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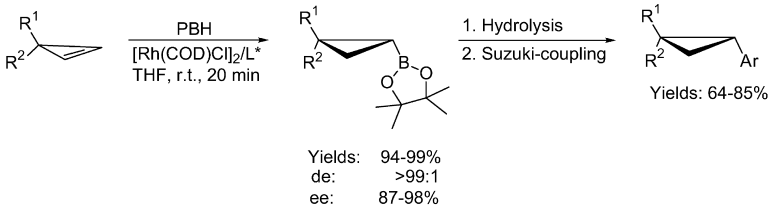

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Catalytic Enantioselective Hydroboration of Cyclopropenes

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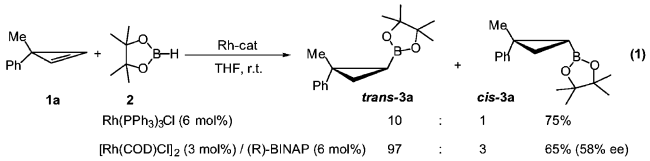
Cyclopropyl boronates increasingly attract attention as enticing building blocks for synthetic organic chemistry.[1] Although a number of approaches toward cyclopropylboronic derivatives have been developed,[2] only a few examples of the preparation of optically active boron-containing cyclopropanes have been reported to date. In all methods, stoichiometric amounts of chiral auxiliaries at the boronic ester were employed, and no examples using more attractive catalytic strategies have been described. Furthermore, the above methodologies are limited to the preparation of 1,2-disubstituted cyclopropanes only. In such systems, high degrees of diastereoselectivity were achieved when *trans*-alkenes were employed,[1g,2e,f] whereas *cis*-analogues gave only moderate diastereomeric excess.[1i] We have recently shown that hydro-, sila-, and distannanes could be added to the double bond of cyclopropenes[3] in a highly diastereoselective fashion.[4] Naturally, we were intrigued by the possibility of developing a catalytic protocol toward stereodefined cyclopropyl boronates as an environmentally benign alternative to the cyclopropylstannyl synthons. Moreover, the usefulness of this approach would be significantly magnified if acceptable degrees of enantioselectivity are achieved. Although catalytic asymmetric hydroboration of olefins is well precedented,[5] no examples of this reaction performed on cyclopropenes have been reported.[6] Herein we report the first rhodium-catalyzed asymmetric hydroboration of cyclopropenes to produce cyclopropyl boronates with very high degrees of diastereo- and enantioselectivity.

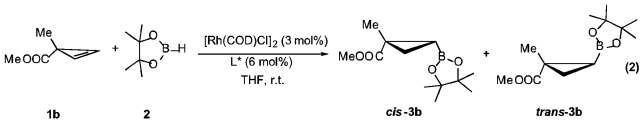
Our initial experiments on hydroboration of cyclopropene **1a** with catecholborane (CBH) in the presence of Wilkinson's catalyst resulted in nonselective formation of two diastereomeric cyclopropyl boronates along with a substantial amount of ring-opening products. In contrast, the reaction with pinacolborane (PBH)[7] proceeded with high degrees of steric control to produce a 10:1 mixture of *trans*- and *cis*-cyclopropyl boronates in 75% yield (eq 1).[8] Significant



(1)

improvement of facial selectivity (97:3) was achieved as we attempted to perform an asymmetric hydroboration of **1a** using [Rh(COD)Cl]$_2$ complex in combination with chiral (*R*)-BINAP ligand.[5b] However, this reaction proceeded sluggishly (6 h vs 2 h with Wilkinson's catalyst), and overall efficacy was disappointingly low (65% yield, 58% ee). Next, we tested the hydroboration reaction with cyclopropene **1b** possessing an ester functionality. To our delight, the reaction with [Rh(COD)Cl]$_2$/(*R*)-BINAP system proceeded very rapidly, producing virtually a single diastereomer of cyclopropyl boronate (***cis*-3b**) in a nearly quantitative yield and, most remarkably, with a high degree of enantioselectivity (eq 2, Table 1, entry 1). The observed strong directing effect of the ester group in the hydroboration of **1b** was rather surprising, since Pd-catalyzed hydrostannation of **1b** was shown to be entirely sterically controlled, leading to the formation of the corresponding *trans*-product.[4] Screening a number of the commercially available chiral phosphine ligands in the hydroboration of **1b** revealed the superiority of BINAP and Tol-BINAP ligands in terms of reaction rates, chemical yields, diastereo- and enantioselectivity (entries 1, 12). NORPHOS and PHANEPHOS exhibited comparable diastereoselectivities and very high enantioselectivities; however, yields were somewhat lower (entries 10, 11). JOSIPHOS,[5d] QUINAP,[5e] and BDPP,[5g] which were previously reported to provide high degrees of enantioselectivity in the hydroboration of olefins, appeared not to be competitive in this reaction (entries 2, 4, 5). Remarkably, a strong directing effect was required (entries 1, 6, 7, 10−12), but not sufficient (entry 9) to obtain high degrees of enantioselectivity. On the other hand, modest enantioselectivities were observed for another facial isomer ***trans*-3b** (entry 10, note d) as well as for **1a** with no directing group present (eq 1).

Table 1. Ligand Effect in the Asymmetric Hydroboration of **1b**[9]



(2)

	ligand[a]	time, h	*cis*/*trans*	yield,%[b]	*cis*-**3b** ee, %[c] (config.)
1	**(*R*)-BINAP**	**0.3**	**>99/1**	**96**	**94 (*1S,2R*)**
2	(*R*)-QUINAP	8	17/83	9	~0
3	(*R,R*)-Et-BPE	3	98/2	67	73 (*1R,2S*)
4	(*R,S*)-JOSIPHOS	8	50/50	47	64 (*1S,2R*)
5	(*S,S*)-BDPP	8	72/28	43	66 (*1R,2S*)
6	(*S,S*)-CHIRAPHOS	3	98/2	47	88 (*1R,2S*)
7	(*S,S*)-Et-FerroTANE	8	95/5	76	89 (*1S,2R*)
8	(*R,R*)-Me-DUPHOS	3	>99/1	82	67 (*1R,2S*)
9	(*R,R*)-Pr^i-DUPHOS	3	98/2	92	11 (*1S,2R*)
10	**(*S,S*)-NORPHOS**	**1**	**98/2**	**86**	**>99[d] (*1R,2S*)**
11	**(*R*)-PHANEPHOS**	**3**	**>99/1**	**89**	**97 (*1R,2S*)**
12	**(*S*)-Tol-BINAP**	**0.3**	**>99/1**	**94**	**96 (*1R,2S*)**

[a] For structures of the ligands, see Supporting Information. [b] Combined GC yield. [c] Enantiomeric excess was determined by GC analysis using CYCLODEX B chiral column. [d] For another facial isomer (***trans*-3b**) ee was found to be 72%.

The best conditions were applied to the asymmetric hydroboration of differently substituted cyclopropenes (eq 3, Table 2). It was found that all 3,3-disubstituted cyclopropenes possessing an ester group reacted very efficiently, producing corresponding cyclopropyl boronates in virtually quantitative yields with very high degrees of diastereo- and enantioselectivity (entries 1−4). Cyclopropene **1f**, containing a methoxymethyl group, provided poor enantioselectivity when subjected to the hydroboration reaction in the presence of BINAP or Tol-BINAP ligands (ca. 10−20%). However, it was found that Et-BPE provided high enantiomeric induction in the hydroboration of **1f** (87%). Similar to the ester functionality, the methoxymethyl substituent served as a very good directing group providing virtually a single facial isomer ***cis*-3f** (entry 5). Under

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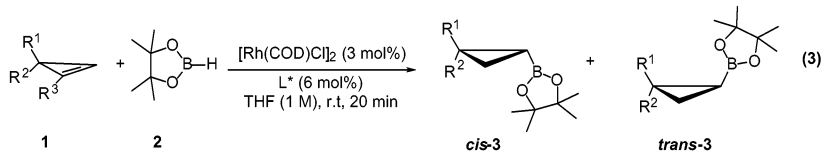
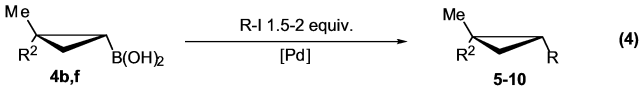
Table 2. Asymmetric Hydroboration of 3,3-Disubstituted Cyclopropenes



	substrate									
	R^1	R^2	R^3		ligand	*cis*/*trans*	yield, %[a]	ee, %[b]	abs.config.	$[\alpha]_D$
1	Me	COOMe	H	**1b**	(*R*)-BINAP	>99:1	94	94	*1S,2R*	−32.9
2	TMS	COOEt	H	**1c**	(*R*)-BINAP	>99:1	99	97	*1R,2R*	−31.9
3	Ph	COOMe	H	**1d**	(*R*)-BINAP	>99:1	99	92	*1S,2R*	−57.5
4	COOMe	COOMe	H	**1e**	(*S*)-Tol-BINAP[c]	−	99	>98[d]	*2S*	+65.2
5	Me	CH_2OMe	H	**1f**	(*R,R*)-Et-BPE[c]	>99:1	98	87	*1R,2S*	+38.8
6	COOMe	COOMe	*n*-Bu	**1g**	(*R*)-BINAP	−	0[e]	−	−	−

[a] Isolated yield. [b] Enantiomeric excess was determined by GC analysis using CYCLODEX B or CYCLOSIL B chiral columns. [c] Reaction was performed in DCM (1 M). [d] Determined by NMR with $Eu(hfc)_3$. [e] Cyclopropene **1g** rearranged into a corresponding furan in 1 h at room temperature.

Table 3. Suzuki Cross-Coupling Reaction of ***cis*-4b** and ***cis*-4f** with Aryl and Vinyl Iodides[13]



	R^2	R	time, h	yield,%
1	COOMe (**b**)	Ph (***1S,2S*-5**)	1	76
2	COOMe (**b**)	*p*-$MeOC_6H_4$ (***1S,2S*-6**)	1	77
3	COOMe (**b**)	*p*-$MeO_2CC_6H_4$ (***1S,2S*-7**)	1	64
4	COOMe (**b**)	1-Nphth (***1S,2S*-8**)	1	85
5	COOMe (**b**)	CH═C(Me)Ph (***1S,2S*-9**)	0.5	65
6	CH_2OMe (**f**)	Ph (***1R,2R*−10**)	7	85

the reaction conditions tested, trisubstituted cyclopropene **1g** did not undergo hydroboration at all due to very facile rearrangement into a corresponding furan derivative (entry 6).[10]

To demonstrate the synthetic utility of the obtained cyclopropyl boronates, compounds ***cis*-3b** and ***cis*-3f** were tested in the Suzuki cross-coupling reaction with aryl and vinyl iodides. Employment of sterically encumbered **3** in this process poses a certain challenge since no examples of Suzuki-coupling with *cis*-substituted cyclopropylboronic derivatives were reported to date. Although the boronic esters failed to undergo cross-coupling, the corresponding boronic acids **4b**,**f**[11] provided good yields of desired products in the presence of Fu's catalyst system[12] (eq 4, Table 3).

In summary, we have demonstrated that enantiopure 2,2-disubstituted cyclopropyl boronates could be easily synthesized via the catalytic asymmetric hydroboration of 3,3-disubstituted cyclopropenes. It was shown that ester and alkoxymethyl substituents serve as effective directing groups in the hydroboration reaction. A directing effect was found to be necessary for achieving high degrees of enantioselectivity. The synthetic usefulness of this methodology was demonstrated in the effective synthesis of optically active trisubstituted aryl- and vinylcyclopropanes.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Conditions: $Pd(t\text{-}Bu_3P)_2$ 10 mol %, CsF (for ***cis*-4b**) or NaOH aq (for ***cis*-4f**) 3 equiv, benzene, 80 °C.

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