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Cooperative Diarylborinic Acid/Chloride-Catalyzed Formal S_Ni Reaction of *cis*-4-Hydroxymethyl-1,2-Cyclopentene Oxides

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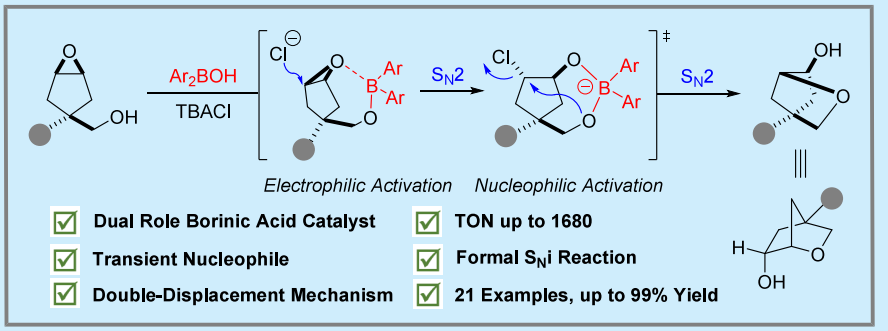

ABSTRACT: A catalytic formal S_Ni reaction was designed to achieve stereoretentive products for *cis*-4-hydroxymethyl-1,2-cyclopentene oxides by using diarylborinic acid as a dual role catalyst and chloride as a catalytic transient nucleophile through a double-displacement mechanism. This reaction offers the advantages of a low catalyst loading of 0.1 mol % and wide substrate scope, even including *N*-substituents. The use of chiral boron acid as a catalyst for this reaction was also attempted.

Chemical transformations catalyzed by enzymes in an organism feature remarkable chemoselectivity, regioselectivity, and stereoselectivity. For instance, the substitution reaction of glycosylation catalyzed by glycosyltransferases can provide the *cis*-glycosylation products with retention of stereochemistry. The S_Ni-type mechanism and double-displacement mechanism[1] have been proposed to explain the stereoselectivity (Scheme 1a). In chemistry, to obtain products from substitution reactions with retention of configuration, we can design such reactions that proceed via the above two mechanisms. A typical noncatalytic example of a substitution reaction based on the S_Ni mechanism is the chlorination of alcohols by thionyl chloride,[2] where the chloride nucleophile attacks from the front side of the hydroxyl group, leading to products with retention of the configuration. Catalytic substitution reactions based on the S_Ni mechanism are more frequently observed in chemical glycosylation research mimicking the natural glycosylation process,[3] yet they are seldom observed in other chemical transformations,[4] possibly due to the particular substrates demands. As mentioned above, substitution reactions based on the double-displacement mechanism can also provide S_Ni products with retention of configuration,[5] so we intend to explore such reactions to obtain the formal S_Ni products.

To achieve formal S_Ni reaction products via catalytic double-displacement mechanisms, a catalytic amount of an additional transient nucleophile (Nu(T)) is required besides the reactant nucleophile (Nu) (Scheme 1b). Nu(T) should possess suitable nucleophilicity and the leaving ability. In the nucleophilic displacement step A, Nu(T) attacks the substrate to form an intermediate. In step B, during nucleophilic displacement by Nu, Nu(T) efficiently leaves the intermediate to yield the final product. Smooth reaction progress also depends on the catalyst, which plays a dual role: electrophilically activating the substrate in step A for Nu(T)'s attack and nucleophilically activating Nu in step B for its attack on the intermediate.

It is well-known that catalytic modes of organoboron acid catalysts[6] vary depending on the substrates. Borinic acid catalysts can serve as Lewis acids to electrophilically activate epoxides and can induce the nucleophilic activation of hydroxy groups of polyols (Scheme 1c). Based on the aforementioned considerations and our previous work on the diarylborinic acid-catalyzed ring-opening of *cis*-4-hydroxymethyl-1,2-cyclopentene oxides,[6g] we envisage that if tetrabutylammonium chloride (TBACl), which has been used in the ring-opening reactions of epoxides,[7] could serve as the transient nucleophile and diarylborinic acid as the dual catalyst, we could obtain an intramolecularly substituted *cis*-product with retained configuration (formal S_Ni reaction product) through dual catalytic

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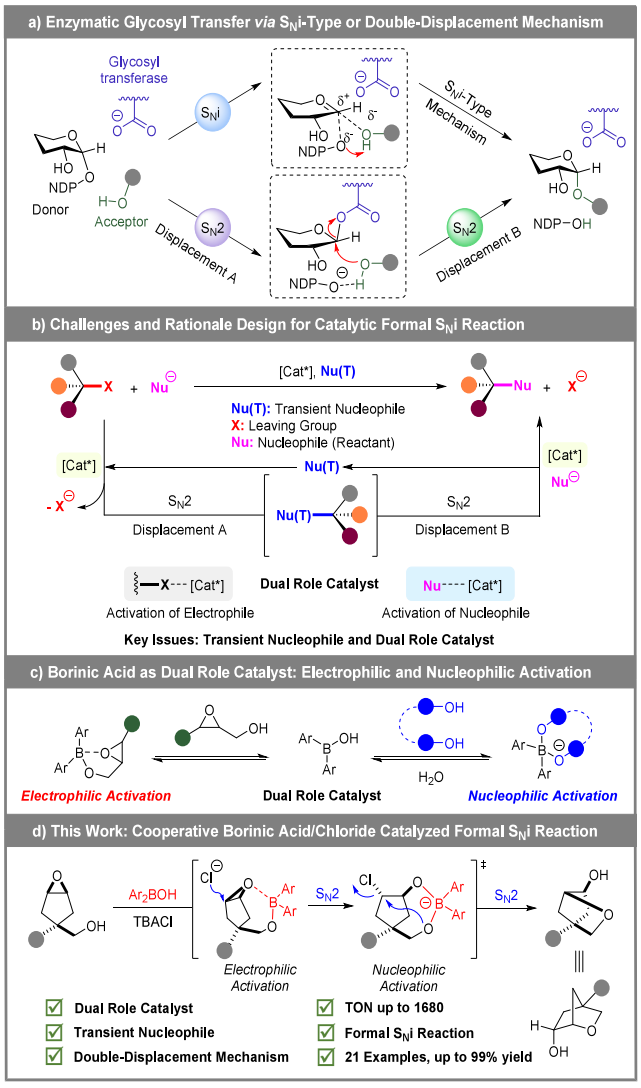
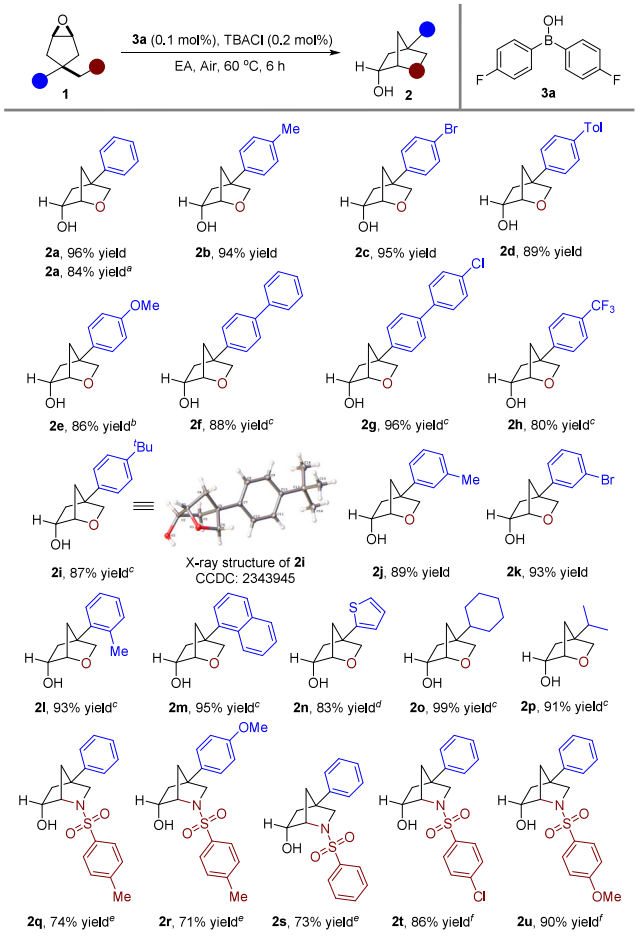
Scheme 1. S_Ni Reaction and Rationale Design for Borinic Acid-Catalyzed Formal S_Ni Reaction



Scheme 2. Substrate Scope



[a]**3a** (0.05 mol %), TABCl (0.1 mol %), 80 °C in N2. [b]10 h. [c]**3a** (0.5 mol %), TABCl (1.0 mol %). [d]16 h. [e]**3a** (0.5 mol %), TABCl (1.0 mol %), 4 days. [f]**3a** (1.0 mol %), TBACl (2.0 mol %), 4 days.

substitution reactions directly from *cis*-4-hydroxymethyl-1,2-cyclopentene oxides (Scheme 1d).

To validate our assumption, using *cis*-4-hydroxymethyl-4-phenyl-1,2-cyclopentene oxide **1a** as the model substrate, bis(4-fluorophenyl)(hydroxyl)-borane **3a** (1 mol %) as the catalyst, and TBACl (2 mol %) as the transient nucleophile, we conducted the reaction in dichloromethane at 40 °C, and we did obtain intramolecularly substituted *cis*-product **2a** in 60% yield after 2 h (see Table S1 in the SI). To further improve the reaction yield, other reaction conditions, including solvents, boron acid catalysts, temperature, and others, were optimized. Finally, the reaction conditions in entry 20 in Table S1 (**3a** (0.1 mol %), TBACl (0.2 mol %), in air, 60 °C, 6 h) gave the product in 99% yield and were selected for the following reactions. The combination of borinic acid and tetrabutylammonium iodide (TBAI) has been used in semipinacol rearrangements of 2,3-epoxy alcohols, where an equivalent of TBAI was needed for high yield.[7d] Though the reaction can be conducted in air, too high air humidity (>40%) is detrimental to the reaction.

With the optimal reaction conditions, we explored the substrate scope (Scheme 2). The substrates bearing substituents on the *para*-position of the benzene ring such as hydrogen (**1a**), methyl (**1b**), bromine (**1c**), and a 4-methylphenyl group (**1d**) exhibited excellent yields (89−96%). Notably, for **1a** with a further reduced catalyst loading of 0.05 mol %, an isolated yield of 84% was achieved after 96 h at 80 °C with a TON of 1680. However, when the *para*-substituent was the methoxy (**1e**), the reaction rate declined, requiring an extended reaction time of 10 h. For substrates with *para*-substituents of phenyl, chlorophenyl, trifluoromethyl, and *t*-butyl groups (**1f**−**1i**), the catalyst loading has to be increased to 0.5 mol % to get good to excellent yields. The *meta*-substituents showed better yields for both the methyl and bromo groups (**2j**, 89%; **2k**, 93%). Substrates with *ortho*-methyl or *ortho*-naphthalene groups required 0.5 mol % catalyst, indicating that steric hindrance impacts the reaction (**2l**, 93%; **2m**, 95%). Substrates with a thiophene substituent (**1n**) and alkyl substituents, like cyclohexyl (**1o**) and isopropyl (**1p**), also required a longer time or 0.5 mol % catalyst.

Interestingly, when using *cis*-4-sulfonamidemethyl-1,2-cyclopentene oxides **1q**−**1u** as substrates, the formal S_Ni product was still obtained, though with higher catalyst loading and longer reaction times (**2q**, 74%; **2r**, 71%; **2s**, 73%; **2t**, 86%; **2u**, 90%), respectively. It is noteworthy that due to its F(sp^3)-rich, conformationally constrained, and 3D-shaped properties, the

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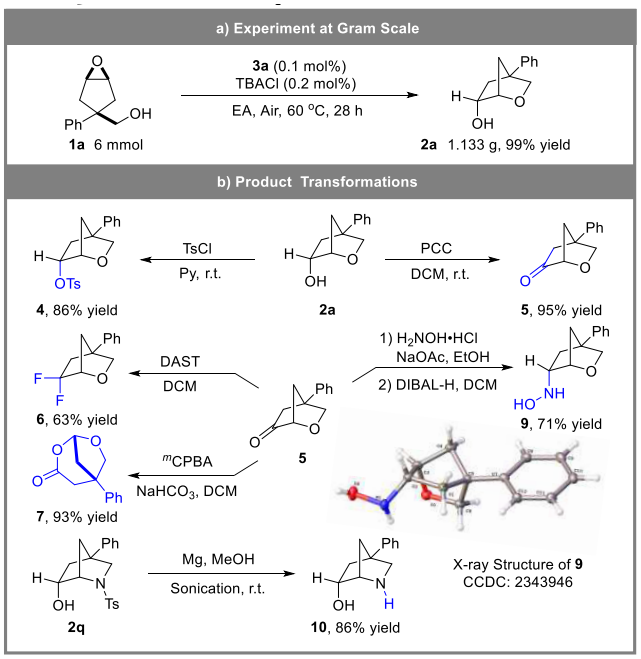
2-azabicyclo[2.2.1]-heptane framework plays a crucial role in the development of potential drug candidates.[8]

To demonstrate the practicality, a scaled-up synthesis was performed with **1a** (Scheme 3a), yielding **2a** (1.133 g) in 99%

Scheme 3. Gram-Scale Synthesis and Transformations

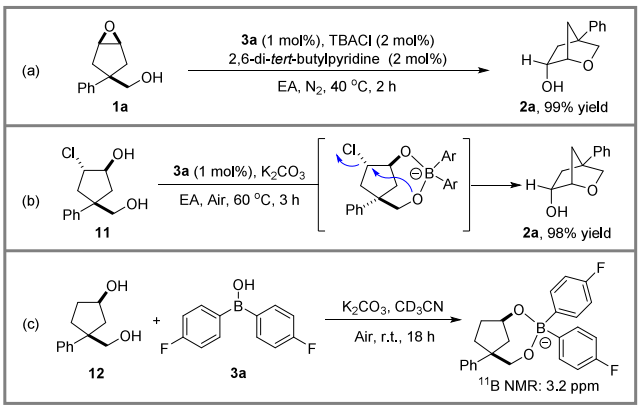


yield. Product **2a** was then converted to an OTs group; additionally, **2a** was oxidized to ketone **5** by using PCC. **5** reacted with DAST to form *gem*-difluoroalkane **6** and underwent a Baeyer−Villiger reaction to produce **7**. Furthermore, ketone **5** was converted to the hydroxylamine derivative **9** through oxime formation and reduction. Besides, **2q** can be converted to the unprotected NH product **10**, which serves as the core skeleton for analogs of the monoacylglycerol lipase inhibitor.[9]

To probe the mechanism of the reaction, several experiments were conducted. First, to exclude the catalytic effect of hydronium ion species[10] produced by the electron-deficient borinic acid on the reaction, a bulky non-nucleophilic base, 2,6-di-*tert*-butylpyridine, as a proton trap was added to the reaction, and product **2a** was still obtained with 99% yield (Scheme 4a), which indicates that the actual catalyst for the reaction is borinic acid.

Then, we attempted to monitor the intermediates generated in the reaction through ^{1}H and ^{11}B NMR using **1a** with an equimolar amount of catalyst **3a** and TBACl. Though the signals in ^{11}B NMR spectroscopy show no obvious change (Figure S1 in SI), the signals in ^{1}H NMR spectroscopy revealed that besides the signals of **1a**, **2a**, **3a**, and TBACl, the proton signals corresponding to the "half-cage" structure (a borinate complex formed from an epoxide and borinic acid), which was demonstrated in our previous work,[6g] were present (Figure S2), indicating the involvement of the electrophilic activation of the substrate by the borinic acid. In addition, when the substrate **1a**′ with a hydroxyl group protected with TBS and inactive in the reaction was used, a new signal in the ^{11}B NMR spectrum was detected (Figure S4), indicating the electrophilic activation of borinic acid toward the epoxy moiety of substrate **1a**′. We believe that the displacement step B of the

Scheme 4. Mechanism Study



reaction is the fast step, and the reaction with **1a** is so fast that we cannot detect the nucleophilic activation intermediate. Considering that the reaction rate with substrate **1q** is slow, we attempted to determine the ^{11}B NMR spectrum of the mixture of **1q** with TBACl and **3a**. To our delight, a new signal at −0.7 ppm appeared (Figure S5) that corresponded to a tetrahedral anionic boron adduct, indicating the presence of the nucleophilic activation. The reaction rate of **1q** is significantly slower than that of **1a**, which is also reflected in the experimental conditions of the mechanism study. Substrate **1q** requires 2.5 h to produce the S_Ni product at 60 °C, while **1a** can produce a significant amount of S_Ni product within 3 min at room temperature. This also explains why a tetrahedral anionic boron complex was not detected when **1a** was used.

Based on the reaction process, after the first substitution step A, possible intermediate **11** would be obtained by removing the borinic acid catalyst. Due to the unavailability of **11** directly from this reaction, we synthesize it through other multistep methods. When compound **11** was subjected for the substitution step B with catalyst **3a** in the presence of potassium carbonate, the same final product was obtained as well (Scheme 4b), indicating that compound **11** might be derived from the reaction process. Because substitution step B is too fast, we could not detect the nucleophilic activated intermediate starting from **11** (Figures S6 and S7). If the substitution step B is stopped, the nucleophilic activated intermediate might be detected. Therefore, we synthesized compound **12** and mixed it with **3a** (Scheme 4c). The ^{11}B NMR spectrum showed a new signal at 3.2 ppm, corresponding to the tetracoordinate boron adduct (Figure S8).

Based on the aforementioned experiments, a plausible catalytic cycle was proposed (Scheme 5). Initially, **3a** reacts with the *cis*-epoxide **1a**, forming the electrophilically activated "half-cage" intermediate **I** by releasing one molecule of water. Subsequently, the transient nucleophile chloride ion attacks the epoxide part of intermediate **I** from the back side of the "half-cage", opening the epoxide and forming a configuration-reversed chloride-substituted tetracoordinated anionic boron complex **II** (displacement step A). Then, the former 4-position of the hydroxyl group nucleophilically activated by borinic acid attacks the carbon atom attached to chloride from the back side of chloride, leading to the departure of the chloride ion and forming a configuration again reversed by intermediate **III** (displacement step B). Finally, in the presence of water and **1a**,

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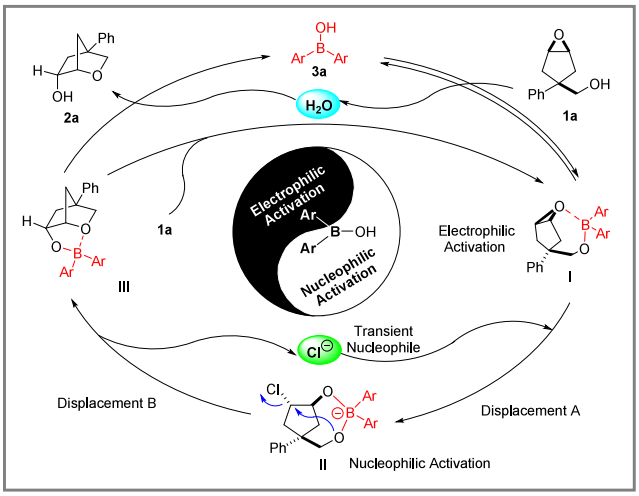
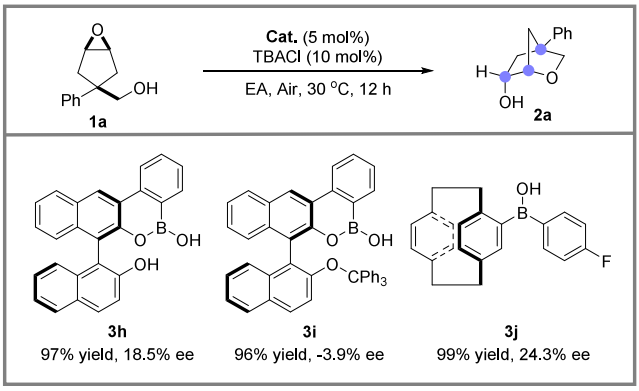
Scheme 5. Proposed Catalytic Cycle



the configuration-recovered *cis*-product **2a** is released while regenerating catalyst **3a** or intermediate **I**.

Finally, we also attempted to employ chiral boron acids in this reaction for the synthesis of a cyclized product featuring three chiral centers (Scheme 6). By employing the axial chiral

Scheme 6. Chiral Boron Acid-Catalyzed Formal S_Ni reactions



hemiboronic acid catalyst **3h**, we achieved a yield of 97% with an enantiomeric excess of 18.5%. However, increasing the steric bulk of catalyst **3i** led to slightly decreased enantioselectivity (−3.9% ee) while maintaining a high yield of 96%. The highest yield and ee value (99% yield, 24.3% ee) were obtained by using borinic acid catalyst **3j** bearing a planar-chiral cyclophane skeleton.

In conclusion, we have developed a catalytic formal S_Ni reaction employing diarylborinic acid as a dual-role catalyst and chloride as a transient nucleophile through the double-displacement mechanism, achieving intramolecular ring opening/closing products of *cis*-4-hydroxymethyl-1,2-cyclopentene oxides. This methodology enables the construction of a configuration retention product with an impressive TON reaching 1680. Furthermore, various substituted substrates including those containing *N*-substituents can also undergo smooth transformations. The chiral borinic acid-catalyzed reaction achieved an enantiomeric excess of 24.3%. Our future endeavor will focus on further exploration of reactions catalyzed by chiral boronic/borinic acids.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c03077.

General information, optimization results, general procedures, characterization data, and spectra(PDF)

Accession Codes

CCDC 2343945−2343946 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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