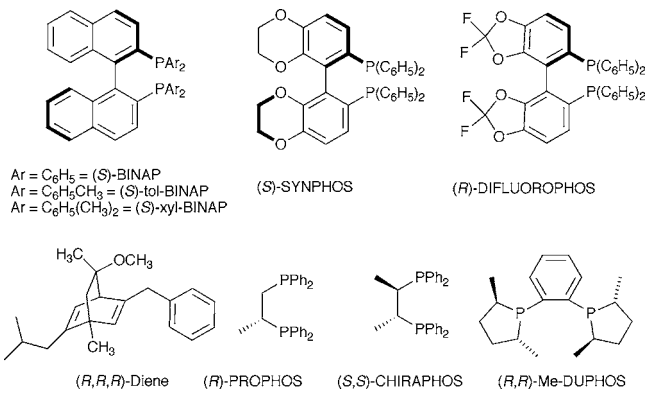
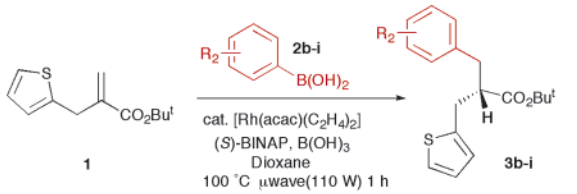
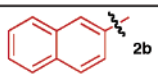
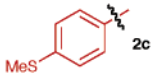
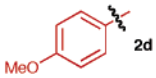
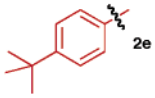
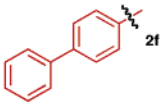
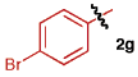
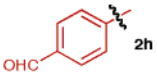
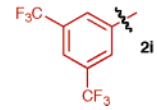


Figure 2. Ligands used.

1, entry 4) as previously reported by Sibi et al. (for β^2-amino acids[4e]) imparted similar results.

Table 2. Rhodium-Catalyzed Conjugate Addition−Enantioselective Protonation: Scope of Boronic Acid[a]



entry	boronic acid	product	yield[b] (%)	er[c]
1	 2b	**3b**	80	90:10
2	 2c	**3c**	81	90.5:9.5
3	 2d	**3d**	93	91:9
4	 2e	**3e**	93	93:7
5	 2f	**3f**	69	91:9
6	 2g	**3g**	73	92:8
7	 2h	**3h**	71	93:7
8	 2i	**3i**	78	92.5:7.5

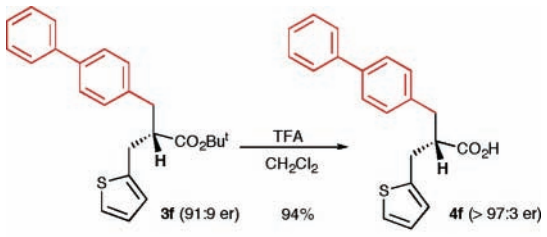
[a] Reaction conditions: **1** (1.0 equiv), boronic acid **2** (4.0 equiv), [Rh(acac)(C_2H_4)$_2$] (4 mol %), dioxane, boric acid (4.0 equiv), microwave reactor (110 W, 100 °C). [b] Isolated yields. [c] Determined by HPLC analysis with use of a Chiralcel OD-H column.

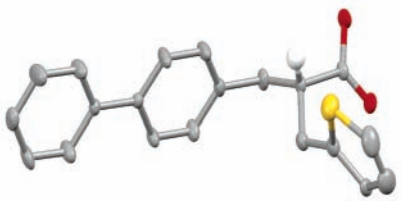
We therefore decided to evaluate further proton sources including BINOL, which is commercially available as a racemate or in either enantiomeric form. Interestingly, the inclusion of BINOL resulted in an improved enantioselectivity but the configuration of the proton source had no affect on the enantiomeric ratio (Table 1, entries 8−10). After further investigation the optimal proton source proved to be boric acid, which afforded the product with good enantioselectivity and excellent yield (Table 1, entries 12−14). Interestingly, the omission of boric acid resulted in a very low conversion to product. A range of other enantiopure ligands were tested in conjunction with boric acid as proton source; however, none surpassed the efficiency and selectivity of the system with BINAP (Table 1, entries 15−18).

With the optimized set of reaction conditions, we next explored the scope of the process with respect to the boronic acid; in all cases the thiophene-substituted *tert*-butyl acrylate **1** was employed as substrate. The yield and enantioselectivity was consistently good for a range of boronic acids (Table 2). It is useful to note that both electron-donating and electron-withdrawing substituents are tolerated. The successful incorporation of thiomethyl, halogen, and aldehyde functionality demonstrates the versatility of the catalytic process (Table 2, entries 2, 6, and 7).

The biphenyl-substituted product **3f** was deprotected by treatment with trifluoroacetic acid to furnish the carboxylic acid **4f** as a crystalline solid. Recrystallization of **4f** resulted in an enhancement of enantiopurity (>97:3 er). The absolute configuration of **4f** was determined to be (*S*) by X-ray crystallography.[11] The mechanism of the rhodium-catalyzed 1,4-addition of boronic acids to enones has been documented[12] but there is little detail on the mode of protonation. However, more recent observations from Hayashi et al. suggest that protonation of a related chiral π-allylrhodium intermediate occurs on the same face as rhodium.[5] The proximity of coordinating functionality in the optimal proton sources utilized by Genet et al. (2-methoxyphenol) and Sibi et al. (phthalimide) supports the notion of protonation taking place via prior coordination to rhodium. In the presented

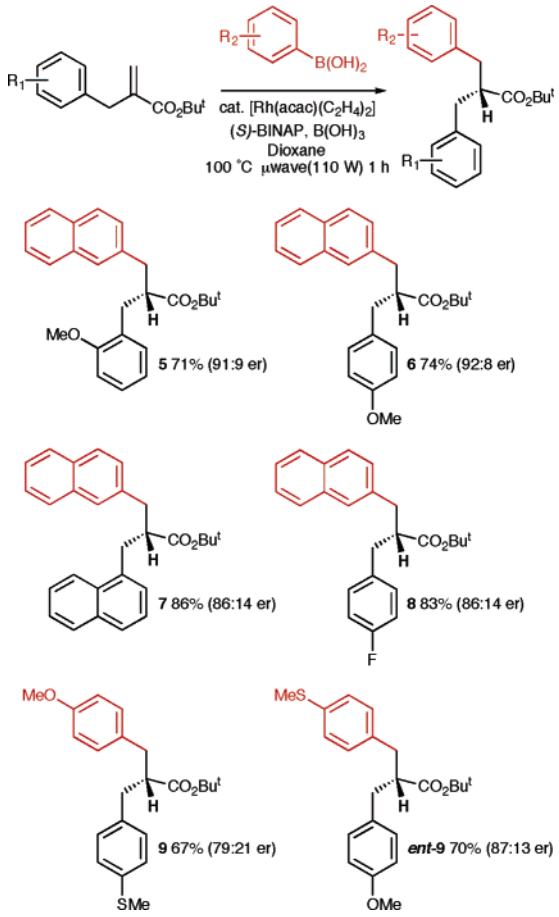
Scheme 2. Deprotection of **3f**





4f (*S*)-configuration confirmed by X-ray of TFA salt

Scheme 3. Scope of Rhodium-Catalyzed Conjugate Addition−enantioselective Protonation



system, it is proposed that the high enantioselectivity arises in a similar manner, by prior coordination of the boric acid to rhodium. An intriguing precedent for this is provided by the recent isolation and characterization of a series of pertinent rhodium boronate complexes by Hartwig et al.[13]

The broad synthetic potential of this protocol arises from the ready availability of the two key reagents: boronic acids and aryl aldehydes. This has been established for a diverse range of substrate−boronic acid permutations, examples of which are shown in Scheme 3. A good illustration of the versatility of this method is the synthesis of either **9** or *ent*-**9** with use of the same enantiopure catalyst and proton source, simply by switching the functional groups on the boronic acid and starting aryl aldehyde.

In conclusion, we have demonstrated that α-substituted *tert*-butyl acrylates are efficient substrates for a tandem rhodium-catalyzed conjugate addition−enantioselective protonation process. The method can tolerate a variety of reactive functional groups on both substrate and boronic acid to deliver highly functionalized products. The adducts are obtained in good yields, and in general with very good levels of enantioselectivity.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The crystal structure of **4f** was determined by using single crystal X-ray data collected on Station 9.8 at the SRS, CCLRC Daresbury Laboratory. Crystal data: $C_{20}H_{18}O_2S$, $M = 322.4$, monoclinic, space group $P2_1$, $a = 8.1857(13)$ Å, $b = 5.4937(9)$ Å, $c = 17.963(3)$ Å, $\beta = 92.876(1)°$, $V = 806.8(2)$ Å^3, $Z = 2$, $T = 150(2)$ K, 8927 measured reflections ($R_{int} = 0.056$), $R_1 = 0.073$, $wR_2 = 0.217$, Flack parameter = 0.10(13).

(12) For a discussion of the mechanism, see: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc*. **2002**, *124*, 5052−5058.

(13) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1876−1877.