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Copper catalyzed diastereoselective and enantioselective hydroborylation of cyclopentenylcarboxyesters†

Yufeng Yao, Ming Huang, Chunyu Chen, Hao Zeng, Ze Li, Guo-Qiao Lai and Pinglu Zhang *

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The optically-enriched cyclopentylborane derivatives containing consecutive stereogenic centers are of great use for the construction of chiral cyclopentanes. The preceding examples are limited to specialized substrates and suffer from a lack of generality, and the access to consecutive stereogenic centers remains elusive. Here we disclose a copper catalyzed conjugative borylation of cyclopentenylcarboxyesters, for accessing cyclopentyl boronates bearing a consecutive stereogenic center in a diastereoselective and enantioselective fashion. This method could be scaled up and the C–B bond in products could be easily transformed in late-stage functionalization. Furthermore, modeling for rationalization of the enantioselectivity and diastereoselectivity is proposed, which suggested that borylcupration is probably the enantio-determining step while the proton-decupration is the diastereo-determining step.

Five membered chiral carbocycles containing consecutive stereogenic centers are prevalently embedded in the structure of natural products and biologically active molecules (Fig. 1).[1] Enantioenriched cyclopentylboranes can serve as versatile building blocks for the synthesis of an array of chiral cyclopentanes, owing to the great convertibility of the C–B bond to a variety of functional groups stereospecifically.[2] Consequently, synthetic methods for the catalytic stereoselective preparation of cyclopentylboranes are highly desired. Cyclization of boronates or borylative cyclizations may access cyclopentylborane frameworks.[3] However, the catalytic stereoselective cyclization of cyclopentylboranes remains a notorious challenge.[4]

Alternatively, a practical and reliable way for accessing enantio-enriched cyclopentyl boronates would be *via* the asymmetric catalytic hydroborylation of cycloalkene derivatives.[5] In the last decade, notable advances toward asymmetric hydroborylation of cyclopentenes have been developed (Scheme 1a). For instance, Yun and Shibasaki reported copper catalyzed enantioselective conjugate borylation of substituted cyclopentenones, respectively.[6] Ito and co-workers developed enantioselective hydroborylation of cyclopentadiene with B_2pin_2.[7] Later, the same group disclosed the enantioselective synthesis of cyclopentyl homoallylboronates using racemic cyclopentyl homoallic ethers in the presence of copper catalysts.[8] However, these preceding examples with good enantioselectivities are limited to specialized substrates and suffer from a lack of generality and substrate scope. Moreover, accessing cyclopentyl boronates bearing multi-stereogenic centers remains elusive to date. This discrepancy is even more remarkable, given that the diastereoselective and enantioselective hydroborylations of cyclopropene and cyclobutene derivatives have been widely reported.[9,10] It is worth mentioning that the diastereoselectivity control might benefit from the rigid backbones of small rings such as cyclopropene and cyclobutene, while relatively flexible 5-membered rings could be more challenging.

Inspired by the stereoselective hydroborylation of cyclopropenylcarboxyesters and cyclobutenylcarboxyesters,[9,10] we would like to develop a general, complementary approach to access optically-enriched boronyl-cyclopentylcarboxyesters. Here we disclose an efficient, clean and operationally simple method to access an array of optically-enriched boronyl cyclo-

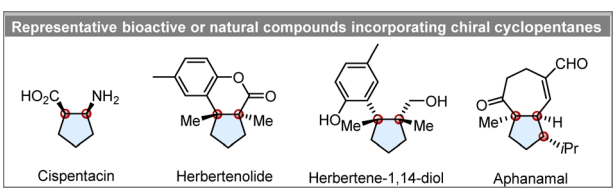

Fig. 1 Representative bioactive or natural cyclopentyl compounds bearing stereogenic centers.

Hangzhou Normal University, College of Material Chemistry and Chemical Engineering, Key Laboratory of Organosilicon Chemistry and Material Technology, Ministry of Education, Key Laboratory of Organosilicon Material Technology of Zhejiang Province, Hangzhou 311121, China. E-mail: zhangpinglu@hznu.edu.cn

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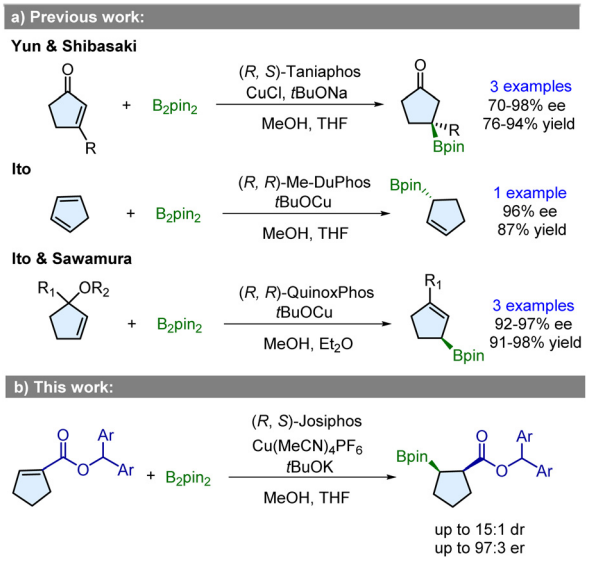


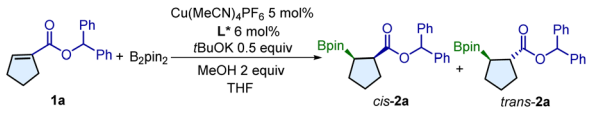
Scheme 1 Catalytic hydroborylation of cyclopentenyl derivatives.

pentylcarboxyester derivatives, by using a copper catalyzed stereoselective hydroborylation. The formed richly functionalized products can be easily applied in further transformation.

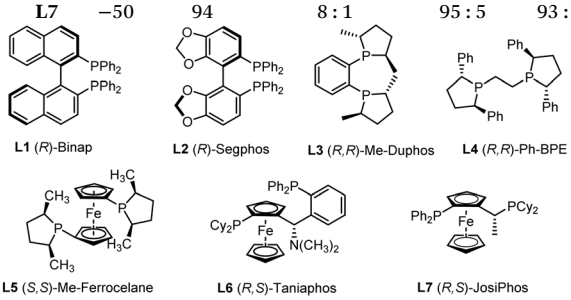
To surmount this challenge, cyclopentene 1-carboxyester **1a** was selected as the model substrate and treated with B_2pin_2 in the presence of 5 mol% copper and various chiral phosphine ligands (Table 1, entries 1–7). Even though several ligands such as Duphos (**L3**) and Taniaphos (**L6**) have been employed in addressing the notorious enantioselectivity issues of asymmetric hydroborylation of cyclopentenes,[6a,8] these ligands did not provide satisfactory results under preoptimized conditions (entries 1–6). Instead, the ferrocene derived Josiphos ligand showed a diastereomeric ratio of 1 : 3 with 83% yield and up to 78% ee (entry 7), with the *trans*-**2a** isomer being the major product. Then, we tried to decrease the reaction temperature for further optimization. Strikingly, when the reaction was set up at −50 °C, the diastereoselectivity was inverted to 8 : 1 compared to that under the reaction conditions at room temperature, affording the *cis*-**2a** isomer as the major product with 95 : 5 er and *trans*-**2a** as the minor product with 93 : 7 er. The inverted diastereoselectivity indicates the *cis*-**2a** might be kinetically favored while *trans*-**2a** tends to be thermodynamically favored. No significant variation in enantioselectivity but a huge discrepancy in diastereoselectivity was observed when using sterically more demanding alcohols (see ESI Table S1†). The relative configuration of *cis*-**2a** was initially suggested by nOe NMR analysis (see ESI Fig. S3†). Its absolute configuration was later confirmed by single-crystal X-ray diffraction.

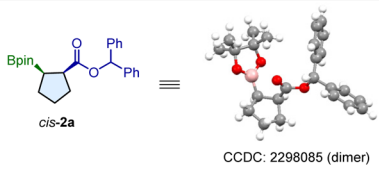
With the optimized reaction conditions in hand, the reaction was further investigated with an array of cyclopentenylcarboxyesters to seek the scope of asymmetric conjugate hydroborylation. In general, the reaction tolerates a wide range of diaryl methyl carboxyesters with different steric and electronic properties. As depicted in Table 2, methyl substituted at the

Table 1 Reaction development[a]



Entry	L*	T (°C)	Yield (%)	Dr cis : trans	er cis-2a	er trans-2b
1	**L1**	rt	74	1 : 2	60 : 40	58 : 42
2	**L2**	rt	75	1 : 2	18 : 82	30 : 70
3	**L3**	rt	85	1 : 1	60 : 40	59 : 41
4	**L4**	rt	74	1 : 2	62 : 38	86 : 14
5	**L5**	rt	91	1 : 2	40 : 60	24 : 76
6	**L6**	rt	45	1 : 4	52 : 48	88 : 12
7	**L7**	rt	83	1 : 3	76 : 24	89 : 11
8	**L7**	−50	94	8 : 1	95 : 5	93 : 7

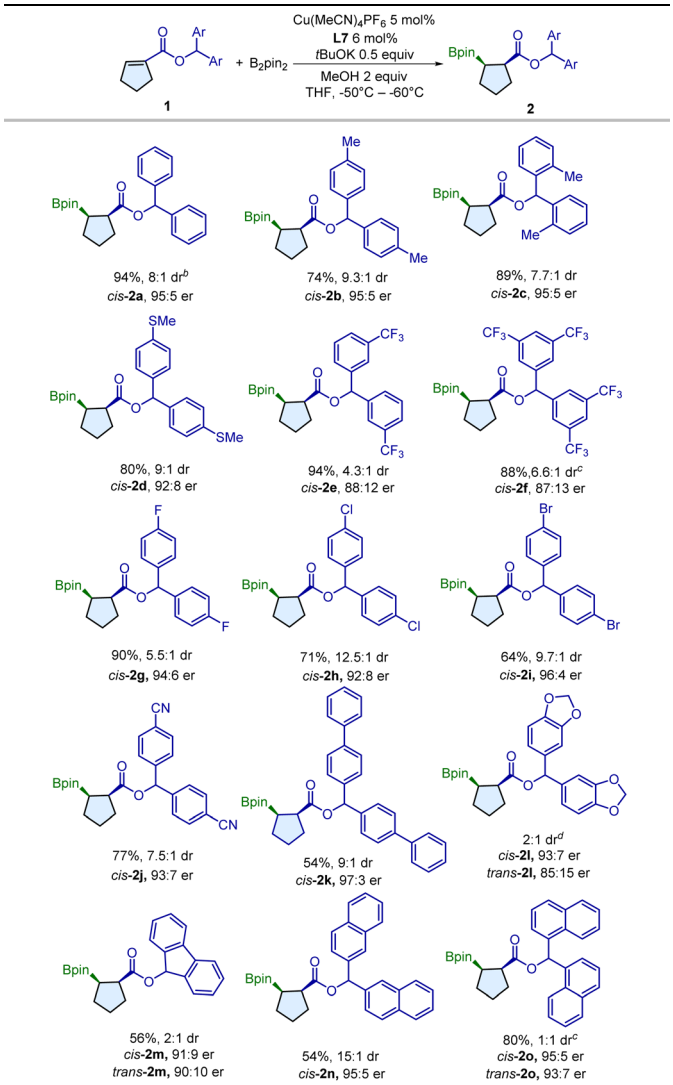




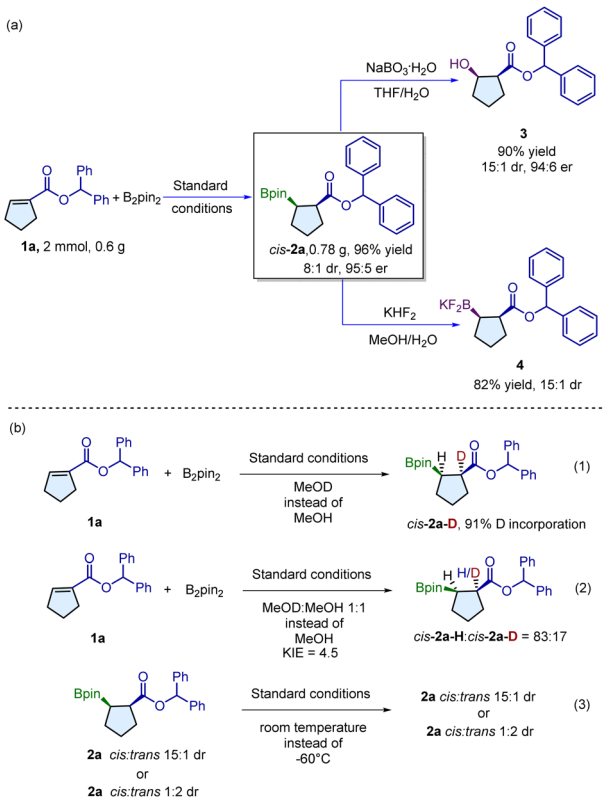
[a] Reactions were performed with substrate **1a** (0.1 mmol), B_2Pin_2 (0.12 mmol, 1.2 equiv.), $Cu(MeCN)_4PF_6$ (5 mol%), ligands (6 mol%), *t*BuOK (0.5 equiv.), MeOH (2 equiv.) in tetrahydrofuran (2 mL); yields are for the isolated compounds; diastereomeric ratio (dr) and enantiomeric ratio (er) were determined by HPLC analysis.

ortho- and *para*-positions of the phenyl group could deliver the products in good diastereoselectivity and 95 : 5 enantiomeric ratio (**2b** and **2c**). In addition, substrates with *meta*-Me substitution, long alkyl chain substitution or multi alkyl substitution on the phenyl group were also tried; however, notorious racemate separation issues in HPLC were observed due to the low polarity of the carbocycle scaffold (see ESI Fig. S1†). Excellent stereoselectivity was afforded with the substrates bearing an electron-donating group such as the –SMe group (**2d**). Notably, the boronyl cyclopentylcarboxyesters bearing electron-donating groups are easily oxidized. Electron-deficient groups, including mono and di-substituted $-CF_3$ groups, were accommodated under these reaction conditions (**2e** and **2f**). Halogens F, Cl, and Br were all tolerated (**2g–2i**), which could be used for potential further transformation handles. Additionally, the nitrile functional group was also tolerated and potentially applicable in further modification (**2j**). The reaction is not limited to phenyl substituted types; the carboxylesters bearing biphenyl, bis-benzo[1,3]dioxol and fluorenyl groups could deliver moderate to good enantioselectivity (**2k–2m**). Besides,

Table 2 Scope of the reaction[a]



[a] Reactions were performed with substrate **1** (0.1 mmol), B_2Pin_2 (0.12 mmol, 1.2 equiv.), $Cu(MeCN)_4PF_6$ (5 mol%), ligands (6 mol%), *t*BuOK (0.5 equiv.), MeOH (2 equiv.) in tetrahydrofuran (2 mL) at −60 °C, yields are for the isolated compounds; diastereoselectivities (dr) were determined by HPLC analysis. [b] Reactions were performed at −50 °C. [c] Sodium *tert*-pentoxide (*t*AmONa) 0.5 equiv. was used. [d] Products could be easily oxidized.



Scheme 2 Synthetic applications and control experiments.

dinaphthyl methyl carboxylesters gave the corresponding boronate products with up to 95 : 5 er. Notably, 2-naphthyl (**1n**) and 1-naththyl (**1o**) substituted esters showed great discrepancy in terms of diastereoselectivity (15 : 1 dr of **2n** and 1 : 1 dr of **2o**, respectively). The absolute configuration of boronyl cyclopentylcarboxyesters was assigned by analogy with *cis*-**2a**.

To further demonstrate the synthetic utility of the products derived from our method, several practical applications were investigated (Scheme 2). First, 2 mmol scale (0.6 g) stereoselective hydroborylation of **1a** was carried out. The reaction furnished 0.78 g of **2a** in 96% yield with 8 : 1 diastereoselectivity and 95 : 5 enantioselectivity (Scheme 2a). The resulting borylated products offered extraordinary synthetic utility for further transformation. Boronate *cis*-**2a** could be oxidatively hydrolyzed to the corresponding alcohol **3** with complete retention of stereogenic centers. Besides, the pinacol ester of *cis*-**2a** could easily transfer to difluoroborolactone **4** after the treatment with KHF_2.

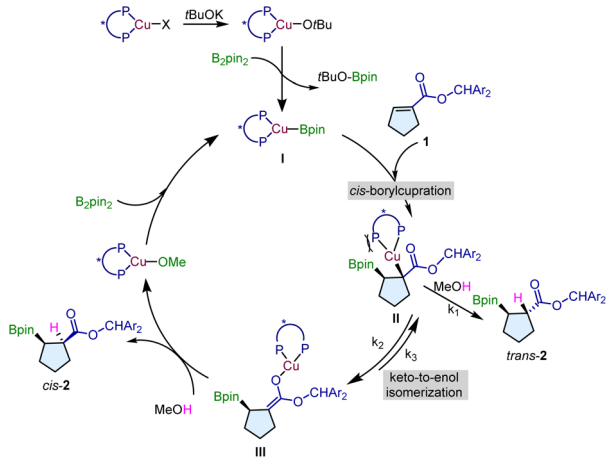
With the aim of gathering preliminary insights into the mechanism, control experiments were performed (Scheme 2b). When deuterated methanol MeOD was applied, the reaction afforded the corresponding product *cis*-**2a-D** with 91% incorporation of deuterium, clearly indicating the protonation of methanol (eqn (1)). Then, an intermolecular competition experiment with MeOH and MeOD was also carried out, and a ratio of 83 : 17 between *cis*-**2a** and *cis*-**2a-D** was afforded with an estimated KIE of 4.5 (ESI Fig. S2†),[11] indicating that the protonation step might be the rate-determining step (eqn (3)).[12] Moreover, control experiments exhibited no significant isomerization of *cis*-**2a** to *trans*-**2a** under the reaction conditions, suggesting an irreversible decupration step in the catalytic cycle (eqn (3)).

The copper catalyzed conjugate borylation has been demonstrated to occur through a *cis*-addition process.[13] However, in this study, the *cis* configuration of compounds **2** caused by a "*trans*-hydroborylative addition" was present as the major isomer. It clearly indicated the involvement of Cu-enolate species in the catalytic cycle, which is isomerized from the carbocupration keto species.[14] On the basis of the literature, Cu-

enolate species in the hydroborylation of α,β-unsaturated ester tends to follow a stepwise mechanism rather than a concerted pathway.[15] Hence, we considered to use modeling calculation to rationalize the high level of enantioselectivity in the presence of **L7**. First, the possible configurations of π complexes were proposed as shown in Fig. 2a, in which the copper was located in prochiral faces of the cyclopentene ring. The DFT calculations suggested that when the copper approached the *Re* face of the cyclopentene ring, the resulting Cu-enolate species **A** was found to be more stable, while its enantiomer **B** would be 12.6 kJ mol^{-1} less favored. Even though it did not provide a detailed transition state analysis, this result clearly showed an estimate of the relatively favored configuration that leads to the major isomer.

In terms of diastereoselectivity, after the tautomerization of the carbocupration keto species, the proton source preferred to approach the carbocupration enolate species from the opposite side of the adjacent boryl group to avoid steric repulsion (**C** in Fig. 2b), which is the key process for the diastereoselective proton-decupration. Moreover, a plausible six-membered transition state in model **C** featuring a geometry with higher stability might be involved.

Accordingly, a tentative mechanism is proposed and displayed in Scheme 3. As the initiator of the reaction, Cu-Bpin species **I** with the bisphosphine ligand was formed by a σ-bond metathesis of copper *tert*-butoxide species with B_2pin_2.[16] This species tends to coordinate to the double bonds and a *cis*-addition gives carbocupration keto species **II**. This borylcupration process is supposed to be the enantio-determining step. The stereospecific protonation of species **II** by methanol could occur rapidly at room temperature, affording the corresponding *trans*-**2** as the major product. In parallel, carbocupration keto species **II** is potentially in equilibrium with Cu-enolate species **III** *via* a keto–enol isomerization. The main driving force would be the steric hindrance between the bisphosphine ligand and diaryl methyl carboxyesters, and the enolate form might be kinetically favored. Then, a diastereoselective protonation of **III** followed to afford the *cis*-**2** products and the regeneration of the copper-alkoxide species. Notably, the level of diastereoselectivity might be a compromised result of proton-decupration of both **II** and **III**, although the isomerization process is likely to be favored ($k_2 > k_1$) at lower temperature.



Scheme 3 Plausible mechanism.

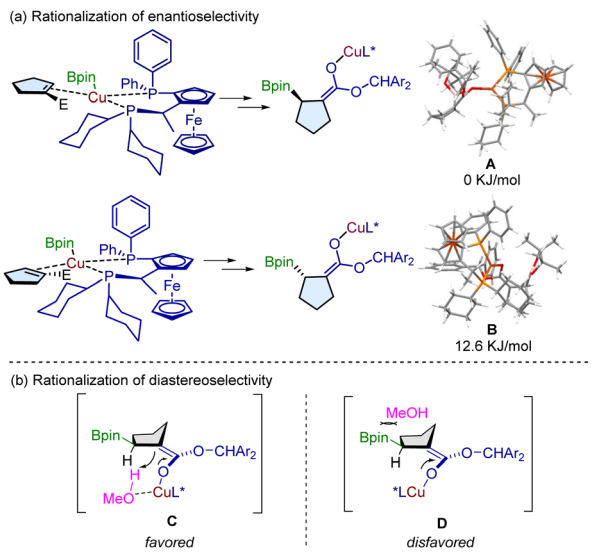


Fig. 2 Proposed enantio- and diastereoselectivity models for the conjugate borylation.

Conclusions

In summary, we have developed an efficient diastereoselective and enantioselective method to synthesize boronyl-cyclopentylcarboxyesters, by using a copper catalyzed conjugate hydroborylation of cyclopentenylcarboxyesters. Our methodology enables access to an array of enantio-enriched boronyl-cyclopentylcarboxyesters bearing consecutive stereogenic centers. The corresponding products represent highly attractive reagents for further synthetic utility. Both enantioselective and diastereoselective models are proposed to rationalize the selectivity, and the rate-determining step, the enantio-determining step and the diastereo-determining step are all carefully explored. This study will enrich the toolbox of the stereoselective synthesis of chiral carbocycles containing consecutive stereogenic centers, illustrating the practical application of using cyclopentyl boronates as platform structures in diverse fields.

Author contributions

Y. Y. developed the methodology of hydroborylation, synthesized the substrates and studied the scope of the reaction; M. H., C. C. and H. Z. helped in synthesizing the substrates; Z. Li and G. L. supervised M. H. P. Zhang designed the study,

supervised it and wrote the paper. All authors contributed to amending the manuscript.

Conflicts of interest

There are no conflicts to declare.

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