Asymmetric Synthesis

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Catalytic Asymmetric Aminoallylation of Aldehydes: A Catalytic Enantioselective Aza-Cope Rearrangement**

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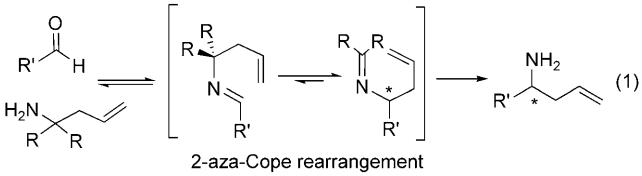
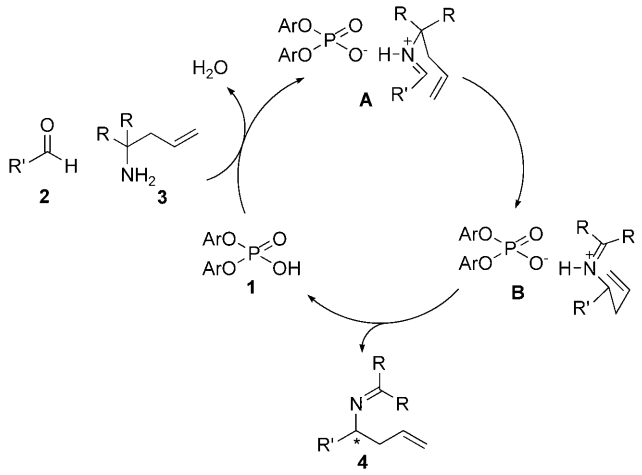
Efficient catalytic enantioselective variants of many significant organic reactions have been developed, including biocatalytic and metal-catalyzed processes, but increasingly also organocatalytic methods. Sigmatropic rearrangements are among the fundamental methods for the preparation of complex organic molecules and have found widespread application in the synthesis of biologically relevant molecules and natural products. A variety of catalytic asymmetric sigmatropic rearrangements have already been reported.[1] Most are based on the use of chiral metal complexes; however, individual organocatalytic enantioselective variants have also been described in which chiral secondary amines,[2] cinchona alkaloids,[3] and guanidium salts[4] serve as the catalysts. Surprisingly, no successful catalytic enantioselective aza-Cope rearrangement has been reported to date,[5] despite the importance of the corresponding products in synthetic organic chemistry. Given the relevance of sigmatropic rearrangements and the resulting products, as well as the limited success in the development of an asymmetric version, we viewed the development of an asymmetric aminoallylation of aldehydes[6] on the basis of a catalytic enantioselective 2-aza- or 2-azonia-Cope rearrangement as an important goal [Eq. (1)]. Such a transformation would provide an efficient route to optically active homoallylic amines, which are particularly useful building blocks for the synthesis of natural products[7] and valuable precursors of other organic compounds, including β-amino acids, aminoalcohols, aminoepoxides, pyrrolidines, and piperidines.[8,9] Herein, we report the development of a catalytic asymmetric aminoallylation of aldehydes on the basis of a condensation–rearrangement sequence.

In continuation of our studies on the organocatalyzed activation of imines[10] and carbonyl compounds,[11] and on the basis of our experience in asymmetric ion-pair and hydrogen-bond catalysis, we decided to examine a phosphoric acid catalyzed 2-aza-Cope rearrangement (Scheme 1). In planning our reaction, we assumed that the aminoallylation of an aldehyde **2** with an amine **3** under the catalysis of a phosphoric acid diester **1** would result initially in the formation of an iminium ion in the form of a chiral ion pair **A**. We further anticipated that activation by the Brønsted acid would be strong enough to accelerate the following aza-Cope rearrangement to the adduct **B**. Subsequent reprotonation should then provide the desired optically active homoallylic amine **4** with regeneration of the chiral Brønsted acid **1**.





Scheme 1. Brønsted acid catalyzed aza-Cope rearrangement.

Our initial experiments revealed that Brønsted acid catalyzed Cope rearrangements can be performed with 1,1-diaryl homoallylic amines **3** in combination with aldehydes **2** and a catalytic amount of diphenyl phosphoric acid diester. Hence, in our attempt to develop an asymmetric variant of the transformation we investigated the application of various chiral phosphoric acid diesters **1a–o** as catalysts (Table 1).[12–14] We observed the best results with regard to the enantiomeric ratio of the product with (*R*)-3,3′-bis-(naphthyl)octahydrobinol (**1h**) as the catalyst (Table 1, entry 8). To further optimize the reaction conditions, we varied the solvent, the concentration of the reaction mixture, the reaction temperature, and the catalyst loading and found that the Brønsted acid catalyzed enantioselective Cope rearrangement can be performed in various aprotic solvents.

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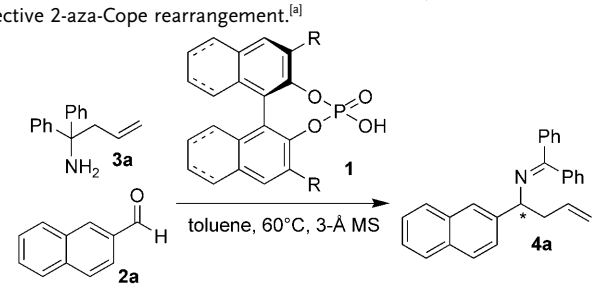
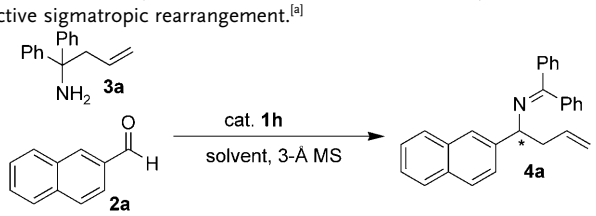
Table 1: Evaluation of chiral Brønsted acid catalysts in the enantioselective 2-aza-Cope rearrangement.[a]



Entry	1	R	e.r.[b]
1	**1a**	2-naphthyl	75:25
2	**1b**	4-biphenyl	72.5:27.5
3	**1c**	9-anthracenyl	51.5:48.5
4	**1d**	9-phenanthryl	51.5:48.5
5	**1e**	3,5-$(CF_3)_2$-Phenyl	racemate
6	**1f**	4-nitrophenyl	51.5:48.5
7	**1g**	3,5-*t*Bu_2-4-$MeOC_6H_2$	racemate
8	**1h** $[H_8]$[c]	2-naphthyl	87.5:12.5
9	**1i** $[H_8]$[c]	4-biphenyl	72:28
10	**1j** $[H_8]$[c]	Ph_3Si	racemate
11	**1k** $[H_8]$[c]	9-phenanthryl	52:48
12	**1l** $[H_8]$[c]	3,5-$(CF_3)_2C_6H_3$	51.5:48.5
13	**1m** $[H_8]$[c]	3,4,5-$F_3C_6H_2$	51.5:48.5
14	**1n** $[H_8]$[c]	4-FC_6H_4	59.5:40.5
15	**1o** $[H_8]$[c]	4-$MeOC_6H_4$	64.5:35.5

[a] Reaction conditions: **3a**, **2a** (1.5 equiv), **1** (10 mol%), 3-Å molecular sieves (MS), toluene, 60°C. [b] The enantiomeric ratio was determined by HPLC on a chiral phase (chiralcel OD-H). [c] The octahydrobinol catalyst was used.

Table 2: Reaction parameters of the Brønsted acid catalyzed enantioselective sigmatropic rearrangement.[a]



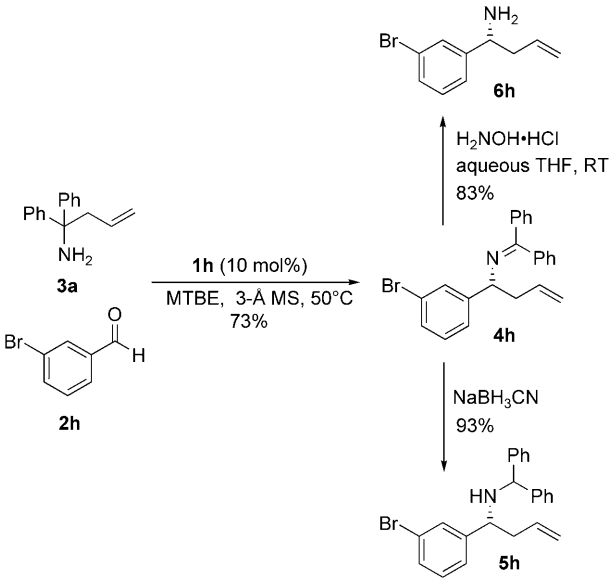
Entry	Solvent	**1h** [mol%]	e.r.[b]
1	toluene	10	87.5:12.5
2	toluene	15	86.5:13.5
3	toluene	5	82.5:17.5
4	toluene	3	59.5:40.5
5	benzene	10	78.5:21.5
6	*o*-xylene	10	86:14
7	*p*-xylene	10	85.5:14.5
8	mesitylene	10	85.5:14.5
9	cyclohexane	10	78:22
10	cumene	10	85.5:14.5
11	ethylbenzene	10	85.5:14.5
12	$PhCF_3$	10	82.5:17.5
13	1,4-dioxane	10	55.5:44.5
14	*n*Bu_2O	10	86:14
15[c]	MTBE	10	91:9

[a] Reaction conditions: **3a**, **2a** (1.1 equiv), **1h** (3–15 mol%), 3-Å MS, 60°C. [b] The enantiomeric ratio was determined by HPLC on a chiral phase (chiralcel OD-H). [c] The reaction was carried out at 50°C.

The highest reactivity and selectivity were observed when the reaction was carried out in methyl *tert*-butyl ether (MTBE) at 50°C (Table 2).

We examined the scope of the Brønsted acid catalyzed enantioselective [3,3] sigmatropic rearrangement under the optimized reaction conditions with respect to the aldehyde substrate (Table 3). Diverse aldehydes with electron-withdrawing and electron-donating substituents underwent the desired transformation to give homoallylic amines **4a**–**k** in good yields with very good enantioselectivities.[15]

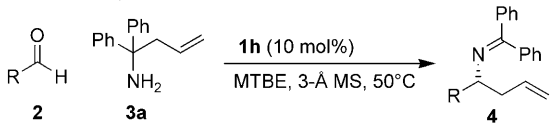
The products **4** of our catalytic enantioselective aminoallylation of aldehydes are important synthetic intermediates, which can, for example, be transformed readily into the free homoallylic amines or *N*-benzhydryl-protected primary amines. To demonstrate the synthesis of such compounds and determine the absolute configuration, we first subjected aldehyde **2h** to catalytic asymmetric transfer aminoallylation (Scheme 2). The optically active product **4h** was transformed into the protected amine **5h** in good yield by treatment with sodium cyanoborohydride. Alternatively, the free primary optically active homoallylic amine **6h** was obtained by the treatment of **4h** with hydroxyamine hydrochloride.[16]



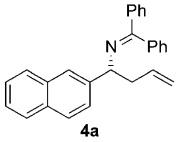
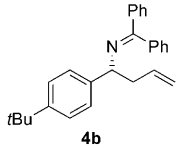
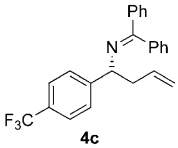
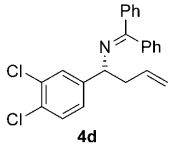
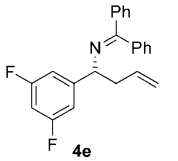
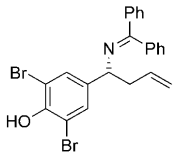
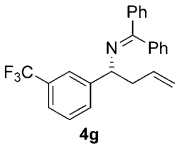
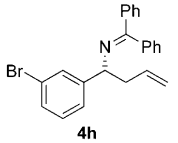
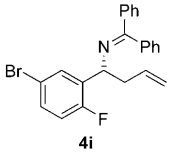
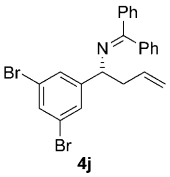
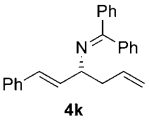
Scheme 2. Catalytic enantioselective transfer aminoallylation and transformation of the product into a chiral primary amine and an *N*-benzhydryl-protected homoallylic amine.

In summary, we have described the development of a Brønsted acid catalyzed asymmetric aminoallylation of aldehydes. The condensation–rearrangement described is not only based on the first enantioselective Brønsted acid catalyzed sigmatropic rearrangement but is also the first example of a catalytic asymmetric aza-Cope rearrangement. This transformation of readily available aldehydes provides efficient access to synthetically useful primary homoallylic amines in good yields and with very good enantioselectivities (e.r. up to 97:3). We expect this asymmetric organocatalytic aza-Cope

Table 3: Scope of the Brønsted acid catalyzed enantioselective aminoallylation of aldehydes.[a]



2 **3a** **4**

Entry	Product	Yield [%][b]	e.r. [%][c]
1	 **4a**	77	91:9
2	 **4b**	67	92.5:7.5
3	 **4c**	87	90.5:9.5
4	 **4d**	61	93.5:6.5
5	 **4e**	74	94:6
6	 **4f**	52	92.5:7.5
7	 **4g**	69	91:9
8	 **4h**	71	90.5:9.5
9	 **4i**	76	90:10
10	 **4j**	75	97:3
11	 **4k**	80	90.5:9.5

[a] Reaction conditions: **3a**, aldehyde (1.1 equiv), **1h** (10 mol%), 3-Å MS, MTBE, 50°C, 48 h. [b] Yield of the isolated product after column chromatography. [c] The enantiomeric ratio was determined by HPLC on a chiral phase.

rearrangement to be very useful for the synthesis of diverse biological compounds and natural products. Our current research is focused of the development of further asymmetric organocatalytic sigmatropic rearrangements with Brønsted acid catalysts.

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