Article

H3PO2-Catalyzed Intramolecular Stereospecific Substitution of the Hydroxyl Group in Enantioenriched Secondary Alcohols by N-, O-, and S-centered Nucleophiles to Generate Heterocycles

Anon Bunrit, Pemikar Srifa, Thanya Rukkijakan, Christian Dahlstrand, Genping Huang, Srijit Biswas, Rahul Watile, and Joseph S. M. Samec

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b03458 • Publication Date (Web): 20 Dec 2019

H_3PO_2-Catalyzed Intramolecular Stereospecific Substitution of the Hydroxyl Group in Enantioenriched Secondary Alcohols by *N*-, *O*-, and *S*-centered Nucleophiles to Generate Heterocycles

Anon Bunrit,[†] Pemikar Srifa,[†] Thanya Rukkijakan,[†] Christian Dahlstrand,[§] Genping Huang,[†,⊥] Srijit Biswas,[¶] Rahul A. Watile,[,†] and Joseph S. M. Samec[*,†]*

[†]Department of Organic Chemistry, Stockholm University, 10691 Stockholm, Sweden.

[§]Department of Chemistry, BMC, Uppsala University, Box 576, 75123 Uppsala, Sweden.

[⊥]Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, P. R. China.

[¶]Department of Chemistry, University College of Science, University of Calcutta, 92, A. P. C. Road, Kolkata - 700009, West Bengal, India.

*Corresponding author. Tel.: +46705592511; Fax: +468162000
E-mail: joseph.samec@su.se (J. S. M. Samec), rahulwatile@gmail.com (R.A. Watile)

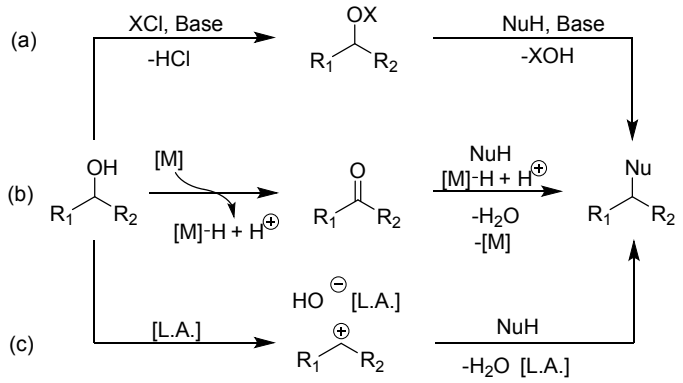
Abstract

The direct intramolecular stereospecific substitution of the hydroxyl group in enantiomerically enriched secondary benzylic, allylic, propargylic, and alkyl alcohols was successfully accomplished by phosphinic acid catalysis. The hydroxyl group was displaced by O-, S-, and N-centered nucleophiles to provide enantioenriched five-membered tetrahydrofuran, pyrrolidine, and tetrahydrothiophene as well as six-membered tetrahydroquinolines and chromanes in up to 99% yield and 100% enantiospecificity with water as the only by-product. Mechanistic studies using both experiments and calculations have been performed for substrates generating 5-membered heterocycles. Rate studies show dependences in catalyst, internal nucleophile, and electrophile, however, independence in external nucleophile, electrophile, or water. Kinetic isotope effect studies show an inverse KIE of $k_H/k_D = 0.79$. Furthermore, phosphinic acid does not promote S_N1 reactivity. Computational studies support a bifunctional role of the phosphinic acid in which activation of both nucleofuge and nucleophile occur in a bridging S_N2-type transition state. In this transition state, the acidic hydrogen of phosphinic acid protonates the leaving hydroxyl group simultaneously as the oxo group partially deprotonates the nucleophile. Thereby, phosphinic acid promotes the substitution of the non-derivatized hydroxyl group in enantioenriched secondary alcohols by uncharged nucleophiles with conservation of the chirality from the alcohol to the heterocycle.

Keywords: stereospecific substitution, alcohols, phosphinic acid catalysis, heterocyclic compounds, atom economy.

Introduction

Enantiomerically enriched alcohols are easily accessible naturally occurring organic compounds. In organic synthesis, alcohols are often used as nucleophiles.[1] When the opposite reactivity is desired, *i.e.* if alcohols are to be used as electrophiles, derivatization of the hydroxyl (OH) group into a better leaving group is required. This derivatization step is either performed *in-situ*[2], *e.g.* in the Mitsunobu reaction[3] or in a separate reaction step, *e.g. via* tosylation (Scheme 1a).[4] These procedures have drawbacks in increasing the cost, the number of synthetic steps, and environmental impact of the transformation.[5] In 2005, the nucleophilic substitution of non-derivatized alcohols was voted as the second most desired reaction that pharmaceutical companies wanted greener alternative to with a special emphasis on stereospecific reactions ("*The challenge of achieving a method of activation for secondary alcohols that maintains control over the stereochemistry of the reaction remains*.").[6] Therefore, the development of methodologies for direct activation of the OH group has emerged. [7] These include: (*i*) hydrogen borrowing that proceed through an initial metal-catalyzed transfer dehydrogenation step to generate the corresponding electrophilic carbonyl, that then condensates with a nucleophile, and then the hydrogen is transferred back from the catalyst to generate the product (Scheme 1b);[4d] (*ii*) direct substitution of the OH group promoted by Lewis acid catalysis that proceed through an S_N1 pathway where the nucleophile attacks the intermediate carbocation to form the product (Scheme 1c).[7] A disadvantage with these methodologies is that they both proceed through an achiral intermediate. Thereby, the inherent chirality in these easily accessible compounds cannot be utilized.[4a,4c,8] Optically pure alcohols are abundant in biomass and efficient methodologies to substitute the OH group would enable the usage of biomass as a raw material for the production of bulk and fine chemicals in the future. Therefore, it would be worthwhile to develop efficient stereospecific methodologies to substitute the OH group in enantioenriched alcohols.

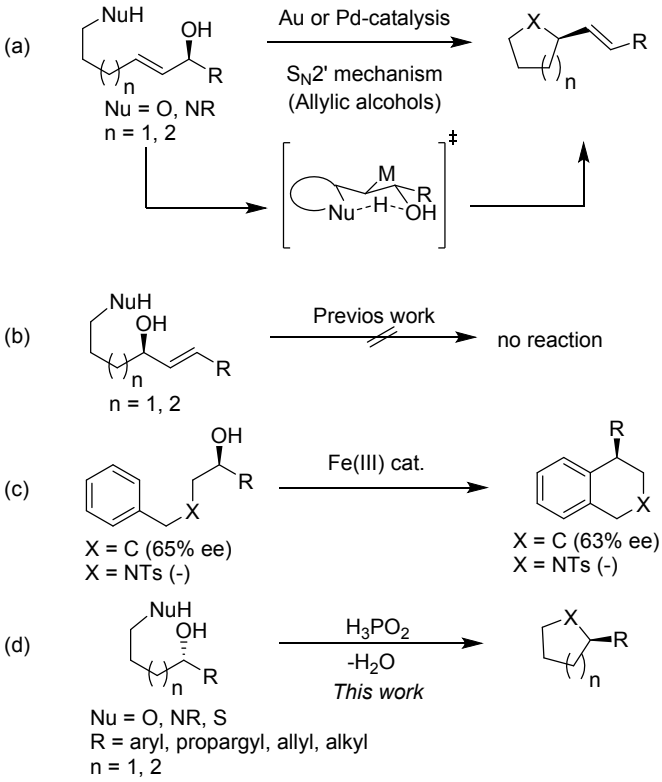


Scheme 1. General substitution reactions *via* different modes of activation of the hydroxyl group of alcohols: (a) preactivation, (b) catalytic hydrogen transfer, and (c) direct catalytic substitution.

To develop direct stereospecific substitution reactions of the OH group without prior derivatization is more challenging than the S_N1 reactions in which control of the C─O bond cleavage is required for chirality transfer to the product to occur.[3a] Recently, Aponick, Widenhoefer, and Uenishi successfully performed intramolecular stereospecific substitution reactions of enantioenriched allylic alcohols using gold and palladium based catalysts (Scheme 2a).[9] The chemical transformation proceeded *via* an S_N2'-type transition-state (TS) which was supported by density functional theory (DFT) calculations.[10] A unique bicylic transition-state was found in which the nucleophile protonated the leaving OH group in a bicyclic transition state. However, the methodology was substrate specific, where no reactivity was observed when the OH group of the allylic and alcohol were juxtapositioned (Scheme 2b). In 2014, Cook and Umani-Ronchi reported iron(III)-catalyzed intramolecular Friedel-Crafts alkylation of unactivated alcohols, where stereospecificity was reported for two substrates (Scheme 2c).[11] They recently extended this to secondary and tertiary alcohols using a N-centered nucleophile.[12] We have previously communicated a direct stereospecific nucleophilic substitution of the OH group of non-derivatized secondary alcohols using phosphinic acid (H_3PO_2) as a catalyst with water as the only byproduct (Scheme 2d). The OH group of enantioenriched benzyl, propargyl, allyl, and alkyl alcohols was substituted by *O*-, *N*-, and *S*-centered nucleophiles to generate five-membered heterocyclic compounds with

conservation of the chirality. Limited mechanistic studies suggested that H_3PO_2 had a bifunctional role and promoted an S_N2-type reaction.[13]

In this study, we expand the study of direct stereospecific intramolecular substitution of various substrates to generate both five- and six-membered heterocyclic compounds. Mechanistic studies using both experiments and calculations have been performed to get better insight into the reaction mechanism.



Scheme 2. Current catalytic methodologies for direct intramolecular substitution of alcohols.

Results and discussion

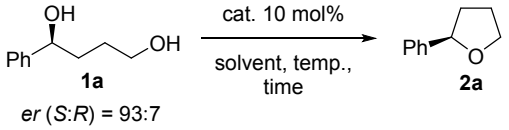
Optimization of reaction parameters

Initially, the weakly nucleophilic *O*-centered (*S*)-1-phenylbutane-1,4-diol (**1a**) was chosen as the model substrate for screening the intramolecular stereospecific substitution reaction to yield (*R*)-2-phenyltetrahydrofuran (**2a**) (Table 1). An initial catalyst screening with various Lewis acidic catalysts (Fe(III), Au(I), and Au(III)) that previously have beeen reported to activate the OH group were chosen.[14] These catalysts showed high reactivity, however low enantiospecificity (e.s.) was observed

(Table 1, entries 1-3). In the presence of 10 mol% of H_3PO_2 product **2a** was obtained in excellent yield with 91% e.s.. Similar phosphorous-based acids such as H_3PO_3, H_3PO_4, PhH_2PO_2, and Ph_2HPO_2 were also tested (Table 1, entries 5-8), however no product formation was observed under the employed reaction conditions. Other Brønsted acids having a O═X–OH motif similar to phosphinic acid such as trifluorometanesulfuric acid (TfOH), acetic acid (AcOH), sulfuric acid (H_2SO_4), and *p*-toluenesulfunic acid (*p*-TSA) were also studied (Table 1, entries 9-12). Stronger acids than H_3PO_2 promoted the nucleophilic substitution to yield **2a** in high yield, but gave lower e.s. (Table 1, entries 10-12). Inspired by the good result obtained using *p*-TSA as a catalyst in entry 12, the reaction was carried out at 25 ^{0}C. However, at this temperature a low conversion was observed (Table 1, entry 13). The p*K*a of the acid affected the reactivity of the reaction where weaker acids (p*K*a > 2) did not promote the substitution reaction and stronger acids (p*K*a < 1) did. However, the correlation between acidity and enantiospecificity of the nucleophilic substitution reaction is not clear.

The solvent effect was also studied. Cyclohexane and toluene which have lower polarity than 1,2-DCE generated **2a** in slightly lower yields (Table 1, entries 14-15). With solvents of higher polarity than 1,2-DCE, *i.e.* acetonitrile and nitromethane, the reaction proceeded to give **2a** in high yields, however, with lower e.s. (Table 1, entries 16-17). Furthermore, the effect of temperature was investigated using toluene with a wide temperature window as solvent. The conversion increases with temperature, however, the enantiospecificity drops when the temperature was raised (Table 1, entries 18-20).

Table 1. Optimization of the reaction conditions for the intramolecular nucleophilic substitution of benzylic alcohol **1a**.



er (*S*:*R*) = 93:7

Entry	Catalyst	p*K*a	Solvent	T (°C)	t (h)	Yield (%)[a]	e.s. (%)[b]
1	$FeCl_3$	-	1,2-DCE	40	12	>95	0
2	AuCl	-	1,2-DCE	80	12	90	0
3	$NaAuCl_4$	-	1,2-DCE	40	12	>95	19
4	**H_3PO_2**	**1.07**	**1,2-DCE**	**80**	**24**	**>95**	**91**
5	H_3PO_3	2.0	1,2-DCE	80	24	0	0
6	H_3PO_4	2.12	1,2-DCE	80	48	0	0
7	PhH_2PO_2	1.86	1,2-DCE	80	48	0	0
8	Ph_2HPO_2	2.3	1,2-DCE	80	48	0	0
9	AcOH	4.76	1,2-DCE	80	48	0	0
10	TfOH	-12	1,2-DCE	40	12	>95	23
11	H_2SO_4	-3	1,2-DCE	40	12	>95	0
12	*p*-TSA	-2.8	1,2-DCE	40	12	>95	84
13	*p*-TSA	-2.8	1,2-DCE	25	24	10	-
14	H_3PO_2	1.07	Cyclohexane	80	24	>80	73
15	H_3PO_2	1.07	Toluene	80	24	>90	91
16	H_3PO_2	1.07	MeCN	80	24	>95	65
17	H_3PO_2	1.07	$MeNO_2$	80	24	>95	60
18	H_3PO_2	1.07	Toluene	100	12	>95	21
19	H_3PO_2	1.07	Toluene	110	12	>95	9
20[c]	H_3PO_2	1.07	Toluene	160	2	>95	0

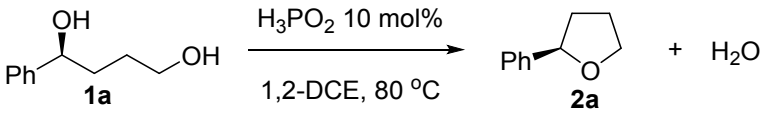
Reaction conditions: **1a** (0.3 mmol), solvent (1.0 mL) and catalyst (10 mol%) was heated in an oil bath. [a]NMR yield. [b]Enantiospecificity was determined by chiral stationary phase HPLC analysis. [c]Reaction performed at 160 °C in which microwave irradiation was used (3 bar).

Water effect

The phosphinic acid used in this study was administrated as an aqueous solution (50 w/w%), while the other catalysts used were dry. Thereby, the reaction with H_3PO_2 as catalyst contained water from the beginning of the reaction. In addition, water is generated during the course of the reaction.

Therefore, the effect of water on the reaction was studied by measuring the initial rate and the enantiospecificity of the reaction (Table 2). The initial rates were determined at below 20% conversion and the enantiospecificity was determined after 24 hours. Dried $CaSO_4$ (oven dried at 250°C for 3h) was used as a neutral drying agent in the reaction where $CaSO_4$ + H_2O form $CaSO_4.2H_2O$. The standard reaction without dried $CaSO_4$ was performed. The observed initial rate was 3.6×10^{-6} $M.s^{-1}$ with 90% e.s. (Table 2, entry 1). Different amounts of dried $CaSO_4$ were added to reaction mixture. Increasing the amount of water did not affect either initial rate or enantiospecificity of the reaction (Table 2, entries 2-6). To study the influence of $CaSO_4$, mole equivalence of water and $CaSO_4$ were added to the reaction. However, no effect on the rate or enantiospecificity was observed (Table 2, entry 7). Without H_3PO_2, $CaSO_4$ did not promote the reaction (Table 2, entry 8). Thereby, water does not affect the rate or the enantiospecificity of the reaction.

Table 2. Water effect on initial rate and enantiospecificity of the reaction



er (*S*:*R*) = 93:7

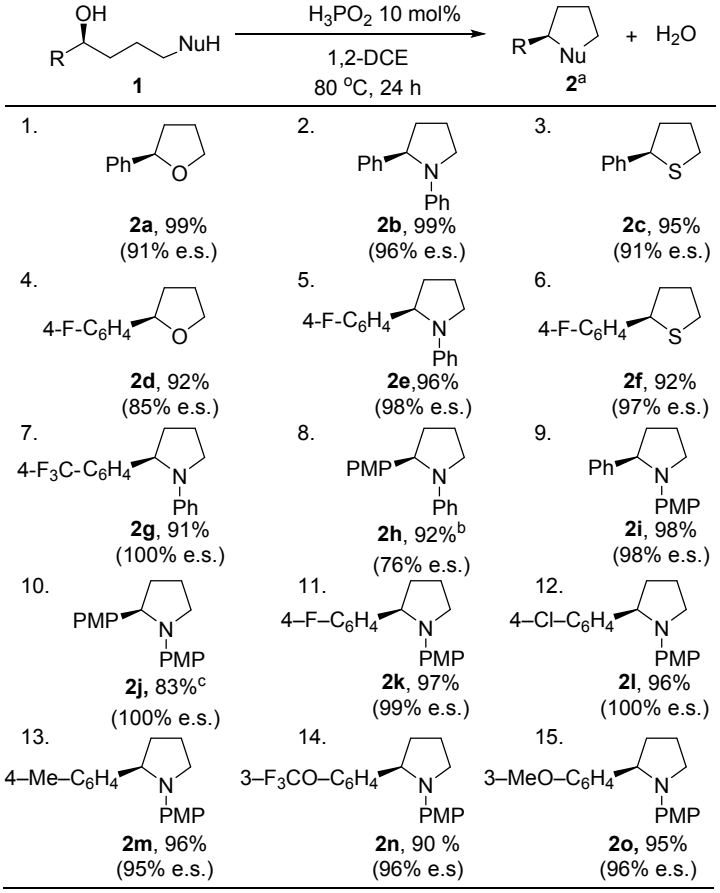
Entry	Amount of water (%)	$CaSO_4$ (mmol)	Initial rate ($\times10^{-6}$ $M.s^{-1}$)	e.s. (%)[a]
1	100	-	3.6	91
2	0	0.070	3.1	90
3	20	0.056	4.1	91
4	40	0.042	3.1	91
5	60	0.028	4.1	91
6	80	0.014	3.6	91
7	100	0.14	3.1	90
8	-	0.14	N/A	-

Reaction conditions: **1a** (0.3 mmol), 1,2-DCE (1.5 mL), H_3PO_2 (10 mol%), $CaSO_4$, and H_2O was heated in an oil bath at 80 °C. N/A = no reaction. [a]Enantiospecificity was determined by chiral stationary phase HPLC analysis.

Stereospecific substitution to generate five-membered heterocycles from benzylic alcohols

Having optimized the reaction conditions, the substrate scope with respect to both nucleophile and benzylic alcohols was studied (Table 3). Substrates with *O*-, *N*-, and *S*-centered nucleophiles generated tetrahydrofuran **2a**, pyrrolidine **2b,** and tetrahyrothiophene **2c** in excellent yields and high e.s. (Table 3, entries 1-3). Substrates with electron-withdrawing *p*-fluoro in the benzyl group generated heterocyclic products **2d**-**2f** in good to excellent yield and high e.s. (Table 3, entries 4-6). The strongly deactivating group, *p*-trifluoromethyl substituent, generated pyrrolidine **2g** in high yield and full e.s. (Table 3, entry 7). Lower e.s. was observed for reaction of **1h** to generate product **2h** having an electron-donating *p*-methoxy group on the benzylic alcohol (Table 3, entry 8). However, exchanging the *N*-centered nucleophile (aniline) with an electron-rich *p*-anisidine overcame this and product **2j** was obtained in high yield and excellent e.s. (Table 3, entry 10). With the PMP group on the *N*-centered nucleophile, all products were obtained in excellent yields and e.s. (Table 3, entries 9-15). The PMP group also has synthetic advantages as it can easily be removed if desired.

Table 3. Intramolecular substitution of benzylic alcohols to generate five-membered heterocylic compounds



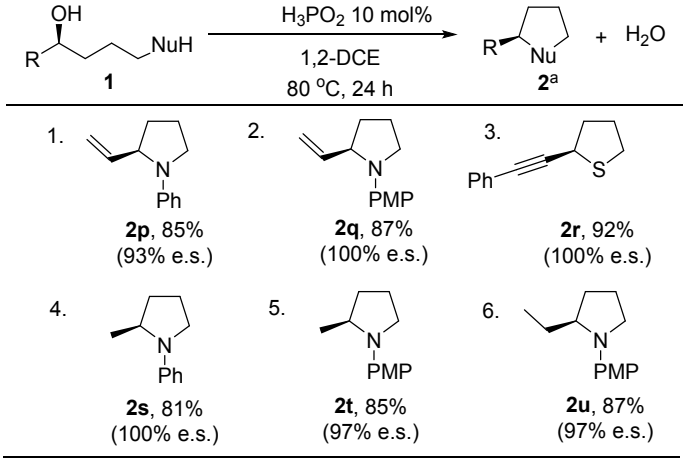
Reaction conditions: **1** (0.5 mmol), 1,2-DCE (1.0 mL) and H_3PO_2 (10 mol %) was heated in an oil bath at 80 °C. [a]Isolated yields. [b]Reaction temp. 65 °C. [c]Reaction temp. 50 °C.

Stereospecific substitution to generate five-membered heterocycles from non-benzylic alcohols

The substrate scope was expanded to more challenging non-benzylic alcohols (Table 4). H_3PO_2 catalyzed the nucleophilic substitution of stereogenic allylic alcohol **1p** to yield pyrrolidine **2p** in 85% yield and 93% e.s. (Table 4, entry 1). Exchanging the nucleophilic moiety from aniline to stronger nucleophilic *p*-anisidine improved the enantiospecificity to 100% in product **2q** (Table 4, entry 2). Noteworthy, this direct intramolecular stereospecific nucleophilic substitution overcame the previous limitation of allylic alcohols that only could proceed *via* an S_N2'-reaction pathway (Scheme 2b).[6,7] Intramolecular substitution of less reactive propargylic alcohol with *S*-centered nucleophiles **1r** was also performed. The reaction generated **2r** in high yield and excellent enantiospecificity (Table 4, entry 3). The nucleophilic substitution of secondary aliphatic alcohols remains challenging

due to the relative difficulty in activating of the OH group and the risk for dehydration reactions. To date, the activation of the OH group of aliphatic secondary alcohols has only been reported a few times for reactions that proceed through an S_N1-pathway.[3e,15] The intramolecular substitution reaction of aliphatic alcohols **1s-1u** with *N*-centered nucleophiles overcame this limitation. The reaction generated pyrrolidines **2s-2u** in good yields and excellent enantiospecificities (Table 4, entries 4-6).

Table 4. Intramolecular substitution of non-benzylic alcohols to generate five-membered heterocylic compounds



Reaction conditions: **1** (0.3 mmol), 1,2-DCE (1 mL) and H_3PO_2 (10 mol %) was heated in an oil bath at 80 °C. [a]Isolated yields.

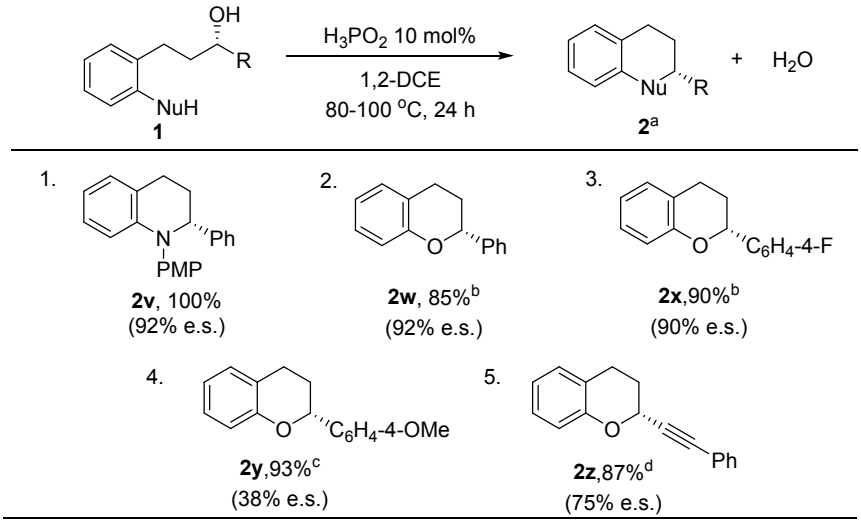
Stereospecific substitution to generate six-membered heterocycles from benzylic alcohols

We wanted to expand the substrate scope to substrates that generate six-membered heterocycles. To our knowledge, there is only one report of a stereospecific substitution of an OH group to generate a six-membered heterocycle (Scheme 2b), however, no reports using *N*- or *O*-centered nucleophiles. The *N*-centered **1w** was tested in the intramolecular substitution reaction and gratifyingly product **2w** was isolated in excellent yield and high e.s. (Table 5, entry 1). This chemical transformation has previously only been reported in non-stereospecific substitution reaction to obtain racemic products.[16] Encouraged by the good results, the more challenging phenol was tried as nucleophile. Phenols have, to the best of our knowledge, never been reported as nucleophiles in any substitution

reactions of OH groups in alcohols. H_3PO_2 catalyzed the intramolecular substitution reaction of alcohol **1x** to generate chromane **2x** in 85% yield and 92% e.s. (Table 5, entry 2). The reaction required a slightly higher temperature (100 °C). Alcohol with an electron-withdrawing *p*-fluoro substituent in benzylic group generate product **2y** in 90% yield and 90% e.s. (Table 5, entry 3).[17] In contrast, alcohol with an electron-donating *p*-methoxy group **1y** generated product **2y** in excellent yield, however with only 38% e.s. (Table 5, entry 4). Intramolecular substitution of less reactive propargylic alcohol **1z** generated **2z** in very good yield with 75% e.s. (Table 5, entry 5).

Thus, we have showed that H_3PO_2 can catalyze the nucleophilic substitution of various secondary alcohols with respect to nucleophile, electrophile, and ring-size to generate enantiomerically enriched heterocyclic compounds with high efficiency in respect to yields and enantiospecificities.

Table 5. Intramolecular substitution of benzylic alcohols to generate six-membered heterocylic compounds



Reaction conditions: **1** (0.3 mmol), 1,2-DCE (1.0 mL) and H_3PO_2 (10 mol %) was heated in an oil bath. [a]Isolated yields. [b]Reaction performed in DCE + Hexane (0.5 + 0.5 mL) at 100 °C. [c]Reaction performed in DCE + Hexane (0.5 + 1.0 mL) at 100 °C for 40 h. [d]Reaction performed with 20 mol% H_3PO_2 in DCE + Hexane (0.5 + 1.0 mL) at 90 °C for 48 h.

Mechanistic studies

Reaction progress

The reaction profile of the transformation of **1a** to **2a** was investigated (Figure 1). The reaction progress was monitored by ^{1}H-NMR spectroscopy where consumption of **1a** and formation of **2a** were measured. It was found that the overall reaction followed first-order kinetics with a half-life of around 10 hours.

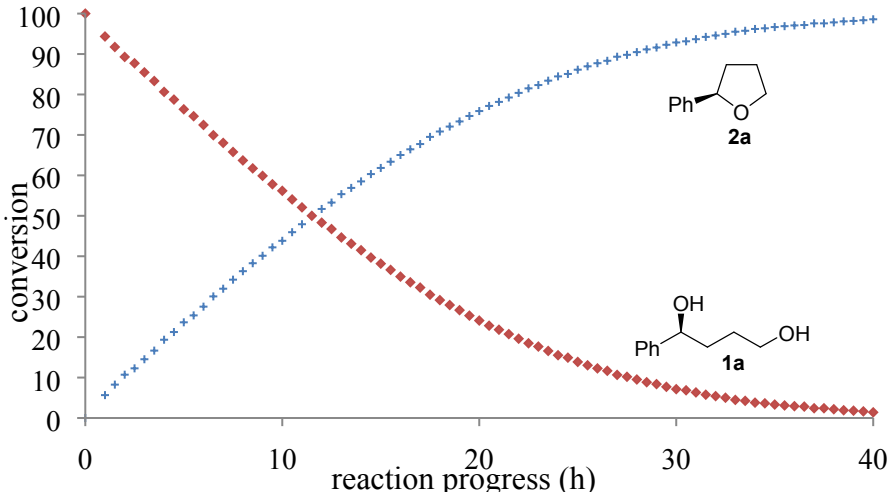


Figure 1. The substitution reaction profile of **1a** with 20 mol% of H_3PO_2.

Reaction condition: 0.1 mmol of **1a** and 20 mol% of H_3PO_2 in 0.5 mL of tetrachlroethane-D_4 at 80 °C

Rate-order determination: Catalyst

To get a better mechanistic understanding, a rate-order determination with respect to the catalyst was examined. The concentration of catalyst was varied in the reaction of **1a** to **2a**. From these results, it appears that the reaction follows a first-order dependence in catalyst concentrations between 0-20 mol% as shown in Figure 2.

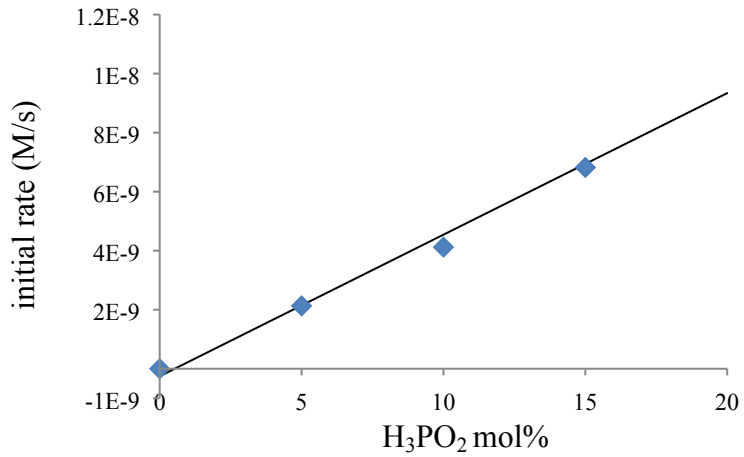
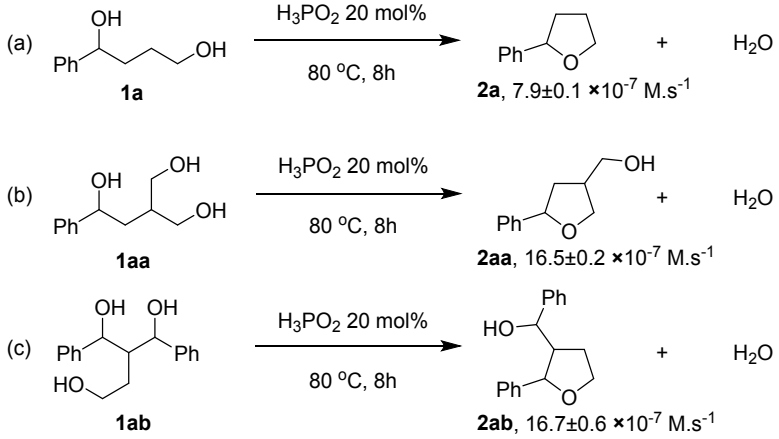


Figure 2. Rate-order determination using substrate **1a** (0.2 mmol in 1 mL of 1,2-DCE) with different concentration of H_3PO_2.

Rate dependencies of the substrate

Due to the nature of the substrate with both electrophile and nucleophile present, rate-order determination of these reactive centers is not possible. However, especially the rate dependency in especially the nucleophile is important in order to determine the reaction mechanism. Therefore, we synthesized substrate 3-(hydroxymethyl)-1-phenylbutane-1,4-diol (**1aa**) which has two terminal *O*-centered nucleophiles. In this experiment, we monitored the initial rate differences between substrate **1a** and **1aa** using 20 mol% of H_3PO_2. Substrate **1a** substituted the OH group to generate product **2a** with an observed rate of 7.9×10^{-7} $M.s^{-1}$ (Scheme 3a). Under the same reaction conditions, substrate **1aa** generated tetrahydrofuran **2aa** with an observed rate of 16.5×10^{-7} $M.s^{-1}$ (Scheme 3b). This discloses that the reaction rate is dependent on the nucleophile.

Next, we wanted to confirm the rate dependency in electrophile. We prepared 2-(hydroxy(phenyl)methyl)-1-phenylbutane-1,4-diol (**1ab**) which has two benzylic electrophiles. Employing the same reaction conditions, substrate **1ab** generated tetrahydrofuran **2ab** with an observed rate of 16.7×10^{-7} $M.s^{-1}$ (Scheme 3c).

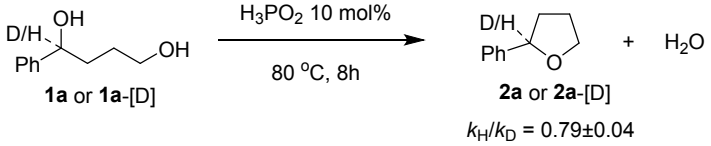


Scheme 3. Rate dependency in nucleophilic and electrophilic centers.

Reaction conditions: substrate (0.12 mmol), 1,2-DCE (1 mL) and H_3PO_2 (20 mol %) was heated in an oil bath at 80 °C. Rates of the reaction at 8 h were determined by ^{1}H-NMR spectroscopy.

Deuterium kinetic isotope effect measurement

Moreover, deuterium kinetic isotope effect (KIE) was measured by comparing the rate of substitution of **1a** and **1a**-[D]. A deuterium kinetic isotope effect (KIE = k_H/k_D = 0.79±0.04) was observed (Scheme 4) (see the Supporting Information for details). This inverse KIE also support an S_N2-like pathway.



Scheme 4. Kinetic Isotope Effect of nucleophilic substitution.

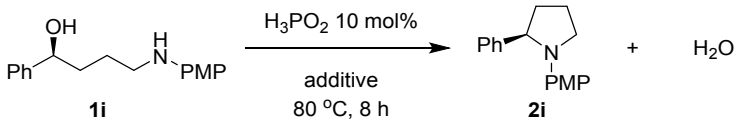
Reaction conditions: substrate (0.3 mmol), 1,2-DCE (1.5 mL) and H_3PO_2 (10 mol %) was heated in an oil bath at 80 °C. Rates of the reaction at 8 h were determined by ^{1}H-NMR spectroscopy.

Competition experiments

Competition experiments between substrate **1i** and external electrophile or nucleophile were performed (Table 6). We wanted to study the effect on both the initial rate of the reaction as well as the enantiospecificity. The substitution reaction of **1i** catalyzed by H_3PO_2 generated product **2i** with an observed rate of 5.1×10^{-7} M.s^{-1} and 96% e.s. after 8 hours reaction time (Table 6, entry 1). Addition of 1-phenylethanol (**1ac**) as an external electrophile to the reaction mixture only marginally affected the rate but not the enantiospecificity (Table 6, entry 2). Similarly, addition of external *N*-

methylaniline (**1ad**) did not inhibit the reaction (Table 6, entry 3). Instead a small increase of the rate was observed. Interestingly, no side-reactions from intermolecular substitution reactions where external nucleophile or electrophile were involved were observed. These experiments show that the catalyst is very selective towards the intramolecular substitution reaction.

Table 6. Competition experiments of **1i** with external electrophile and nucleophile.



Entry	Additive	Initial rate ($\times 10^{-7}$ M.s^{-1})[a]	e.s. (%)
1	-	5.1	96
2	1-phenylethanol (**1ac**)	4.4	98
3	*N*-methylaniline (**1ad**)	5.9	98

Reaction conditions: **1i** (0.08 mmol), additive (0.08 mmol), 1,2-DCE (1 mL) and H_3PO_2 (10 mol %) was heated in an oil bath at 80 °C. [a]Initial rates of the reaction at 8 h were determined by ^{1}H-NMR spectroscopy.

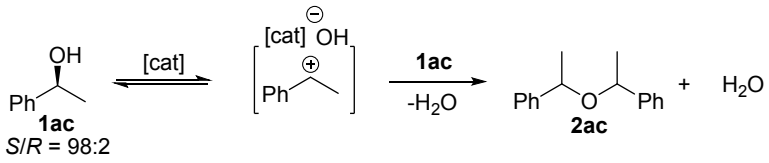
With this we can conclude that the rate of the reaction is dependent on catalyst and substrate having both internal nucleophile and electrophile, however independent on external nucleophile and electrophile. Therefore, the overall reaction shows a rate-order of second order according to the equation depicted in equation 1

$$d\frac{[\text{product}]}{\text{t}} = k[\text{H}_3\text{PO}_2][\text{substrate}] \qquad \text{(eq 1)}$$

Excluding S_N1 reactivity for H_3PO_2 catalysis

Rate-order determination studies showed that the rate is dependent on both internal nucleophile and electrophile. This is in agreement with a bimolecular reaction mechanism and supports an S_N2 pathway. Therefore, we wanted to furthermore exclude the S_N1 pathway. One way to do this is to study the etherification reaction of enantioenriched 1-phenylethanol ((*S*)-**1ac**) that proceed through an S_N1 pathway to generate racemic ether **2ac** (Scheme 5). In an S_N1 reaction, the rate determining step is the C─O bond cleavage to generate the carbocation. Once the carbocation is formed, the

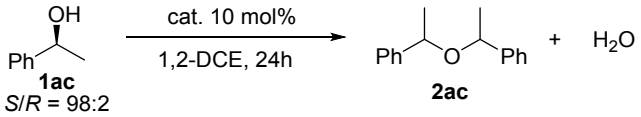
nucleophilic attack by another molecule of (*S*)-**1ac** occurs in a fast step. Thereby, substrate (*S*)-**1ac** act as both electrophile and nucleophile in this experiment.



Scheme 5. An S_N1 reaction using 1-phenylethanol **1ac**.

Interestingly, no reaction of substrate **1ac** was observed when H_3PO_2 was employed as catalyst. Only **1ac** was recovered after the reaction where a negligible racemization had occurred (Table 7, entry 1). In contrast, other catalysts that gave either low or good enantiospecificity in the catalyst screening (Table 1) promoted the formation of racemic **2ac**. For example, *p*-TSA that showed high enantiospecificity, gave racemic ether in a quantitative yield (Table 7, entry 3). These reactions clearly show that H_3PO_2 does not promote S_N1 reactivity under the employed reaction conditions.

Table 7. Racemization experiment of **1ac**



Entry	Catalyst	**2ac**[a]	T (°C)	Recovered **1ac**
1	-	-	80	> 99% (S/R = 98:2)
2	H_3PO_2	< 5%	80	> 95% (S/R = 96:4)
3	*p*-TSA	> 95%	40	0%
4	TfOH	> 20%	40	0%
5	$FeCl_3$	> 95%	40	0%

Reaction Condition: **1ac** (1 mmol), 1,2-DCE (1.5 mL) and catalyst (10 mol %) was heated in an oil bath. [a]NMR yield.

To conclude the results from the experiments, the H_3PO_2 gives rise to a unique reactivity that promotes an S_N2 pathway for substrates that have an internal nucleophile. Interestingly, H_3PO_2 does not promote C─O bond cleavage in the absence of an internal nucleophile. To shed more light on the reaction mechanism and the transition state, DFT studies were performed.

Density Functional Theory calculations

The phosphinic acid catalyst has a Brønsted acid site that presumably protonates the OH group of the electrophile in the transition state. However, this activation is not sufficient to promote C─O bond cleavage as showed in the etherification reaction of **1ad** (Table 7). Thereby, H_3PO_2 might have an additional role in the reaction. Plausibly, H_3PO_2 acts as a bifunctional catalyst. Previous reports support that the oxo group in phosphorous acids may act as a Brønsted base. [18] In this case, H_3PO_2 may act as a bifunctional catalyst that simultaneously activates both the nucleophile and the nucleofuge in an S_N2-type reaction. DFT calculations were performed to study the transformations from **1a-1c** to **2a-2c** using the B3LYP functional as implemented in the Gaussian 09 package (see the Supporting Information for details).[11] Early on, low TS was located in which H_3PO_2 showed a bifunctional role. In this TS, the acidic hydrogen protonates the leaving OH group of the electrophile to promote C–O bond cleavage, simultaneously as the oxo-group of the catalyst partially deprotonates the nucleophile. As shown in Figure 3, this bridging TS between substrate and catalyst results in an S_N2-type reaction mechanism. The energy barriers for the calculated transition states for *O*-, *N*-, and *S*-centered nucleophiles (**1a** → **2a**, **1b** → **2b** and **1c** → **2c**) were found and calculated to be 27.3, 23.1 and 26.8 kcal/mol, respectively. These values are in accordance with experimental results where *N*-centered nucleophiles were reactive at a lower reaction temperature (60 °C), than *O*- and *S*-centered nucleophiles (80 °C).

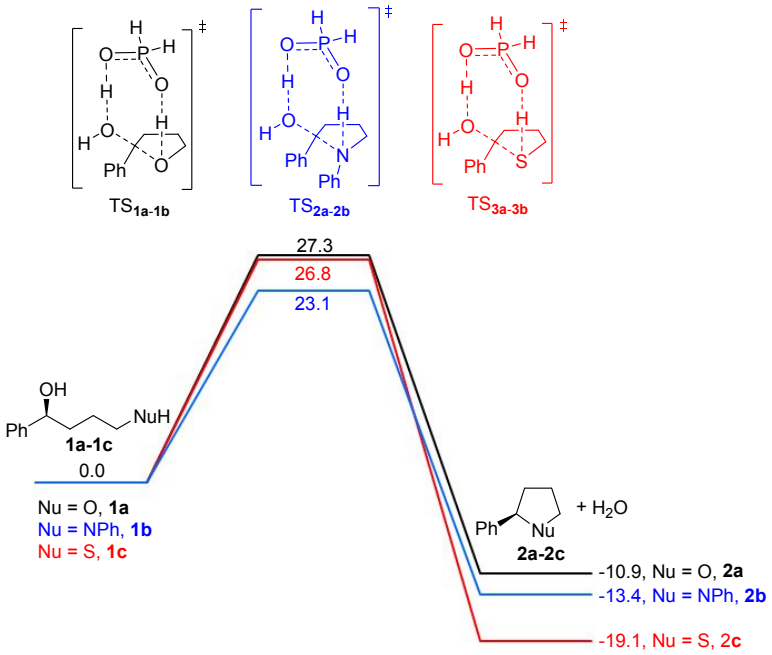


Figure 3. Calculated transition state structures with H_3PO_2 and their calculated energies (kcal/mol) for transformations from **1a-1c** to **2a-2c**.

Transition states for other acids (*p*-TSA, Ph_2HPO_2 and AcOH) seemingly similar to H_3PO_2 were also calculated. We used *O*-centered nucleophile **1a** as a model substrate (Table 1, Figures 1 and 2). As can be seen in Figure 4, the TS calculated for *p*-TSA was 21.1 kcal/mol. This result corresponds to the experimental outcome in which the stronger acid promotes the reaction at a lower temperature (40 °C). On the other hand, weaker acids did not promote reactivity under the employed reaction conditions (80 °C). For example, acetic acid did not promote reactivity in the intramolecular substitution. The transition state was calculated to 36.6 kcal/mol. The seemingly similar Ph_2HPO_2 gave a calculated transition state of 27.6 kcal/mole which is very close to H_3PO_2. We performed the reaction of **1a** to **2a** using a slightly higher reaction temperature. Interestingly, and in accordance to the calculations, Ph_2HPO_2 became reactive when the temperature was raised (reflux, toluene). Thereby, the calculations correlate with experimental data for the transformations and support an S_N2 TS for the intramolecular substitution reaction catalyzed by H_3PO_2.

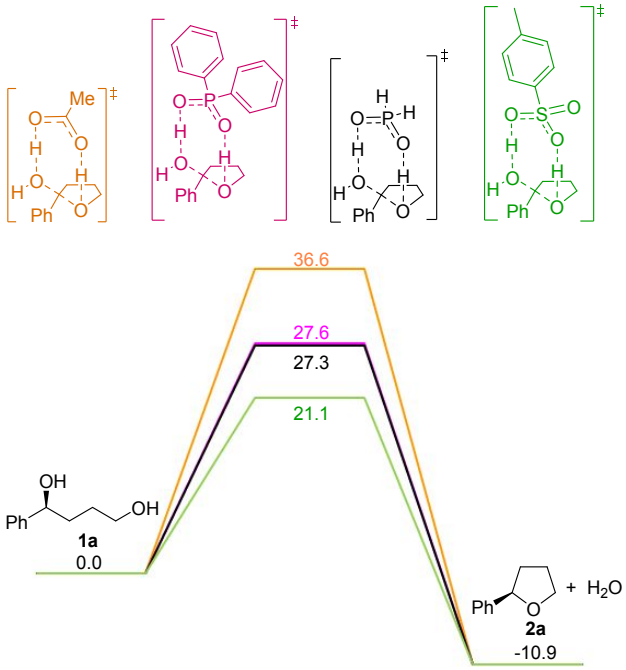


Figure 4. Calculated transition state structures with H_3PO_2, *p*-TSA, AcOH, and Ph_2HPO_2 and their calculated energies (kcal/mol) for transformations from **1a** to **2a**.

Conclusions

The direct intramolecular stereospecific substitution of the OH group of enantioenriched secondary alcohols catalyzed by phosphinic acid has been developed. The OH group of aryl, allyl, propargyl, and alkyl alcohols was substituted by *O*-, *S*-, and *N*-centered nucleophiles to generate five- and six-membered heterocycles in good to excellent yield with high enantiospecificity. Experimental studies show that phosphinic acid does not promote S_N1 reactivity. Studies of rate dependencies show dependency in catalyst and both nucleophilic and electrophilic center. Kinetic isotope effect studies disclose an inverse KIE. DFT calculations corroborate a reaction pathway in which the phosphinic acid operates as a bifunctional Brønsted acid/Brønsted base to simultaneously activate both the nucleophile and nucleofuge in an S_N2-type transition state. The acidic proton of the phosphinic acid protonates the hydroxyl group enhancing the leaving group ability simultaneously as the oxo group of phosphinic acid partially deprotonate the nucleophile enhancing the nucleophilicity in a bridging transition state to promote the reactivity. Thereby, a broad range of easily accessible enantioenriched secondary alcohols can be used as substrates in intramolecular substitutions by various nucleophiles

to generate heterocyclic compounds in which the chirality from the starting material has been conserved to the product.

Experimental Section

General procedure for H_3PO_2-catalyzed intramolecular stereospecific substitution

A glass vial was charged with alcohol **1a** (50 mg, 0.30 mmol) in 1.0 mL of 1,2-DCE, was added 50% (*v*/*v*) aqueous solution of H_3PO_2 (7.5 µL, 0.1 mmol). The reaction vial was capped and the mixture was heated up to 80 °C for 24 hours. After completion (TLC), the crude was concentrated under reduced pressure (without work-up) and a fast column chromatographic purification was performed using silica gel (mess 100-200) and 10% ethyl acetate/*n*-pentane to obtain pure **2a** (48 mg, 0.29 mmol, 99% yield) as colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.34–7.31 (m, 4 H, H-arom), 7.27–7.24 (m, 1 H, H-arom), 4.91–4.88 (m, 1 H, H-2), 4.13–4.07 (m, 1 H, H-5), 3.97–3.91 (m, 1 H, H-5), 2.37–2.29 (m, 1 H, H-3), 2.05–1.97 (m, 1 H, H-4), 1.86–1.79 (m, 1 H, H-3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 144.1, 128.7, 127.9, 125.7, 73.9, 68.0, 34.7, 24.6 ppm. The enantiomeric ratio of **2a** was determined by HPLC analysis using Daicel Chiralcel AD column: *n*-hexane : isopropanol = 99.8:0.2, flow rate 0.5 mL/min, λ = 254 nm (channel 1): t_1 (minor) = 10.2 min, t_2 (major) = 11.6 min.

Associated Content

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXX.

Experimental details, computational details, spectroscopy data and HPLC chromatograms (PDF).

Author Information

Corresponding Author

*E-mail: joseph.samec@su.se (J. S. M. Samec), rahulwatile@gmail.com (R.A. Watile)

ORCID

Anon Bunrit: 0000-0003-0203-8478

Pemikar Srifa: 0000-0002-4233-9075

Christian Dahlstrand: 0000-0003-2485-8661

Thanya Rukkijakan: 0000-0003-3020-631X

Genping Huang: 0000-0002-2249-1248

Srijit Biswas: 0000-0003-2363-7381

Rahul A. Watile: 0000-0002-5890-0867

Joseph S. M. Samec: 0000-0001-8735-5397

Notes

The authors declare no competing financial interest.

Acknowledgements

J.S.M.S. thanks the Swedish Research Council (FORMAS), Olle Engkvist Byggmästare, and Wenner-Gren for financial support. Computer time was generously granted by the Swedish National Infrastructure for Computing.

References

[1] (a) Trost, B. M. The Atom Economy--A Search for Synthetic Efficiency. *Science* **1991**, *254*, 1471–1477. (b) Corma, A.; Iborra, S.; Velty, A. Chemical Routes for the Transformation of Biomass into Chemicals. *Chem. Rev.* **2007**, *107*, 2411–2502.

[2] Nacsa, E. D.; Lambert, T. H. Cyclopropenone Catalyzed Substitution of Alcohols with Mesylate Ion. *Org. Lett.* **2013**, *15*, 38–41. (b) Kelly, B. D.; Lambert T. H. Aromatic Cation Activation of Alcohols: Conversion to Alkyl Chlorides Using Dichlorodiphenylcyclopropene. *J. Am. Chem. Soc.* **2009**, *131*, 13930–13931.

[3] Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, *1981*, 1–28.

[4] (a) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. Catalytic Carbonyl Addition through Transfer Hydrogenation: A Departure from Preformed Organometallic Reagents. *Angew. Chem., Int. Ed.* **2009**, *48*, 34–46. (b) Kumagai, N.; Shibasaki, M. Recent Advances in Direct Catalytic

Asymmetric Transformations under Proton-Transfer Conditions. *Angew. Chem., Int. Ed.* **2011**, *50*, 4760–4772. (c) Dobereiner, G. E.; Crabtree, R. H. Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis. *Chem. Rev.* **2010**, *110*, 681–703. (d) Guillena, G.; Ramon, D. J.; Yus, M. Hydrogen Autotransfer in the N-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev.* **2010**, *110*, 1611–1641. (e) Han, X.; Wu, J. Redox Chain Reaction—Indole and Pyrrole Alkylation with Unactivated Secondary Alcohols. *Angew. Chem., Int. Ed.* **2013**, *52*, 4637–4640.

[5] (a) Katritzky, A. R.; Brycki, B. E. The Mechanisms of Nucleophilic Substitution in Aliphatic Compounds. *Chem. Soc. Rev.* **1990**, *19*, 83–105. (b) Sheldon, R. A. Atom Efficiency and Catalysis in Organic Synthesis. *Pure Appl. Chem.* **2000**, *72*, 1233–1246. (c) Asai, S.; Kato, Monguchi, Y.; Sajiki, H.; Sawama, Y. Cyclic Ether Synthesis from Diols Using Trimethyl Phosphate. *Chem. Commun.*, **2017**, *53*, 4787–4790.

[6] Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R., Jr.; Leazer, J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. Key Green Chemistry Research Areas—A Perspective from Pharmaceutical Manufacturers. *Green Chem.* **2007**, *9*, 411–420.

[7] (a) Dryzhakov, M.; Richmond, E.; Moran J. Recent Advances in Direct Catalytic Dehydrative Substitution of Alcohols. *Synthesis* **2016**, *48*, 935–959. (b) Emer, E.; Sinisi, R.; Capdevila, G.; Petruzziello, D.; Vincentiis, F. D.; Cozzi P.G. Direct Nucleophilic S_N1-Type Reactions of Alcohols. *Eur. J. Org. Chem.* **2011**, *2011,* 647–666. (c) Tamaru, Y. Activation of Allyl Alcohols as Allyl Cations, Allyl Anions, and Amphiphilic Allylic Species by Palladium. *Eur. J. Org. Chem.* **2005**, *2005,* 2647–2656. (d) Muzart, J. Procedures for and Possible Mechanisms of Pd-Catalyzed Allylations of Primary and Secondary Amines with Allylic Alcohols. *Eur. J. Org. Chem.* **2007**, *2007,* 3077–3089. (e) Muzart, J. Palladium-Catalysed Reactions of Alcohols. Part B: Formation of C-C And C-N Bonds from Unsaturated Alcohols. *Tetrahedron* **2005**, *61*, 4179–4212. (f) Biswas, S.; Samec, J. S. M. The Efficiency of the Metal Catalysts in the Nucleophilic

Substitution of Alcohols is Dependent on the Nucleophile and not on the Electrophile. *Chem. Asian J.* **2013**, *8*, 974–981.

[8] It should be noted that usage of chiral catalysts can achieve enantioenriched products from the hydrogen borrowing methodology, see for example: (a) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. Catalytic Carbonyl Addition through Transfer Hydrogenation: A Departure from Preformed Organometallic Reagents. *Angew. Chem., Int. Ed.* **2009**, *48*, 34–46. (b) Kumagai, N.; Shibasaki, M. Recent Advances in Direct Catalytic Asymmetric Transformations under Proton-Transfer Conditions. *Angew. Chem., Int. Ed.* **2011**, *50*, 4760–4772. (c) Dobereiner, G. E.; Crabtree, R. H. Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis. *Chem. Rev.* **2010**, *110*, 681–703.

[9] (a) Aponick, A.; Biannic, B. Chirality Transfer in Au-Catalyzed Cyclization Reactions of Monoallylic Diols: Selective Access to Specific Enantiomers Based on Olefin Geometry. *Org. Lett.* **2011**, *13*, 1330–1333. (b) Mukherjee, P.; Widenhoefer, R. A. The Regio- and Stereospecific Intermolecular Dehydrative Alkoxylation of Allylic Alcohols Catalyzed by a Gold(I) N-Heterocyclic Carbene Complex. *Chem.—Eur. J.* **2013**, *19*, 3437–3444. (c) Mukherjee, P.; Widenhoefer, R. A. Gold(I)-Catalyzed Intramolecular Amination of Allylic Alcohols with Alkylamines. *Org. Lett.* **2011**, *13*, 1334–1337. (d) Mukherjee, P.; Widenhoefer, R. A. Gold(I)-Catalyzed Amination of Allylic Alcohols with Cyclic Ureas and Related Nucleophiles. *Org. Lett.* **2010**, *12*, 1184–1187. (e) Kawai, N.; Jean-Marie, L.; Ohmi, M.; Uenishi, J. Palladium-Catalyzed Stereospecific Synthesis of 2,6-Disubstituted Tetrahydropyrans: 1,3-Chirality Transfer by an Intramolecular Oxypalladation Reaction. *J. Org. Chem.* **2006**, *71*, 4530–4537. (f) Mukherjee, P.; Widenhoefer R. A. Gold(I)-Catalyzed Enantioselective Intramolecular Dehydrative Amination of Allylic Alcohols with Carbamates. *Angew. Chem. Int. Ed.* **2012**, *51*, 1405–1407.

[10] (a) Ghebreghiorgis, T.; Biannic, B.; Kirk, B. H.; Ess, D. H.; Aponick, A. The Importance of Hydrogen Bonding to Stereoselectivity and Catalyst Turnover in Gold-Catalyzed Cyclization of Monoallylic Diols. *J. Am. Chem. Soc.* **2012**, *134*, 16307–16318. (b) Ghebreghiorgis, T.; Biannic,

B.; Kirk, B. H.; Aponick, A.; Ess, D. H. Multiple Mechanisms in Pd(II)-Catalyzed S_N2' Reactions of Allylic Alcohols. *J. Org. Chem.* **2013**, *78*, 7664–7673.

[11] (a) Jefferies, L. R.; Cook, S. P. Iron-Catalyzed Arene Alkylation Reactions with Unactivated Secondary Alcohols. *Org. Lett.* **2014**, *16*, 2026–2029. (b) Bandini, M.; Tragni, M.; Umani-Ronchi A. Iron(III)-Catalyzed Intramolecular Friedel–Crafts Alkylation of Electron-Deficient Arenes with π-Activated Alcohols. *Adv. Synth. Catal.* **2009**, *351*, 2521–2524.

[12] Marcyk, P. T.; Jefferies, L. R.; Abu Salim, D. I.; Pink, M.; Baik, M.-H.; Cook, S. P. Stereoinversion of Unactivated Alcohols by Tethered Sulfonamides. *Angew. Chem. Int. Ed.,* **2019**, *58*, 1727–1731.

[13] Bunrit, A.; Dahlstrand, C.; Olsson, S. K.; Srifa, P.; Huang, G.; Orthaber, A.; Sjöberg, P. G. R.; Biswas, S.; Himo, F. Samec, J. S. M. Brønsted Acid-Catalyzed Intramolecular Nucleophilic Substitution of the Hydroxyl Group in Stereogenic Alcohols with Chirality Transfer. *J. Am. Chem. Soc.* **2015**, *137*, 4646–4649.

[14] (a) Kischel, J.; Mertins, K.; Michalik, D.; Zapf, A.; Beller, M. A General and Efficient Iron-Catalyzed Benzylation of 1,3-Dicarbonyl Compounds. *Adv. Synth. Catal.* **2007**, *349*, 865–870. (b) Biswas, S.; Maiti, S.; Jana, U. New and Efficient Iron Halide Mediated Synthesis of Alkenyl Halides through Coupling of Alkynes and Alcohols. *Eur. J. Org. Chem.* **2009**, 2354–2359. (c) Nishimoto, Y.; Onishi, Y.; Yasuda, M.; Baba, A. α-Alkylation of Carbonyl Compounds by Direct Addition of Alcohols to Enol Acetates. *Angew. Chem. Int. Ed.* **2009**, *48*, 9131–9134. (d) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. An Efficient and General Iron-Catalyzed Arylation of Benzyl Alcohols and Benzyl Carboxylates. *Angew. Chem. Int. Ed.* **2005**, *44*, 3913–3917.

[15] (a) Yi, W.-B.; Cai, C. Rare Earth(III) Perfluorooctanesulfonates Catalyzed Friedel-Crafts Alkylation in Fluorous Biphase System. *J. Fluorine Chem.* **2005**, *126*, 831–833. (b) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. Dehydrative C–H Alkylation and Alkenylation of Phenols with Alcohols: Expedient Synthesis for Substituted Phenols and Benzofurans. *J. Am. Chem. Soc.* **2012**, *134*, 7325–7328.

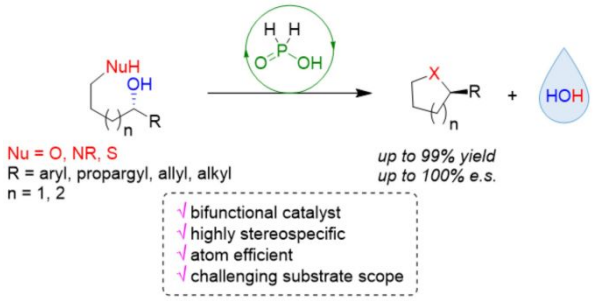
[16] Mortelmans, C.; Van Binst, G. Synthesis of 9,10-Dihydro-8bh-Quino[1,2-f]Phenanthridine- and 6-Phenyl-4,5,6,7-Tetrahydropyrido[3,2,1-j,k]-Carbazole-Derivatives. *Tetrahedron* **1978**, *34*, 363–369.

[17] (a) Lipshutz, B. H.; Chung, D. W.; Rich, B.; Corral R. Simplification of the Mitsunobu Reaction. Di-*p*-chlorobenzyl Azodicarboxylate: A New Azodicarboxylate. *Org. Lett.* **2006**, *8*, 5069–5072. (b) Kelly, B. D.; Lambert, T. H. Cyclopropenium-Activated Cyclodehydration of Diols. *Org. Lett.*, **2011**, *13*, 740–743. (c) Wilkinson, J. A.; Raiber, E. A.; Ducki, S. New Stabilising Groups for Lateral Lithiation of Ortho-Cresol Derivatives and a New Route to 2-Substituted Chromans. *Tetrahedron* **2008**, *64*, 6329–6333. (d) Hullio, A. A.; Mastoi G. M. Ionic Liquid Based Vilsmeier Reagent as a Substitute for Mitsunobu Reagent: Direct Conversion of Alcohols into Different Compounds under Ionic Liquid Conditions. *Int. J. Chem.* **2013**, *3*, 57–69.

[18] (a) Chen, M.; Sun, J. How Understanding the Role of an Additive Can Lead to an Improved Synthetic Protocol without an Additive: Organocatalytic Synthesis of Chiral Diarylmethyl Alkynes. *Angew. Chem. Int. Ed.* **2017**, *56*, 11966–11970. (b) Chatterjee, S.; Hintermann, L.; Mandal, M.; Achari, A.; Gupta, S.; Jaisankar, P. Fiaud's Acid: A Brønsted Acid Catalyst for Enantioselective Friedel–Crafts Alkylation of Indoles with 2-Alkene-1,4-diones. *Org. Lett.* **2017**, *19*, 3426–3429. (c) Xie, E.; Rahman, A.; Lin, X. Asymmetric Synthesis of CF_3- and Indole-Containing Tetrahydro-β-Carbolines via Chiral Spirocyclic Phosphoric Acid-Catalyzed Aza-Friedel–Crafts Reaction. *Org. Chem. Front.* **2017**, *4*, 1407–1410. (d) Dai, W.; Jiang, X-L.; Tao, J-Y.; Shi, F. Application of 3-Methyl-2-vinylindoles in Catalytic Asymmetric Povarov Reaction: Diastereo- and Enantioselective Synthesis of Indole-Derived Tetrahydroquinolines. *J. Org. Chem.* **2016**, *81*, 185–192. (e) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047–9153. (f) Chen, D.-F.; Han, Z.-Y.; Zhou, X.-L.; Gong, L-Z. Asymmetric Organocatalysis Combined with Metal Catalysis: Concept, Proof of Concept, and Beyond. *Acc. Chem.*

Res. **2014**, *47*, 2365–2377. (g) Reuping, M.; Kuenkel, A.; Atodiresei, I. Chiral Brønsted Acids in Enantioselective Carbonyl Activations–Activation Modes and Applications. *Chem. Soc. Rev.* **2011**, *40*, 4539–4549. (h) Simón, L.; Goodman, J. M. Theoretical Study of the Mechanism of Hantzsch Ester Hydrogenation of Imines Catalyzed by Chiral BINOL-Phosphoric Acids. *J. Am. Chem. Soc.* **2008**, *130*, 8741–8747. (i) Marcelli, T.; Hammar, P.; Himo, F. Phosphoric Acid Catalyzed Enantioselective Transfer Hydrogenation of Imines: A Density Functional Theory Study of Reaction Mechanism and the Origins of Enantioselectivity. *Chem.—Eur. J.* **2008**, *14*, 8562–8571. (j) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. Chiral Brønsted Acid Catalyzed Enantioselective Mannich-Type Reaction. *J. Am. Chem. Soc.* **2007**, *129*, 6756–6764. (k) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568.

TOC


NuH
OH
R
n
H H
O P OH
X
R
n
+
HOH
Nu = O, NR, S
R = aryl, propargyl, allyl, alkyl
n = 1, 2
up to 99% yield
up to 100% e.s.
√ bifunctional catalyst
√ highly stereospecific
√ atom efficient
√ challenging substrate scope