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Brønsted Acid-Catalyzed Intramolecular Nucleophilic Substitution of the Hydroxyl Group in Stereogenic Alcohols with Chirality Transfer

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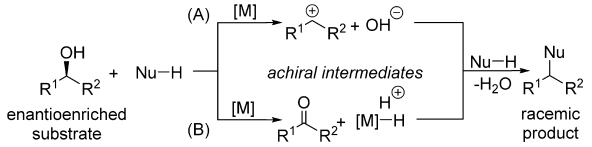
Supporting Information

ABSTRACT: The hydroxyl group of enantioenriched benzyl, propargyl, allyl, and alkyl alcohols has been intramolecularly displaced by uncharged O-, N-, and S-centered nucleophiles to yield enantioenriched tetrahydrofuran, pyrrolidine, and tetrahydrothiophene derivatives with phosphinic acid catalysis. The five-membered heterocyclic products are generated in good to excellent yields, with high degree of chirality transfer, and water as the only side-product. Racemization experiments show that phosphinic acid does not promote S_N1 reactivity. Density functional theory calculations corroborate a reaction pathway where the phosphinic acid operates as a bifunctional catalyst in the intramolecular substitution reaction. In this mechanism, the acidic proton of the phosphinic acid protonates the hydroxyl group, enhancing the leaving group ability. Simultaneously, the oxo group of phosphinic acid operates as a base abstracting the nucleophilic proton and thus enhancing the nucleophilicity. This reaction will open up new atom efficient techniques that enable alcohols to be used as nucleofuges in substitution reactions in the future.

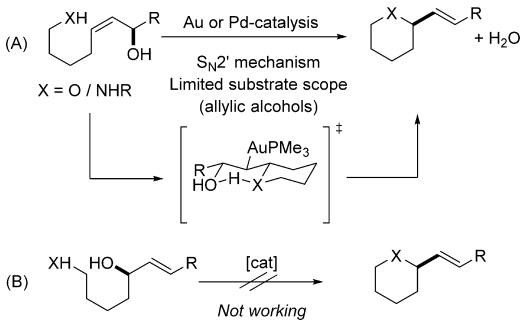
Functional group interconversion (FGI) of nonderivatized stereogenic alcohols by direct substitution of the hydroxyl group with chirality transfer is a major challenge in C-heteroatom bond-forming reactions.[1] Traditional methodologies include: use of stoichiometric and harmful reagents, multistep reaction sequences, and purification issues, all giving low atom economy and high environmental factors.[2,3] Therefore, the FGI of nonderivatized alcohols was recently voted as the second most desired reaction that pharmaceutical companies wanted a greener version of.[4] Efficient methodologies to substitute the hydroxyl group without racemizing the stereogenic center during a substitution reaction are important for the development of techniques to utilize biomass as starting material in organic synthesis.[5] There has been a significant advancement in the direct substitution of the hydroxyl group of alcohols by Lewis and Brønsted acid catalysis (Scheme 1A).[1] However, these reactions proceed via an S_N1-type pathway in which the enantioenrichment of the substrate is lost.[2] Another methodology is the elimination−addition that also suffers from the formation of an achiral carbonyl intermediate (Scheme 1B).[6]

Scheme 1. Current Substitution Methodologies Based on Catalysis Proceed via Achiral Intermediates to Yield Racemic Products



Recently, Aponick, Widenhoefer, and Uenishi demonstrated chirality transfer in gold- and palladium-catalyzed intramolecular amination and etherification reactions of stereogenic allylic alcohols that proceeded through an S_N2'-type transition state (Scheme 2).[7] A mechanistic study by density functional theory

Scheme 2. Gold- and Palladium-Catalyzed S_N2'-Type Allylic Amination and Etherification



(DFT) calculations suggested a unique transition-state stabilization through intramolecular hydrogen bonding to achieve high degree of chirality transfer (Scheme 2A).[8] No reactivity was observed when the position of the double bond was changed to the other vicinal side of the hydroxyl group (Scheme 1B). Thus, the reported methodologies are limited to allyl alcohols that can form the bicyclic transition state (Scheme 2A).[9] To our knowledge, the direct substitution of a hydroxyl group in nonallylic stereogenic alcohols with chirality transfer has not yet been reported and motivated further study.[10]

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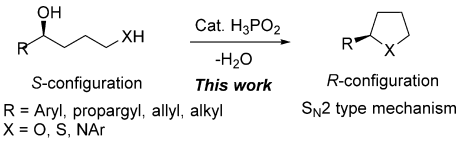
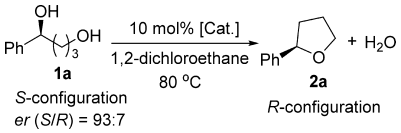
We herein report a phosphinic acid-catalyzed intramolecular substitution of the hydroxyl group of enantioenriched aryl, allyl, propargyl, and alkyl alcohols by O-, N-, and S-centered nucleophiles with good to excellent chirality transfer to generate enantioenriched five-membered tetradydrofuran, pyrrolidine, and tetrahydrothiophene derivatives with inversion of configuration (Scheme 3).

Scheme 3. Phosphinic Acid-Catalyzed S_N2-Type Intramolecular Substitution of the Hydroxyl Group in Alcohols Proceeds with Chirality Transfer



The weakly nucleophilic O-centered (*S*)-1-phenylbutane-1,4-diol (**1a**) was chosen as the model substrate for screening the chirality transfer in the intramolecular substitution reaction to yield (*R*)-2-phenyltetrahydrofuran (**2a**) (Table 1). Performing

Table 1. Optimization of Reaction Conditions[a]



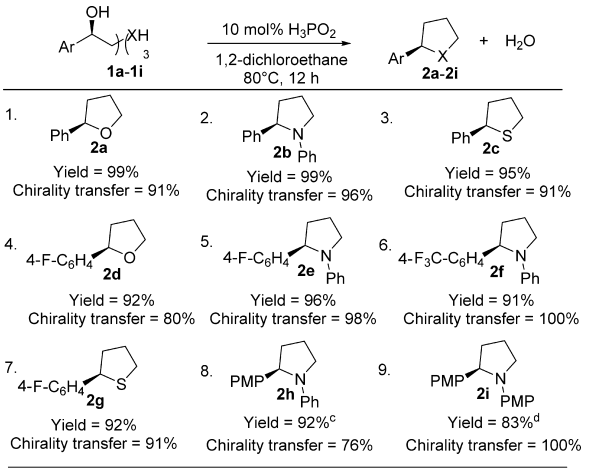
entry	catalyst	pKa[14]	T (°C)	t (h)	yield (%)[b]	chirality transfer (%)[c]
1	H_3PO_2	1.07	80	12	99	91
2	PhH_2PO_2	1.86	80	48	0	0
3	H_3PO_3	2.0	80	12	0	0
4	H_3PO_4	2.12	80	48	0	0
5	Ph_2HPO_2[d]	2.3	80	48	0	0
6	*p*-TSA	-2.8	40	12	98	84
7	TfOH	-12	40	12	91	23
8	AcOH	4.76	80	48	0	0
9	H_2SO_4	-3	40	12	92	0
10	$FeCl_3$	–	40	12	96	0
11	AuCl	–	80	12	88	0
12	$NaAuCl_4$	–	40	12	96	19

[a]Reaction Condition: **1a** (1 mmol), solvent (2 mL), and catalyst (10 mol %) was heated in an oil bath. [b]NMR Yield. [c]By chiral HPLC analysis. [d]When the reaction was performed at 120 °C, poor reactivity was observed (SI).

the reaction using 10 mol % phosphinic acid in 1,2-dichloroethane generated **2a** in a quantitative yield with 91% chirality transfer (Table 1, entry 1). The reaction is sensitive to the reaction temperature where the chirality transfer drops to 9% when the reaction is performed at 110 °C (SI). Other solvents were inferior with respect to reactivity and chirality transfer (SI). Similar phosphorus acids were also evaluated in which no formation of **2a** was observed even after prolonged reaction times (Table 1, entries 2–5).[11] Other Brønsted acids such as *p*-toluenesulfonic acid (*p*-TSA), trifluoromethanesulfonic acid (TfOH), acetic acid (AcOH), and sulfuric acid (H_2SO_4) having a O═X–OH structural motif similar to phosphinic acid were also studied and found to be inferior in terms of products' yields and chirality transfers (Table 1, entries 6–9).[12] There is no clear correlation between yield, ee, and p*K*a. Lewis acidic catalysts based on iron(III), gold(I), or gold(III) previously reported to activate the hydroxyl group in nucleophilic substitution of alcohols generated **2a** in high yields but with poor chirality transfers (Table 1, entries 10–12).[13] The phosphinic acid used in this study was a 50% aqueous solution. The other catalysts used were dry. Therefore, the effect of water was investigated for both phosphinic acid and *p*-TSA. It was found that neither the initial rate nor the chirality transfer was affected by the water concentration (SI).

O-, N-, and S-centered nucleophiles were utilized in the intramolecular substitution of different enantioenriched benzylic alcohols (Table 2). Substrates with N- and S-centered

Table 2. Intramolecular Substitution of Benzylic Alcohols[a,b]



[a]Reaction Condition: **1** (1 mmol), DCE (2 mL) and catalyst (10 mol %) was heated in an oil bath. [b]Isolated yields. [c]Reaction temp. 65 °C; PMP = *para*-methoxyphenyl. [d]Reaction temp. 50 °C, time 24 h.

nucleophiles generated 1,2-diphenylpyrrolidine (**2b**) and 2-phenyltetrahydrothiophene (**2c**) in excellent yields with 96% and 91% chirality transfer, respectively (Table 2, entries 2 and 3). Derivatives of the products **2b** and **2c** were crystallized, and the absolute configurations were determined by X-ray crystallography showing *R*-configurations of **2b** and **2c** (Figure 1). This

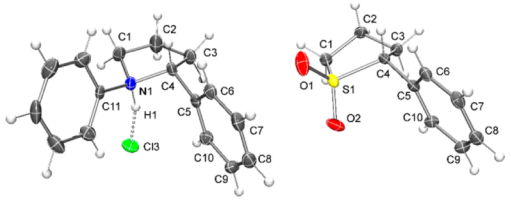


Figure 1. X-ray structures of the HCl salt of **2b** and the corresponding sulfone of **2c** showing the absolute configurations (*R*) ORTEP plots with thermal ellipsoids drawn at the 50% probability level.

demonstrates that an inversion of configuration at the chiral center has occurred under the substitution reactions. Substrates with electron-withdrawing *p*-fluoro and *p*-trifluoromethyl substituents in the benzyl group generated products **2d**–**2g** in good to excellent yields and with high degrees of chirality transfers (Table 2, entries 4–7). A decrease in chirality transfer was observed for **1h** with an electron-donating *p*-methoxy group in the phenyl-ring (Table 2, entry 8). Excellent chirality transfer could be obtained also for a substrate with an electron-rich benzyl group by exchanging the nucleophile from aniline to the stronger

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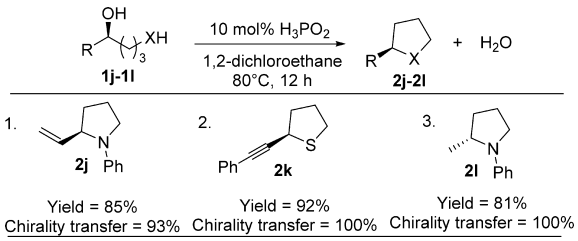
nucleophilic *p*-anisidine (Table 2, entry 9). The 1,4 relation between nucleofuge and nucleophile is pivotal for reactivity. Phosphinic acid did not promote the substitution reaction with substrates that generate three-, four-, or six-membered heterocyclic compounds or in intermolecular substitutions (*vide infra*).

To expand the substrate scope of the phosphinic acid-catalyzed substitution with chirality transfer, more challenging nonbenzylic alcohols were screened (Table 3). Alcohol **1j**

Table 3. Intramolecular Substitution of Allyl, Propargyl, And Alkyl Alcohols[a,b]

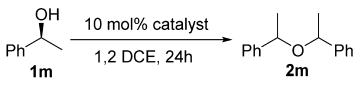


[a]Reaction Condition: **1** (1 mmol), DCE (2 mL) and catalyst (10 mol %) was heated in an oil bath. [b]Isolated yields.

activated with an allyl group generated **2j** in a 85% yield and 93% chirality transfer (Table 3, entry 1). It is noteworthy that this class of allyl alcohols has not previously been transformed in intramolecular substitution reactions with chirality transfer (Scheme 2B).[5,10] Less reactive propargyl alcohol **1k**,[1] generated enantioenriched 2-(phenylethynyl)tetrahydrothiophene **2k** in a 92% yield and 100% chirality transfer (Table 3, entry 2). This is, to our knowledge, the only example of a substitution reaction of a propargyl alcohol with chirality transfer.[1f] Secondary aliphatic alcohols were anticipated to be most challenging due to poor reactivity and the risk for competing elimination reactions. To date, only a handful of reports are available for direct nucleophilic substitution of secondary aliphatic alcohol, and these give racemic mixtures.[6,15] Gratifyingly, transformation of aliphatic alcohol **1l** generated the product 2-methyl-1-phenylpyrrolidine (**2l**) in a 81% yield and 100% chirality transfer (Table 3, entry 3).

To get a better insight into the unique activation of the hydroxyl group by phosphinic acid and to compare to other acids, racemization experiments were performed. Enantioenriched 1-phenylethanol (**1m**) was exposed to substitution reaction conditions with different catalysts (Table 4). Using phosphinic acid as catalyst, negligible racemization of **1m** and trace amount formation of symmetrical ether **2m** were observed (Table 4, entry 1). This shows that phosphinic acid does not promote S_N1-

Table 4. Racemization Experiment of 1m[a]



S/*R* = 90:10

entry	catalyst	**2m**	*T* (°C)	recovered **1m**
1	H_3PO_2	<5%	80	>95% (*S*/*R* = 85:15)
2	*p*-TSA	<95%	40	0%
3	TfOH	>20%	40	0%
4	$FeCl_3$	>95%	40	0%

[a]Reaction Condition: **1** (1 mmol), DCE (2 mL), and catalyst (10 mol %) were heated in an oil bath. Yields were determined by ^{1}H NMR, and enantioenrichment by chiral HPLC.

reactivity to yield **2m** under these reaction conditions. Using the stronger acidic *p*-TSA gave full conversion to the symmetrical and fully racemized **2m** (Table 4, entry 2), which is produced via an S_N1 reaction pathway. Using TfOH as catalyst gave full conversion of **1m** to yield racemized **2m** and side-products at 40 °C. Also, iron(III) gave full conversion to racemic **2m**. These experiments demonstrate that the activation of phosphinic acid is unique where no S_N1-reactivity is observed under the reaction conditions employed. They furthermore show that a favored five-membered ring formation is pivotal for the substitution reaction to proceed, where no intermolecular substitution reaction of **1m** to generate the symmetrical ether **2m** occurred in the presence of phosphinic acid. The racemization observed with the stronger Brønsted acids, such as *p*-TSA, could be explained by that the stronger acids promote a more S_N1-like transition state (TS). This is also in accordance with the results in which *p*-TSA and TfOH gave lower chirality transfer than phosphinic acid in the transformation of **1a** to **2a** (Table 1, entries 6 and 7). To get further insight into the reaction mechanism, a rate-order determination in catalyst was performed. The reaction follows first-order dependence in catalyst concentration (SI).

The experiments disclosed above suggest that the phosphinic acid promotes intramolecular substitution reactions that proceed through a unique reaction mechanism. Depending on the electronic properties of both the nucleophile and the nucleofuge, the intramolecular reactions proceed with 80−100% chirality transfer (Tables 2 and 3). Furthermore, negligible reactivity was observed in the intermolecular reaction (Table 4). Hence, from this it can be concluded that phosphinic acid does not promote an S_N1 reaction. Plausibly, the catalyst can act in a bifunctional Brønsted acid/Brønsted base fashion to activate both the nucleophile and the leaving group in an S_N2-type reaction. This would be analogous to the bifunctional role of the phosphoric acid catalyst demonstrated in a number of organocatalytic reactions.[11,16] To investigate the feasibility of this kind of mechanism and to characterize the TS involved, we used DFT methodology to study the transformations from **1a−c** to **2a−c**.[17] The optimized structures of the TSs are given in Figure 2, along with the calculated barriers and reaction free energies. In these TSs, the catalyst has a bifunctional role in which the acidic proton of the phosphinic acid protonates the oxygen of the leaving hydroxyl group to promote the C−O bond cleavage. Concomitantly, the oxo-group of the catalyst deprotonates the nucleophile, thus increasing the nucleophilicity. This results in an S_N2-type reaction mechanism with an inversion of configuration at the carbon center, in accordance with the experimental findings. Indeed, the TSs were found to have plausible energies. The barriers for the O-, N- and S-centered nucleophiles (i.e., transformations **1a** → **2a**, **1b** → **2b** and **1c** → **2c**, respectively) were calculated to be 27.3, 23.1, and 26.8 kcal/mol, respectively. These values are consistent with the fact that the N-centered nucleophiles were reactive at 60 °C, but not the S- or O-centered nucleophiles, for which the reactions proceed only at 80 °C. For comparison, we have also calculated the TSs for the O-centered nucleophile using *p*-TSA, acetic acid, and diphenyl phosphinic acid as catalysts. The results are given in the SI.

A Brønsted acid-catalyzed intramolecular reaction that promotes a direct substitution of the hydroxyl group in enantioenriched alcohols in good to excellent yields with high degree of chirality transfer has been developed. The hydroxyl group of aryl, allyl, propargyl, and alkyl alcohols was substituted by O-, S-, and N-centered nucleophiles to generate enantiomerically enriched five-membered heterocyclic compounds. DFT

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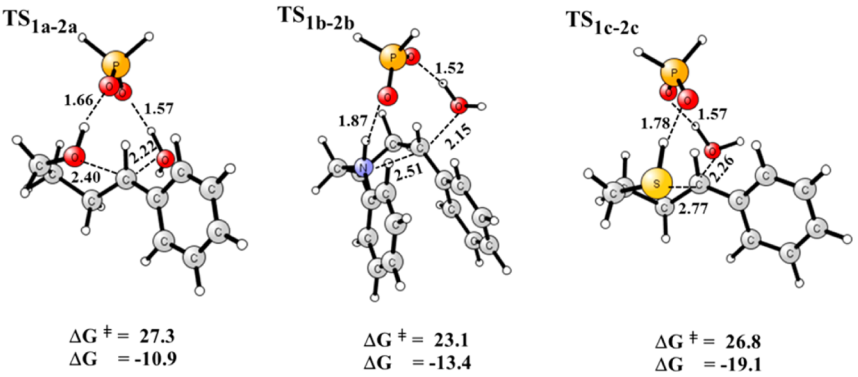

Figure 2. Optimized TS structures and calculated energies (kcal/mol) for the intramolecular direct substitution utilizing O, N, and S nucleophiles.

calculations corroborate a bifunctional role of the phosphinic acid, i.e., promoting an S_N2-type reaction mechanism by activation of both nucleofuge and nucleophile in a bridging TS.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) The calculations were performed with the B3LYP functional, and the reported Gibbs free energies are corrected for solvation and dispersion. See SI for full details.

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