Asymmetric Organocatalysis

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Brønsted Acid Catalyzed Asymmetric S_N2-Type O-Alkylations**

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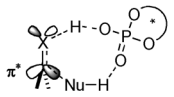
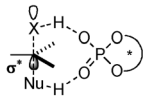
Asymmetric Brønsted acid catalysis has flourished in recent years especially in the context of nucleophilic additions to carbon-based electrophiles.[1] These reactions generally involve the formal approach of nucleophiles at the π* orbital of an sp^2-hybridized carbon atom of electrophiles, typically imines, but also aldehydes, ketones, or certain Michael acceptors.[2] In contrast, substitution reactions involving nucleophilic attack at the σ* orbital of an sp^3-hybridized carbon atom are underexplored in this context. The bifunctional nature of chiral phosphoric acids could offer unique opportunities for catalyzing such reactions. We hypothesized that these acids could bridge the trigonal bipyramidal transition state of an S_N2 reaction, to simultaneously activate both the leaving group and the nucleophile.[3]



chiral phosphoric acid catalyzed nucleophilic addition to an sp^2-hybridized carbon center
established activation mode



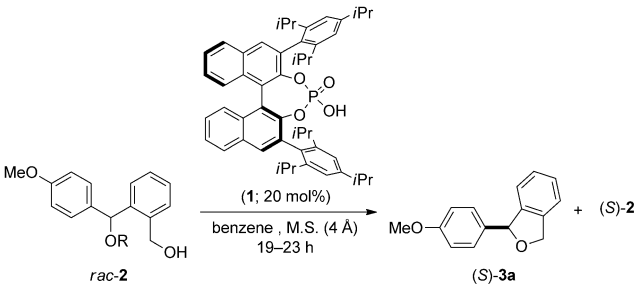
chiral phosphoric acid catalyzed nucleophilic substitution at an sp^3-hybridized carbon center
underexplored activation mode

The proposed activation mode could potentially enable access to a large group of S_N2-type alkylation reactions. Asymmetric Brønsted acid catalysis has already been successfully applied to various alkylation reactions that proceed through an S_N1-type mechanism,[4] but the analogous S_N2 reactions are rare.[5–7] Herein, we describe the development of Brønsted acid catalyzed asymmetric S_N2-type O-alkylation reactions employing benzylic ethers as electrophiles. We show that the phosphoric acid TRIP catalyzes highly enantioselective intramolecular transetherification reactions of hydroxy ethers resulting in an efficient kinetic resolution.

Encouraged by our recent discovery that chiral phosphoric acids are able to activate an acetal moiety,[8] we hoped that Brønsted acids of this type could potentially also activate the relatively unreactive ether groups and catalyze an analogous though previously unprecedented and much more challenging asymmetric transetherification reaction.[9]

For the initial studies we selected ethyl benzhydryl ether as substrate and (*S*)-TRIP (**1**) as catalyst (Table 1, entry 1).[10] The benzhydryl ether was chosen as it was expected to be a good substrate for either S_N2- or S_N1-type reactions.[11] Indeed, the reaction proceeded at a slightly elevated temperature with 20 mol% of the catalyst and furnished 1,3-dihydroisobenzofuran **3a** with moderate enantioselectivity (Table 1, entry 1). When free alcohol was used instead of the ethyl ether, the enantioselectivity dropped sharply (Table 1, entry 2). However, an increase in the steric bulk of the leaving group to *iso*-propyl ether had a positive impact on the selectivity (Table 1, entry 3). These results suggested that the leaving group is involved in the enantiodetermining step of the reaction. Encouraged by this observation, we prepared substrate with a bulky $(i\text{Pr})_2\text{CH}$ group (Table 1, entry 4). However, the enantioselectivity was decreased in comparison to the *i*Pr substituted ether. Gratifyingly, by using *tert*-butyl ether **2a**, product **3a** could be obtained with a high enantiomeric ratio of 93.5:6.5 at 49% conversion (Table 1, entry 5). Interestingly, substrate **2a** also exhibited a significantly higher reactivity compared to the other ether substrates. Examining the remaining starting material revealed that a kinetic resolution had taken place. The e.r. of recovered ether (*S*)-

Table 1: Reaction development.



Entry	R	*T*	Conv. [%][a]	e.r. (**3a**)[b]
1	Et	40 °C	26	81:19
2	H	RT	32	63:37
3	*i*Pr	40 °C	35	87.5:12.5
4	$(i\text{Pr})_2\text{CH}$	40 °C	29	73.5:26.5
5	*t*Bu (**2a**)	40 °C	49	93.5:6.5 (*s*=37)
6[c]	*t*Bu (**2a**)	50 °C	56	89:11 (*s*=33)

[a] Determined by ^{1}H NMR analysis or calculated from *ee* values of the product and the recovered starting material. [b] Determined by HPLC analysis on a chiral stationary phase. [c] 5 mol% of the catalyst, PhCl as the solvent, without molecular sieves (M.S.).

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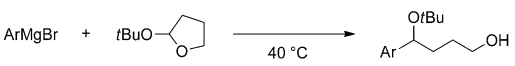
2a was 91.5:8.5, corresponding to a selectivity factor (*s*) of 37, where the selectivity factor = (rate of fast-reacting enantiomer)/(rate of slow-reacting enantiomer). Further optimization enabled us to use only 5 mol% of the catalyst while retaining high selectivity (Table 1, entry 6).

Having optimized the reaction conditions we explored the generality of the transformation (Table 2). We were particularly interested in applying the reaction to less-reactive substrates. As expected, removing the electron-donating methoxy group from the substrate had a negative effect on the reaction rate and selectivity (Table 2, entry 2). At 80 °C, product **3b** could be obtained with a moderate selectivity factor of 8. However, kinetic resolution employing tertiary alcohols proceeded with an exceptional enantioselectivity giving selectivity factors of 142 and 179 (Table 2, entries 3 and 4). Notably, the tertiary alcohol substrates exhibited significantly higher reactivity than primary alcohol *rac*-**2b**. Chloro-substituted substrate *rac*-**2e** gave a similarly high enantioselectivity, albeit the reaction was slightly slower (Table 2, entry 5). The combination of a tertiary alcohol nucleophile and an electron-rich aromatic system resulted in a superb kinetic resolution with a selectivity factor greater than 500, which is similar to the values obtained for enzyme-catalyzed reactions (Table 2, entry 6). Encouraged by these results, we next explored simpler substrates that lack the aromatic tether. Gratifyingly, the reaction of ether *rac*-**2g** proceeded with a selectivity factor of 44 at 50 °C (Table 2, entry 7). The reaction of the isomeric *ortho*-methoxy-substituted benzyl ether *rac*-**2h** proceeded with a selectivity factor of 25 although a significantly higher temperature of 80 °C was necessary (Table 2, entry 8). With the simple unsubstituted benzyl ether *rac*-**2i**, an even higher temperature of 120 °C was required. Remarkably, the reaction still proceeded with good selectivity (Table 2, entry 9). Tertiary alcohols *rac*-**2j** and *rac*-**2k** underwent the transetherification reaction at the same temperature with impressive selectivity factors of 82 and 58 (Table 2, entries 10 and 11). Such excellent enantioselectivity is rarely encountered in Brønsted acid catalysis at high temperatures,[2,12,13] therefore suggesting the reaction has a well-organized transition state.

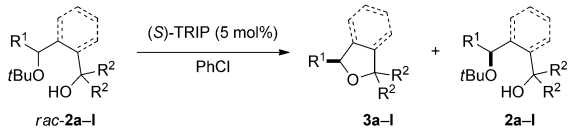
Heteroaryls can also be used in our alkylation reaction. Bisheterocycle **3l** could be readily obtained with a selectivity factor of 36 (Table 2, entry 12). Our transetherification reaction is particularly suitable for obtaining biologically relevant[14] 2-substituted tetrahydrofurans, such as **3g–i** and **3l**, as the starting alcohols can be easily obtained from the corresponding (hetero)aryl bromides [Eq. (1); see the Supporting Information].[15]

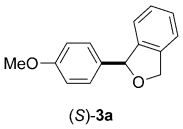
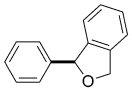
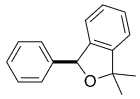
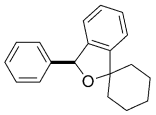
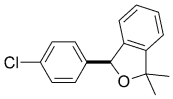
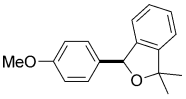
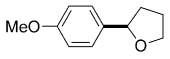
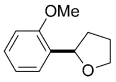
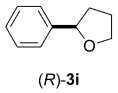
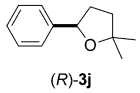
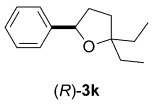
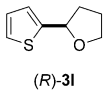


(1)

The absolute configurations of product **3i** and of the recovered enantioenriched **2i** were determined to be (*R*) by comparison of the optical rotation with literature data and with an authentic sample made by an alternative synthesis, respectively (see the Supporting Information). A single crystal X-ray analysis of compound (*S*)-**3f** confirmed that benzene tethered substrates show the same sense of enan-

Table 2: TRIP-catalyzed asymmetric benzylation of alcohols.

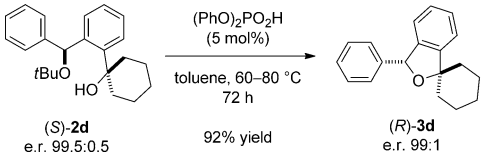


Entry	*T* [°C] (*t* [h])	Conv. [%][a]	Product	*s*
1	50 (22)	56	 (*S*)-**3a**	33
2	80 (46)	42	 (*S*)-**3b**	8
3	60 (16)	50	 (*S*)-**3c**	142
4	60 (16)	51	 (*S*)-**3d**	179
5	60 (25)	48	 (*S*)-**3e**	161
6	20 (10)	51	 (*S*)-**3f**	570
7	50 (24)	50	 (*R*)-**3g**	44
8	80 (21)	43	 (*R*)-**3h**	25
9	120 (22)	48	 (*R*)-**3i**	16
10	120 (22)	47	 (*R*)-**3j**	82
11	120 (24)	53	 (*R*)-**3k**	58
12	40 (70)	49	 (*R*)-**3l**	36

[a] Calculated from *ee* values of the product and the recovered starting material.

tioinduction (see the Supporting Information, Figure S1). The absolute configurations of other products were assigned by analogy.

The fact that the reaction proceeds with an inversion of the configuration of the secondary benzyl stereocenter is consistent with an S_N2-type mechanism. The strong influence of the leaving group (Table 1) and the alcohol nucleophile (Table 2, entries 2–4 and 9–11) on the reaction enantioselectivity indicates that both are involved in the transition state, which further corroborates an S_N2-type reaction. In accordance with an S_N2 mechanism, stereospecific inversion also occurred when an enantioenriched starting material was treated with an achiral Brønsted acid [Eq. (2)].[16] Trans-



(2)

etherification of ether (*S*)-**2d** catalyzed by diphenyl phosphoric acid furnished tetracycle (*R*)-**3d**, demonstrating that neither the product nor the starting material racemize to a significant extent during the reaction. In addition, the participation of an S_N1-type pathway that would lead to loss of enantiomeric purity of the product could be excluded.

The reaction mechanism of the TRIP-catalyzed intramolecular alkylation of **2i** (Table 2, entry 9) was further studied using density functional theory. Geometry optimizations and intrinsic reaction coordinate (IRC) calculations were performed at the B3LYP/6-31G* level. Single-point calculations at the gas-phase optimized geometries were carried out with larger basis sets (6-31 + G**) and with inclusion of continuum solvation and empirical dispersion corrections to arrive at more accurate energetics. The Supporting Information contains details on the applied computational methods and the numerical results (Tables S1–S4) as well as additional computational data on other pathways considered (Scheme S1 and Figure S2).

Rewardingly, our initial predictions were indeed confirmed by theory showing the Brønsted acid to act as a bifunctional activator bridging the pentacoordinate transition state. For substrate **2i**, the barrier to nucleophilic substitution through the S_N1-type pathway was found to be significantly higher than the barrier to cyclization through the S_N2-type pathway. In the lowest-energy transition state for the S_N2-type substitution reaction (Figure 1), the leaving group is activated by proton transfer from the catalyst, the alcohol nucleophile is activated by hydrogen bonding to the Brønsted basic oxygen atom of the catalyst, and there is an additional stabilizing interaction between the catalyst and the hydrogen atom (H2) on the reacting carbon atom. The reaction profile along the IRC path resembles a classic S_N2 process (Figure 2) accompanied by two proton transfers.

The catalyst initially protonates the leaving group (at O4) to facilitate its later departure, the actual substitution (at C1) with the synchronous formation and splitting of bonds occurs in the transition state region of the IRC path, and in the final stage of the reaction, the catalyst recovers a proton from the

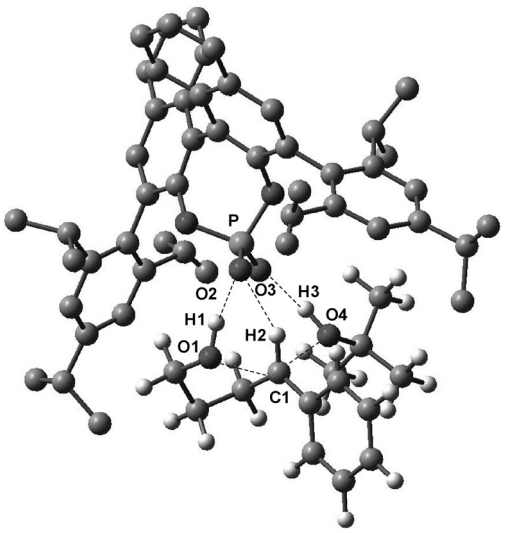


Figure 1. B3LYP/6-31G* optimized structure of the S_N2-type transition state leading to (*R*)-**3i**. Selected distances (Å): O2—H1 1.72, O2—H2 2.17, O3—H3 1.69, C1—O1 2.50, C1—O4 2.19.

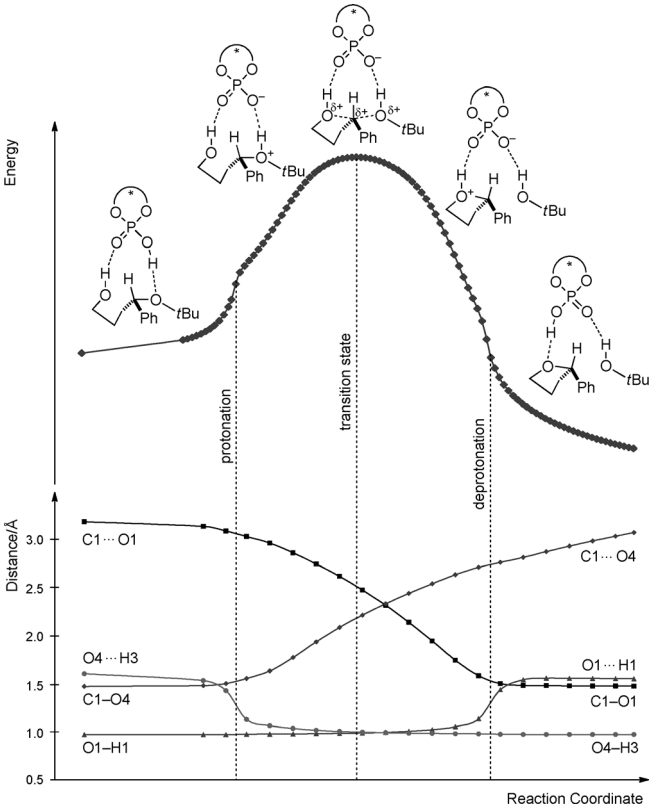


Figure 2. Energy and selected distances along the intrinsic reaction coordinate. For atom designations see Figure 1.

nucleophile (at O1). This theoretical scenario is in accordance with the experimentally observed increase in reactivity of the starting ethers in the order: *t*Bu > *i*Pr > Et (Table 1, entries 1, 3, and 5), with more electron-rich ethers favoring the initial protonation event. The transition state for (*S*)-**3i** was found to be 2.4 kcal mol^{-1} higher in free energy than the transition

state for (*R*)-**3i** (see the Supporting Information, Table S1); this value is in excellent agreement with the free energy difference of 2.2 kcal mol^{-1} calculated from the experimentally determined selectivity factor.[17] A highly organized S_N2-type transition state, such as that shown in Figure 1, can be regarded as the origin of the excellent enantioselectivity observed even at 120 °C (Table 2).

In summary, we demonstrate a novel mode of activation with chiral Brønsted acid catalysts that formally involves nucleophilic attack at the σ* orbital of saturated carbon electrophiles. Phosphoric acids were shown to catalyze an intramolecular asymmetric S_N2-type alkylation reaction of alcohols with racemic secondary benzylic ethers to result in a catalytic asymmetric transetherification reaction. The very high selectivity observed even at 120 °C, demonstrates the potential of asymmetric Brønsted acid catalysis for the activation of normally unreactive functional groups such as ethers and potentially other less reactive substrates. The generality of the new S_N2 activation mode reported here is currently under investigation.

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