A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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Accepted Article

Title: Cobalt-Catalyzed Enantioselective Synthesis of Chiral gem-Bisborylalkanes

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201805705
Angew. Chem. 10.1002/ange.201805705

Link to VoR: http://dx.doi.org/10.1002/anie.201805705
http://dx.doi.org/10.1002/ange.201805705

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10.1002/anie.201805705

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Cobalt-Catalyzed Enantioselective Synthesis of Chiral *gem*-Bisborylalkanes

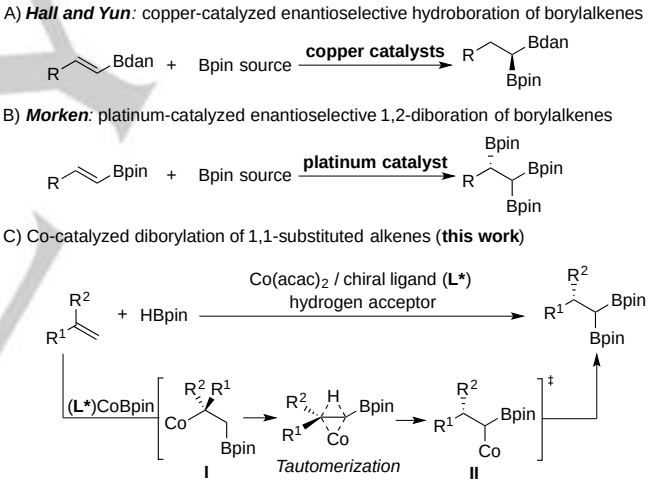
Wei Jie Teo and Shaozhong Ge*

Abstract: We report an asymmetric synthesis of enantio-enriched *gem*-bisborylalkanes via enantioselective diborylation of 1,1-disubstituted alkenes catalyzed by $Co(acac)_2$/(*R*)-DM-segphos. A range of activated and unactivate alkenes underwent this asymmetric diborylation in the presence of cyclooctene as a hydrogen acceptor, affording the corresponding *gem*-bisborylalkanes with high enantioselectivity. The synthetic utilities of these chiral organoboronate compounds were exemplified through several stereospecific derivatizations and the synthesis of sesquiterpenes and sesquiterpenoids natural products.

gem-Bisborylalkanes have been emerging as synthetically versatile building blocks for organic synthesis owing to their diverse reactivity developed in recent years.[1] For example, the carbanion[2],[3] generated from the *gem*-bisborylalkanes in the presence of base is stabilized by the adjacent boron atom through hyperconjugation[3a] and enables stereo- and chemoselective C-C bond construction with the possibility for further functionalization of the C-B bond.[2j, 3f, 3r] Accordingly, the development of protocols for the synthesis of such *gem*-bisboronate compounds has been extensively explored and well established.[4] Nevertheless, these synthetic methodologies are mainly focused on the synthesis of achiral *gem*-bisborylalkanes or non-asymmetric synthesis of their chiral congeners. Due to their potential stereospecific transformations, it is of particular importance to develop enantioselective protocols for the asymmetric synthesis of chiral *gem*-bisborylalkanes.

To date, asymmetric catalytic synthesis of *gem*-bisborylalkanes has been limited to enantioselective metal-catalyzed hydroboration or diborylation of (*E*)-vinylboronates. In 2011 and 2013, the Hall[5] and Yun[6] groups, respectively, reported the synthesis of chiral *gem*-bisborylalkanes via copper-catalyzed hydroboration of vinylboronates (Scheme 1A). In 2014, Morken and coworkers reported a platinum-catalyzed diborylation of vinylboronates to prepare chiral 1,1,2-trisborylalkanes (Scheme 1B).[7] However, a general enantioselective method for the synthesis of chiral *gem*-bisborylalkanes from readily available starting materials still remains unknown. As part of our group's continuing effort in developing base-metal-catalyzed hydrofunctionalization of olefins,[8] we are interested in developing a general, enantioselective method to synthesize chiral *gem*-bisborylalkanes from 1,1-disubstituted olefins, thus enhancing the synthetic utility of chiral *gem*-bisborylalkanes in chemical synthesis.

We have previously reported a cobalt-catalyzed non-asymmetric diborylation of 1,1-substituted vinylarenes with pinacolborane (HBpin).[9] This reaction occurs through a Co-Bpin intermediate, which is generated through cobalt-mediated hydrogenation of norbornene with HBpin. To develop an asymmetric diborylation (Scheme 1C), we rationalized that enantioselective migratory insertion of 1,1-disubstituted into a chiral cobalt-boryl species (**L***)Co-Bpin generates a diastereomeric intermediate **I**, which undergoes stereospecific tautomerization to form a chiral α-(boryl)alkyl cobalt species **II**. This alkylcobalt intermediate reacts with HBpin to yield an enantiomerically enriched *gem*-bisborylalkane product. In this communication, we report the development of this catalytic asymmetric diborylation with a cobalt catalyst supported by a chiral bisphosphine ligand and with cyclooctene as a hydrogen acceptor. In addition, we also demonstrate the synthetic utilities of these *gem*-bisborylalkane products by showing that they can be readily derivatized into a variety of other synthetically versatile chiral molecules, including several naturally occurring sesquiterpenes and sesquiterpenoids.



Scheme 1. Synthetic access to chiral *gem*-sisboryl compounds.

We initiated the study by identifying a selective chiral cobalt catalyst and reliable conditions for enantioselective diborylation of α-methylstyrene with HBpin. A variety of chiral bisphosphine ligands and hydrogen acceptors were evaluated, and the selected examples are summarized in Table 1. These reactions were conducted with 2 mol % $Co(acac)_2$ and 2.2 mol % ligand at room temperature in the presence of 1.2 equiv. of cyclic olefins as a hydrogen acceptor. In general, these reactions proceeded to full conversion of α-methylstyrene under identified conditions in 24 h and afforded mono-boronate **2a** and *gem*-bisborylalkane **3a** with various ratios. Alkylboronate compounds **2a** and **3a** can be readily separated by flash chromatography on silica.

The data in Table 1 indicate that hydrogen acceptors do not affect the enantioselectivity, but do have a noticeable influence on the chemoselectivity of this reaction when catalyzed by

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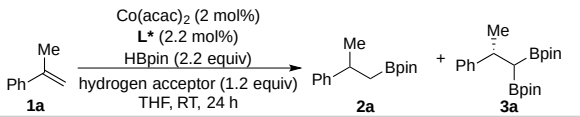
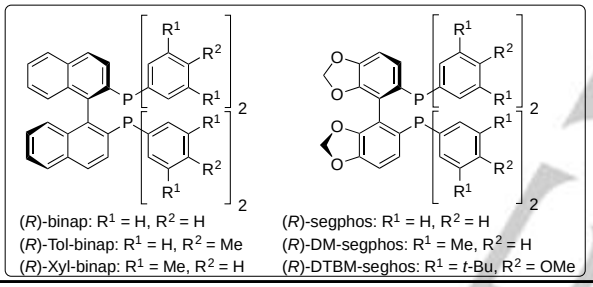
10.1002/anie.201805705

$Co(acac)_2$/(*R*)-DM-segphos (entries 1–5), with the use of cyclooctene providing a high yield of **3a** (entry 5). The reactions conducted with the catalysts generated from the combination of $Co(acac)_2$ and other bisphosphine ligands, such as (*R*)-binap, (*R*)-Tol-binap, (*R*)-Xyl-binap, (*R*)-segphos, or (*R*)-DTBM-segphos, proceeded with modest enantioselectivity (entries 6–10). Furthermore, the reaction run at a lower concentration occurred in a lower yield than the reaction run at a higher concentration (entries 5 and 11).

Table 1. Evaluation of Conditions for Diborylation of *α*-methylstyrene.[a]



entry	hydrogen acceptor	Ligand	2a:3a[b]	yield of 3a[b]	ee% of 3a[c]
1	--	(*R*)-DM-segphos	65:35	34%	92%
2	norbornene	(*R*)-DM-segphos	69:31[d]	27%	92%
3	cyclohexene	(*R*)-DM-segphos	30:70	57%	92%
4	cycloheptene	(*R*)-DM-segphos	40:60	58%	92%
5	cyclooctene	(*R*)-DM-segphos	20:80[d]	67%	92%
6	cyclooctene	(*R*)-binap	63:37	33%	44%
7	cyclooctene	(*R*)-Tol-binap	58:42	37%	68%
8	cyclooctene	(*R*)-Xyl-binap	41:59	49%	84%
9	cyclooctene	(*R*)-segphos	43:57	39%	62%
10	cyclooctene	(*R*)-DTBM-segphos	83:17	<10%	not detected
11[e]	cyclooctene	(*R*)-DM-segphos	42:58	49%	92%

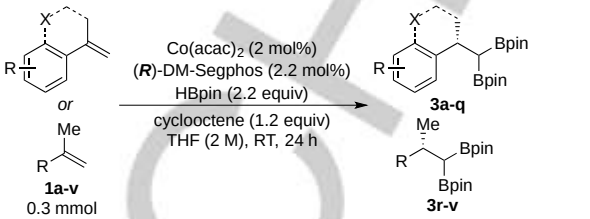


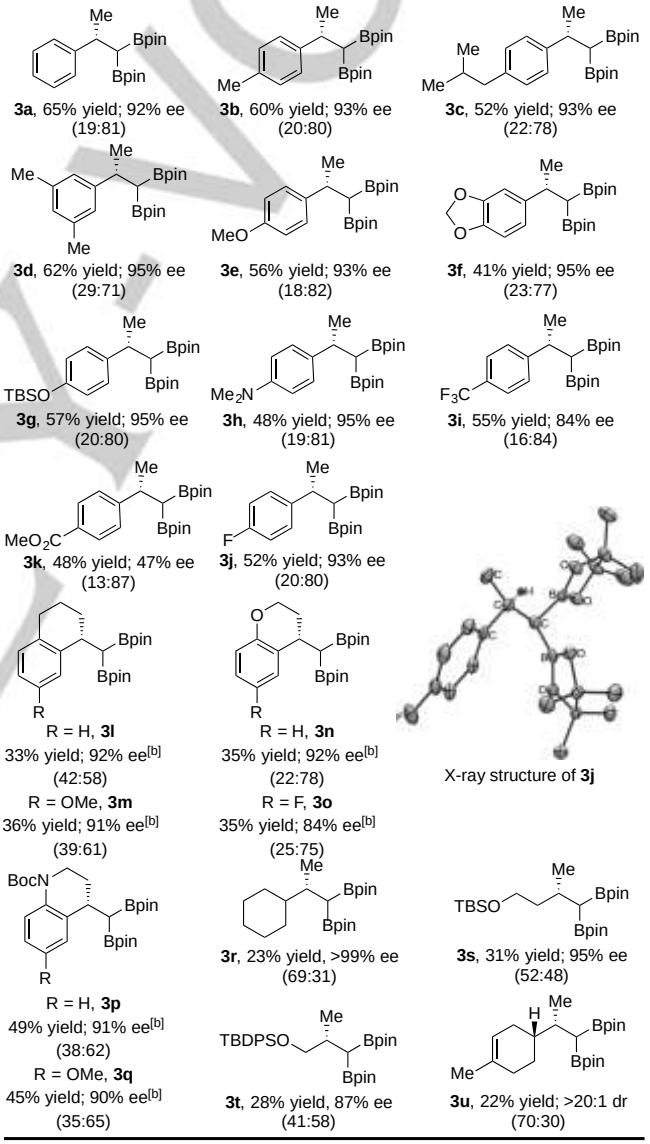
[a] Conditions: *α*-methylstyrene (0.10 mmol), pinacolborane (0.22 mmol), $Co(acac)_2$ (2.0 μmol), ligand (2.2 μmol), hydrogen acceptor (0.12 mmol), THF (50 μL), RT, 24 h; [b] ratio of **2a**:**3a** and yield of **3a** were determined by ^{1}H NMR with toluene (0.10 mmol) as the internal standard; [c] ee was determined by chiral HPLC analysis; [d] ee of **2a** is 6% ee for entry 2 and 4% for entry 5; [e] THF (100 μL).

Under the identified conditions (entry 5 in Table 1), we studied the scope of 1,1-disubstituted alkenes that undergo this cobalt-catalyzed diborylation, and the results are summarized in Table 2. In general, a range of 1,1-disubstituted alkenes reacted smoothly to afford the corresponding chiral *gem*-bisborylalkanes (**3a**–**3u**) in modest to good isolated yields with high enantioselectivity (84–99% ee). The absolute configuration of **3j** was assigned as (*R*) by single crystal X-ray diffraction analysis.

The data in Table 2 indicate that the electronic property of aryl groups of vinylarenes has a noticeable influence on the enantioselectivity of this asymmetric transformation. For example, vinylarenes containing electron rich aryl groups (**3e**–**3h**) reacted with much higher enantioselectivity than vinylarenes containing electron poor aryl groups (**3i** and **3j**). In addition, the substitution pattern of aryl groups also has a significant effect on this reaction. For example, a variety of vinylarenes (**1b**–**1h**) containing *para*- or *meta*-substituted aryl group reacted to give bisboryl compounds **3b**–**3h** in good isolated yields (48-62%) and high enantioselectivity (93-95% ee), but vinylarenes containing *ortho*-substituted aryl groups reacted very sluggishly and yielded only trace amounts of the desired bisboryl products. Furthermore, 6-membered cyclic vinylarenes resembling naturally occurring tetralones (**3l** and **3m**), chromanones (**3n** and **3o**) and quinines (**3p** and **3q**) also reacted with high enantioselectivity (84–92% ee), albeit in low to moderate isolated yields (33–49%).

Table 2. The scope of alkenes for this asymmetric diborylation. [a]



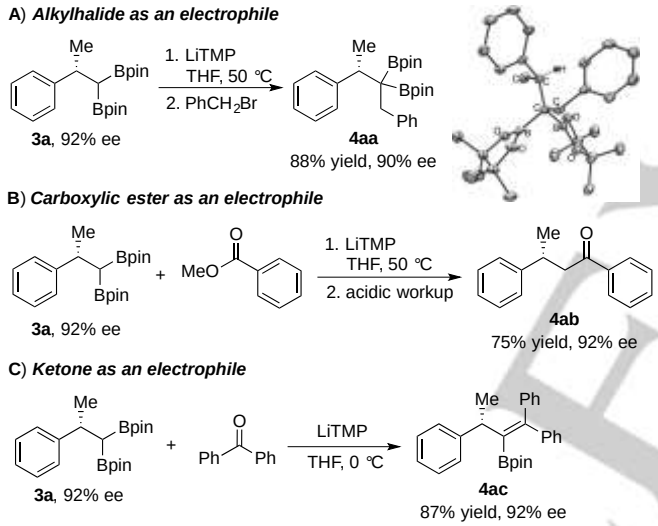


[a] Conditions: alkene (0.300 mmol), pinacolborane (0.660 mmol), $Co(acac)_2$ (4.0 μmol), (*R*)-DM-segphos (4.4 μmol), cyclooctene (0.360 mmol), THF (150 μL), RT, 24 h, yields of isolated products; the ratio of monoborylalkane and bisborylalkane products (**2**:**3**, determined by GC analysis) was listed in parentheses. [b] $Co(acac)_2$ (9.0 μmol), (*R*)-DM-segphos (9.9 μmol).

Unactivated 1,1-substituted alkenes (**1r**–**1u**) also underwent this transformation to provide enantiomerically enriched *gem*-bisborylalkanes in good to excellent enantioselectivity (87 to >99% ee), albeit in low isolated yields. The absolute

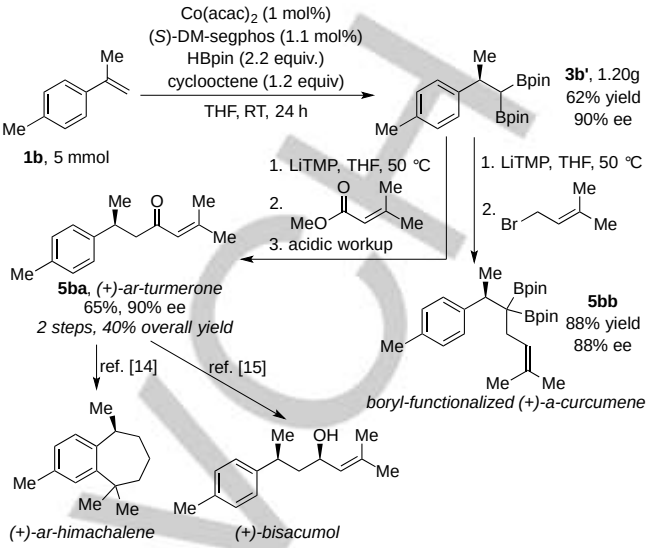
configuration of **3s** was determined by converting **3s** to the corresponding aldehyde and comparing its optical rotation with a known chiral aldehyde analog (see supporting information). In addition, an enantiomerically pure 1,1-disubstituted alkene **1u** also reacted to afford *gem*-bisborylalkane **3u** with excellent diastereoselectivity (dr > 20:1). The low yields for the reactions of these unactivated alkenes are resulted from poor chemoselectivity caused by the comparable reactivity of the hydrogen acceptor and the alkene substrate.

The synthetic significance of these chiral *gem*-bisborylalkane products has been shown by several stereospecific transformations they underwent without significant loss of enantiopurity, and the selected examples are summarized in Scheme 2. The carbanion generated from the deprotonation of **3a** with LiTMP was readily alkylated with benzyl bromide to yield a chiral internal *gem*-bisborylalkene **4aa** (Scheme 2A). Methyl benzoate also reacted with the carbanion derived from **3a**, affording a chiral ketone **4ab** in 75% isolated yield after quenching with a proton source (Scheme 2B). In addition, **3a** underwent a boron-Wittig reaction with benzophenone to generate a chiral vinylboronate **4ac** in high yield and with high enantioselectivity (Scheme 2C).

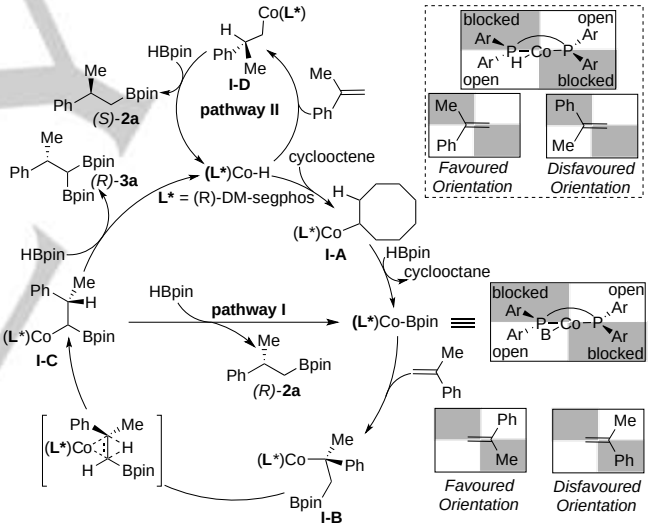


Scheme 2. Transformations of product **3a**. TMP = tetramethylpiperidide.

Subsequently, we studied the synthetic applications of these *gem*-bisborylalkanes for natural product synthesis.[10] A library of naturally occurring sesquiterpenoid, sesquiterpene and their derivatives can be accessed through this asymmetric *gem*-diborylation reaction (Scheme 3). First, a gram-scale production of **3b'**, the opposite enantiomer of **3b**, was developed with 1 mol % $Co(acac)_2$ and 1.1 mol % (*S*)-DM-segphos. This gram-scale reaction proceeded with a yield and enantioselectivity similar to those of a 0.200 mmol scale reaction. Then, we achieved the synthesis of (+)-*ar*-turmerone **5ba**, an active compound found in rhizome of *Curcuma longa* with known biological properties,[11] in 65% isolated yield and 90% ee from **3b'** through the lithiation with LiTMP, the reaction with methyl 3,3-dimethylacrylate, and acidic workup. This represents the simplest method to date for the total synthesis of (+)-*ar*-turmerone,[12] which can be further converted to natural occurring flee beetle pheromone, (+)-*ar*-himachalene[13] and cytotoxic (+)-*bisacumol*,[14] found in the roots of *Curcuma xanthorrhiza*. In addition, *gem*-bisboryl functionalized (+)-*α*-curcumene, **5bb**, could also be synthesized from **3b'** in high isolated yield with good enantioselectivity.



Scheme 3. Formal synthesis of natural products from chiral *gem*-bisborylalkanes. TMP = tetramethylpiperidide.



Scheme 4. Proposed catalytic pathways for the production of **2a** and **3a**.

Based on our previously mechanistic study on the achiral Co-catalyzed *gem*-diborylation reaction,[9] we depict, in Scheme 4, the catalytic pathways for the production of monoborylalkane **2a** and *gem*-bisborylalkane **3a**. For the asymmetric production of **3a**, the chirality induction step is the insertion of α-methylstyrene to a chiral Co^{I}-Bpin species to form intermediate **I-B**, which undergoes stereospecific σ,π,σ-tautomerization to form **I-C** through a highly ordered cyclic transition state.[15] Using the quadrant model for C_2-symmetical bisphosphine ligands,[16] we propose that α-methylstyrene approaches the Co-Bpin bond in a way that can minimize the steric repulsion between the phenyl group of the olefin and the aryl group of the ligand. Monoborylalkane **2a** can be generated through two pathways via a Co-Bpin (for **pathway I**) or Co-H intermediate (for **pathway II**), respectively. However, product **2a** generated via these two

pathways has opposite absolute configurations ((*R*)-**2a** for **pathway I** and (*S*)-**2a** for **pathway II** as predicted using the quadrant model), which may account for the low ee obtained for **2a** in Table 1.

In summary, we have developed an enantioselective protocol to prepare chiral *gem*-bisborylalkanes by cobalt-catalyzed diborylation of 1,1-disubstituted alkenes with pinacolborane in the presence of cyclooctene as a hydrogen acceptor. Both activated and non-activated 1,1-disubstituted alkenes underwent this asymmetric diborylation with high enantioselectivity. These chiral *gem*-bisborylalkane products can be converted readily to a variety of chiral molecules and natural products by standard functional group manipulations. Further applications of this cobalt-catalyzed asymmetric diborylation on the synthesis of complex molecules will be the subjects for future studies.

Acknowledgements

This work was supported by the National University of Singapore (R-143-000-630-133) and the Ministry of Education (MOE) of Singapore (No. R-143-000-A07-112).

Keywords: asymmetric diborylation • cobalt • *gem*-bisborylalkane • alkenes • homogeneous catalysis

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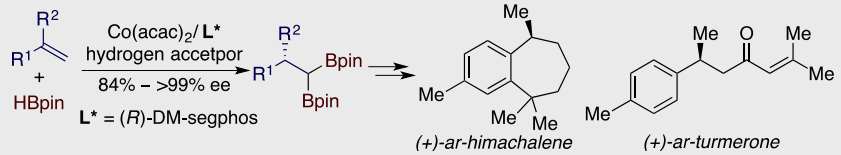

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Cobalt-Catalyzed Enantioselective Synthesis of Chiral *gem*-Bisborylalkanes

Asymmetric Catalysis: A highly enantioselective synthesis of chiral bisborylalkanes through cobalt-catalyzed asymmetric diborylation of *gem*-disubstituted alkenes was developed (see the Picture). The synthetic utilities of these chiral gem-bisborylalkane products were exemplified through several stereospecific derivatizations and the synthesis of sesquiterpenes and sesquiterpenoids natural products.