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Enantioselective Reductive Coupling of Imines Templated by Chiral Diboron

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ABSTRACT:. We herein report a general, practical, and highly efficient method for asymmetric synthesis of a wide range of chiral vicinal diamines via reductive coupling of imines templated by chiral diboron. The protocol features high enantioselectivity and stereospecificity, mild reaction conditions, simple operating procedures, use of readily available starting materials, and a broad substrate scope. The method signifies the generality of diboron-enabled [3,3]-sigmatropic rearrangement.

Chiral vicinal diamines are privileged substructures ubiquitously found in active pharmaceutical ingredients,[1] natural products,[2] agrochemicals,[3] as well as a number of ligands or catalysts in the field of asymmetric catalysis.[4] Their syntheses have drawn considerable attention in organic chemistry. However, most known methods (Figure 1a) including olefin diamination,[5] nucleophilic addition of diimines,[6] diimine reduction,[7] and radical coupling of imines only lead to racemic mixtures of vicinal diamines,[8] half of which are undesired waste. Moreover, the often concomitant formation of the *meso* diastereomer with most methods further compromises the yield of the desired product in addition to the requirement of a tedious purification procedure. Syntheses from chiral building blocks or auxiliaries provide improved yields but require additional synthetic steps on the expenses of valuable chiral starting materials (Figure. 1b).[9,10] It remains a significant challenge for efficient synthesis of chiral vicinal diamines with excellent yields, selectivities, and practicality. We herein report a general, simple, and practical method for the synthesis of a wide range of chiral vicinal diamines by developing a chiral diboron-templated reductive coupling of imines. The protocol features excellent yields, enantioselectivities and stereospecificities, mild reaction conditions, simple operating procedures, use of readily available starting materials,[11] and a broad substrate scope.

Diborons are often applied to carbon-boron bond-forming reaction under action of a transition metal catalyst.[12] They are also able to react with electrophiles in the presence of a base under transition metal-free conditions through heterolytic activation (Figure. 1c),[13,14] or generate radical species via

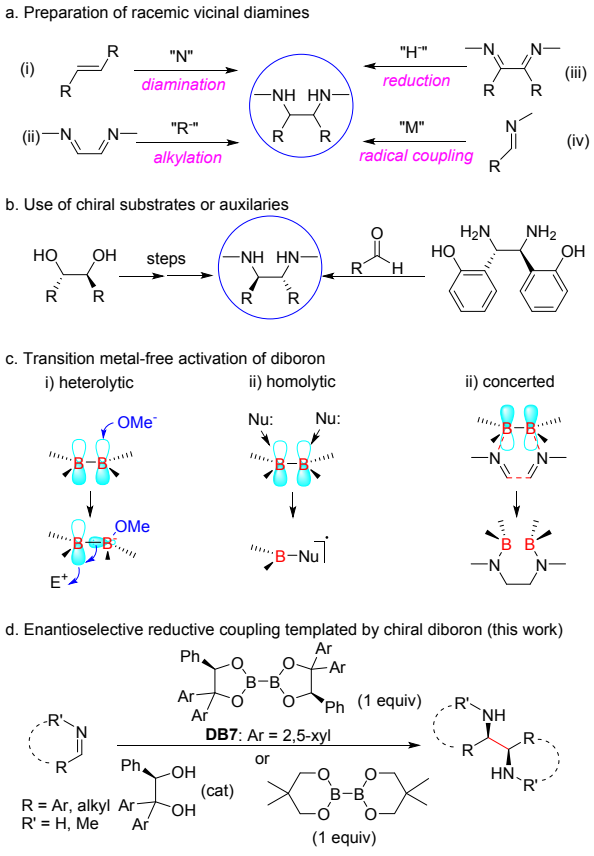

Figure. 1. Syntheses of vicinal diamines.

homolytic cleavage in the presence of nucleophiles.[15,16] Activation of two reactants by a diboron species in a concerted

fashion is rarely explored and will be particularly interesting and synthetically useful in forming a carbon-carbon bond with high stereochemical fidelity. With the employment of a diboron modified by a chiral diol, the chiral diboron can act as an excellent reductive "template" for constructing a carbon-carbon bond with high stereospecificity and enantioselectivity. We previously reported a reductive coupling of isoquinolines in high yields, excellent enantioselectivities, and stereospecificities by employing a chiral diboron reagent, where a concerted diboron-enabled [3,3]-sigmatropic rearrangement was discovered to form a carbon-carbon bond with excellent stereochemical fidelity.[17] We envisioned that the chiral diboron-templated reductive couplings would be applicable to various imine substrates and the application of the concerted diboron-enabled [3,3]-sigmatropic rearrangement can be expanded to a more general term.[18] Herein we report a general, practical, and highly efficient method for the synthesis of a wide range of chiral vicinal diamines via reductive coupling of various imines templated by chiral diboron (Figure. 1d).

Our proof-of-concept experiment started with reductive coupling of phenylmethanimine **2a**, which can be generated *in situ* from benzaldehyde **1a** and ammonia. A series of chiral diboron **DB1-7** were applied to the reaction using THF as the solvent at room temperature (Figure. 2). Encouragingly, the diboron **DB1** derived from chiral pinanediol provided **3a** in 80% yield and 20% ee. Use of **DB2** derived from (*R*)-1,1-diphenylpropane-1,2-diol formed **3a** in 70% yield and 36% ee. 51% ee was obtained when **DB3** prepared from (1*R*,2*R*)-1,2-diphenylethane-1,2-diol was employed. Interestingly, the diboron **DB4** derived from a non-C_2-symmetric chiral diol was also applicable, forming **3a** in 57% ee. Use of a sterically bulkier diboron **DB5** provided an excellent yield (87%), but did not give a better ee. Pleasingly, product **3a** was formed in 80% ee when **DB6** derived from a more hindered chiral diol, (*R*)-2-phenyl-1,1-di-*o*-tolylethane-1,2-diol, was employed. Further optimization of the diboron structure led to the development of **DB7**, which provided an excellent yield (90%) and ee (95%).

The chiral diboron **DB7** proved to be highly effective for reductive coupling of a wide range of aromatic aldimines. Excellent ee's and yields were achieved through the single-step process for a series of 1,1'-diaryl-substituted vicinal diamines **3**. Various substituents either with electron-donating or withdrawing properties regardless at *para*, *ortho*, *meta* position of the benzene ring were all compatible. A number of functionalities such as halogen, ester, alkoxy, alkynyl, and tertiary amine were well tolerable. Heterocycles such as furan and thiophene as well as naphthalene ring were applicable. It should be noted that no formation of *meso* diamine side-product was observed in every example listed in Figure 3, and most products were formed in extremely high enantioselectivities (99% ee's). A chiral steroid skeleton was also compatible, while the chirality of the diamine moiety in homocoupling product was dictated by the chirality of the diboron, leading to a diastereomeric mixture of **3bb** or **3cc** with either ~9:1 or ~1:9 ratio. Besides aromatic aldimines, aliphatic aldimines could also be applied to the single-step protocol to form a series of 1,1'-dialkyl-substituted vicinal diamines **6** in satisfactory yields and almost perfect enantioselectivities. Unlike aromatic aldimines which could be prepared from the corresponding aldehydes, aliphatic aldimines **5** were prepared *in situ* from the corresponding nitriles **4** through DIBAL-H reduction and applied directly with **DB7** for the reductive coupling.[19] Besides chiral vicinal diamines **6a-c**, **6n** with primary alkyl substituents, substituents with secondary alkyl (**6d-e**), benzyl and substituted benzyl, thiophene-, alkene-, and alkyne-incorporated alkyl were all compatible. The presence of halogen, alkene, and alkyne functionalities were amenable for further derivatization. Cyclic imines **7** were also applicable for enantioselective reductive couplings.[20] Thus, chiral 2,2'-bipyrrolidine (**8a**), 2,2'-bipiperidine (**8b**), 1,1'-octahydrobiisoquinoline (**8c**), and 5,5'-tetrahydrobidibenzo[*c*,*e*]azepine (**8d**) were formed in almost perfect ee's and good yields in a single step from corresponding cyclic imines. *N*-Methyl aromatic aldimines **9** could also be efficiently prepared from corresponding aldehyde **1**. We were pleased that such imines were suitable substrates for the diboron-templated reductive coupling, for a range of *N,N'*-dimethyl 1,1'-diaryl-substituted vicinal diamines in excellent ee's and yields. Such chiral building blocks required a lengthy synthetic sequence otherwise, which were applied frequently as ligand in transition metal-catalyzed cross-coupling reactions.[21] Unfortunately, a bulkier *N*-alkyl aromatic aldimines such as *N*-ethyl benzaldimine was inactive.

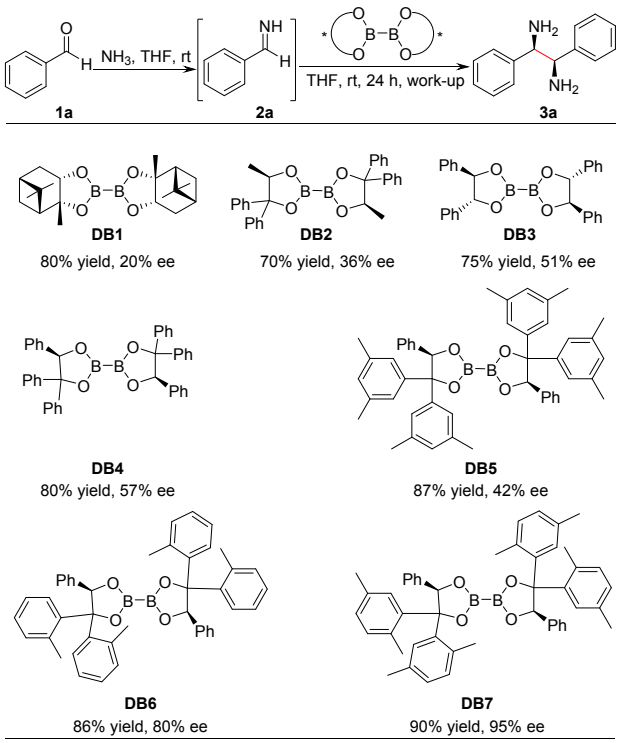

Figure. 2. Proof-of-concept experiment. Reactions were carried out at rt in THF (2 mL) with **1a** (0.5 mmol) and ammonia (15 equiv, 7.5 mmol, 7 M in MeOH) for 1 h followed by addition of chiral diboron (0.5 equiv, 0.25 mmol). The mixture was further stired at rt for 24 h. Isolated yields. The ee values were determined by chiral HPLC analysis.

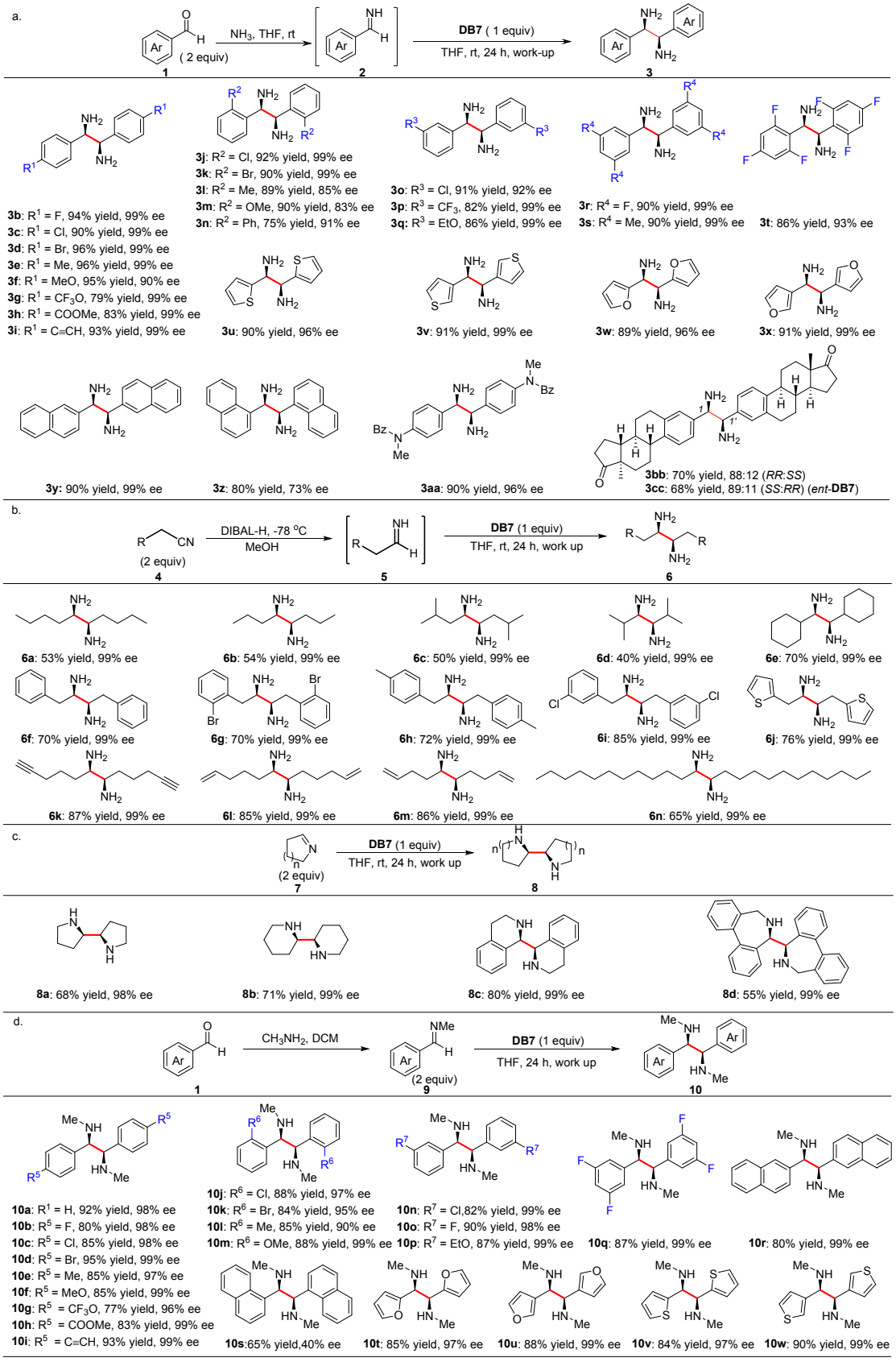

Figure. 3. Chiral diboron-templated enantioselective reductive coupling of imines. All yields are of isolated products. The ee values were determined by chiral HPLC analysis. **a**. Reactions were carried out at rt in THF (1 mL) with **1** (0.2 mmol) and ammonia (15 equiv,

3.0 mmol, 7 M in MeOH) for 1 h followed by addition of **DB7** (0.1 mmol). The mixture was further stired at rt for 24 h. **b**. Reactions were carried out in THF (1 mL) at -78 °C with nitrile **4** (0.6 mmol) and DIBAL-H (0.6 mmol) for 3h, and then warmed to rt, followed by the addition of **DB7** (0. 3 mmol) and MeOH (0.66 mmol) at -78 °C. The mixture was further stirred at rt for 12 h. **c**.Reactions were carried out at rt in THF (1 mL) with **7** (1.0 mmol) and **DB7** (0.5 mmol) for 12 h. **d**. Imine **9** was prepared from **1** and $MeNH_2$ in DCM. Reductive couplings of **9** were carried out at rt in THF (1 mL) with **9** (0.5 mmol) and **DB7** (0.25 mmol) for 12 h

The chiral diboron templated reductive coupling of imines were not limited to the stoichiometric use of chiral diboron **DB7**. For reductive coupling of stable aromatic imines **2** or **9**, the employment of a stoichiometric amount of $(BNeop)_2$ (**11**) and a catalytic amount of chiral diol **12** for the enantioselective reductive coupling was equally effective (Figure. 4). Thus, by employing bis(neopentyl glycolato)diboron as the nonchiral diboron source and 30 mol % of chiral diol **12** as the catalyst, the enantioselective reductive coupling of **9a** proceeded

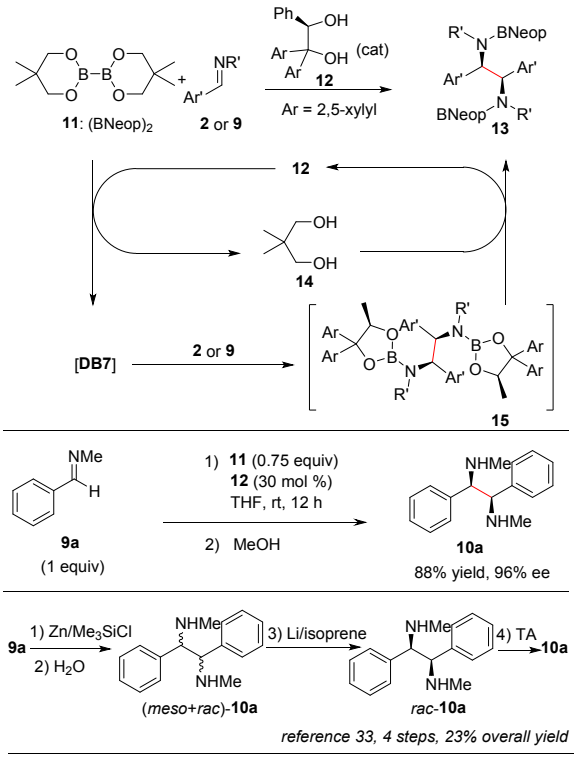

Figure. 4. Asymmetric reductive coupling with a catalytic amount of chiral diol

smoothly to form **10a**, an effective chiral ligand for asymmetric hydrogenation, in 88% yield and 96% ee. Besides a much simpler operation procedure, the yield was significantly better than the reported 23% yield using the zinc-mediated radical coupling-lithium-mediated isomerization-resolution protocol.[22] Noteworthy was the dramatic acceleration effect by chiral diol **12**. No reductive coupling was observed when $(BNeop)_2$ was mixed with **9a.** The reaction proceeded to completion over 24 h when **12** was added, indicating the significance of chiral diboron **DB7** in promoting both enantioselectivity and reactivity.

To test the scalability of the reaction, synthesis of **3a** at a decagram scale was pursued (Figure. 5a). Treatment of (*R*)-mandelic acid derivative **16** with 2,5-xylyl Grignard reagent formed chiral diol **12** in 62% yield. Reaction of **12** with tetrahydroxydiboron in THF formed **DB7** in almost quantitative yield, which was prepared in a kilogram scale. To a solution of **1a** (50 g) dissolved in NH_3/MeOH (7 M, 1.1 L) was charged **DB7** (168 g) and the mixture was stirred at rt for 24 h. Acidic/basic work-up provided product **3a** (40 g) as white solid in 80% isolated yield and 95% ee, along with 90% recovery of chiral diol **12** (147 g). The method constituted one of most efficient protocols for the synthesis of a wide array of chiral vicinal diamines.

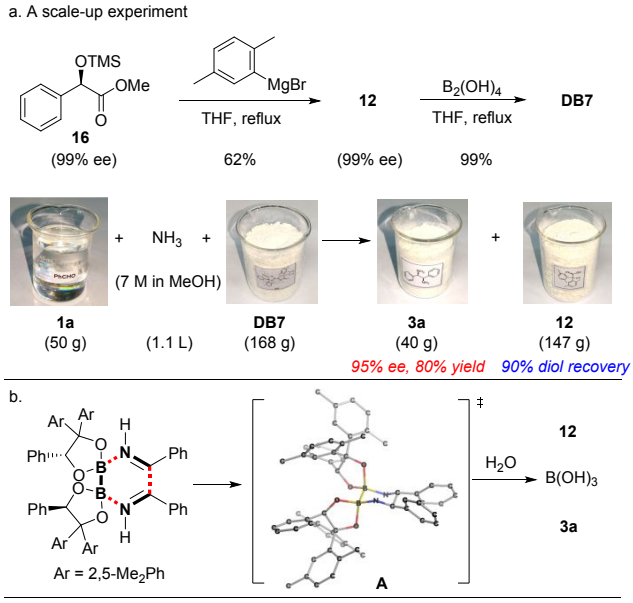

Figure. 5. A scale-up experiment and stereochemical model

The high yields and enantioselectivities achieved on a variety of chiral vicinal diamines and the fact that no *meso* products were observed in any case further corroborated the generality of diboron-enabled [3,3]-sigmatropic rearrangement process. The successful protocol of employment of $(BNeop)_2$ as the diboron source and diol **12** as the catalyst further proved the importance of the chiral diboron structure in promoting both reactivity and enantioselectivity. It appeared that the sterically bulky and rigid dioxaborolane of the diboron are crucial in providing an effective six-membered ring transition state **A** (Figure. 5b), thereby allowing the highly efficient reductive coupling to proceed. With the compact and rigid diboron moiety with four 2,5-xylyl substituents, the chirality on the diboron can be effectively translated to the aldimine boron coordination, leading to excellent stereocontrol. Interestingly, the *ortho*-methyl groups are in close proximity to the aldimine coordination, manifesting their importance in enhancing the enantioselectivity.

We anticipate that this simple, effective, and practical synthetic methodology will significantly facilitate the chemistry of chiral vicinal dimines as ligands and building blocks for pharmaceutical and fine chemistry. From a view of basic science, the enriched diboron-enabled [3,3]-sigmatropic rearrangement from this study has provided a new addition to the repertoire of valuable pericyclic reactions in organic chemistry, and the discovery of new interesting reactions and applications is expected by further exploiting this theory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Full experimental details and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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