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Lewis Base Catalyzed Enantioselective Allylation of α,β-Unsaturated Aldehydes

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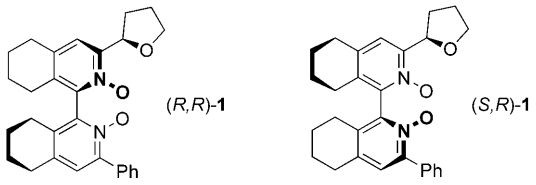
The invention and development of highly enantioselective catalytic reactions with a low catalyst loading is one of the current challenges in organic chemistry. One such area is the activation of reactants by Lewis base/acid pairing.[1] Especially attractive in this regard is the enantioselective allylation of carbonyl compounds (Sakurai–Hosomi reaction) with allylmetals to give chiral homoallylic alcohols that can be used as building blocks in the synthesis of complex molecules.[2]

In the last decade, considerable attention has been paid to a possible variant of this reaction based on the activation of allyltrichlorosilane or its derivatives by chiral Lewis bases, such as pyridine *N*-oxides. A variety of bi- or monodentate[2–6] catalysts have been synthesized and applied in the catalytic allylation of aromatic aldehydes, which is used as a benchmark reaction to assess the catalytic activity and the scope of asymmetric induction. Although in some cases high enantioselectivity was observed, this trend was not general and the asymmetric induction was often highly dependent on the presence of electron-accepting or -donating groups. Another problem is the synthesis of the catalyst being often complicated.

We showed that the above-mentioned problems could be overcome by the use of unsymmetrical diastereoisomeric bis(tetrahydroisoquinoline) *N*,*N*′-dioxides **1** and appropriate choice of solvent.[7] Lewis bases **1** were prepared in three steps by a one-pot microwave-induced cross-cyclotrimerization[8] of hexadecatetrayne with benzonitrile and (*R*)-tetrahydrofurannitrile followed by oxidation with MCPBA.



The presence of the additional center of chirality within the molecular framework allowed easy separation of both diastereoisomers by using simple column chromatography on silica gel. The correct configuration was unequivocally confirmed by a single-crystal X-ray analysis (Figure 1). Second, the allylation of various benzaldehydes catalyzed by **1** (1 mol%, −78°C, 1 h) in THF proceeded with high enantioselectivity (up to 96%) and high yields regardless of electronic properties of the substituents on the aromatic ring.[7a]

Although the *N*-oxide-catalyzed allylation of benzaldehydes has been extensively studied, the reaction with α,β-unsaturated aldehydes has been rather neglected. There have been reported allylations of three aldehydes: cinnamaldehyde,[3,4b,c,5b–d,9–11] α-methylcinnamaldehyde,[5c,9] and 2-decenal[3] with maximum enantioselectivities of 83, 76, and 81% *ee*, respectively. The lack of data in this area provided the necessary impetus to study enantioselective allylation by using **1**.

Initially, the allylation of cinnamaldehyde **2a** with allyltrichlorosilane in the presence of (*R*,*R*)-**1** (1 mol%, 1 h) was carried out in various solvents and gave **3a** with the following results: 92% yield, 97% *ee* in THF; 40% yield, 88% *ee* in dichloromethane; 43% yield, 88% *ee* in toluene; 84% yield, 96% *ee* in methoxycyclopentane; and 52% yield, 96% *ee* in 2-methylTHF[12]. Interestingly, the reaction in MeCN did not proceed at all. The reaction catalyzed by (*S*,*R*)-**1** in THF gave **3a** in 95% yield and 93% *ee*. The allylation of other cinnamaldehydes **2b–g** to homoallyl alcohols

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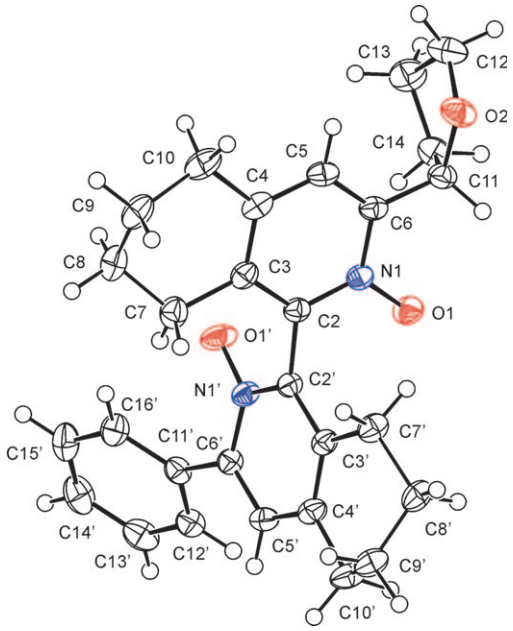


Figure 1. ORTEP drawing of (*R*,*R*)-**1** with the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

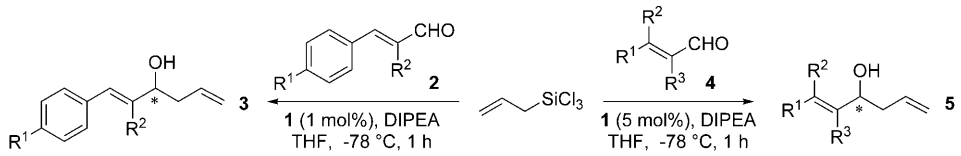
3 was performed with chiral *N*,*N*′-dioxides (*R*,*R*)-**1** and (*S*,*R*)-**1**. In general, both *N*,*N*′-dioxides catalyzed the highly enantioselective allylation of most of the aldehydic substrates (see Table 1). The enantioselectivity is not influenced by substitution of Me (**3b**) or Cl (**3c**) at the α-position of the double bond (Table 1, entries 2 and 3). Similarly, the presence of electron-withdrawing halide groups (F and Br) attached to the aromatic ring gave **3d** and **3e** with high asymmetric induction (Table 1, entries 4 and 5). Only homoallyl alcohols with nitro (**3f**) or, surprisingly, methoxy groups (**3g**) were formed with diminished enantioselectivity (Table 1, entries 6 and 7).

We then studied the allylation of aliphatic α,β-unsaturated aldehydes **4**. Because of the slower reaction rate, the reactions were run with 5 mol% of catalyst to ensure higher yields. In general, the reactions proceeded in all cases; however, a strong dependence of the asymmetric induction on the chiral backbone of the catalyst was observed (Table 1). The allylation of crotylaldehyde **4a** to **5a** proceeded with an average enantioselectivity of 85% *ee* for both catalysts (Table 1, entry 8). Aldehydes with longer aliphatic chains (Et and *n*Bu) gave homoallylic alcohols **5b** and **5c** with excellent enantioselectivities of up to 99% *ee* (Table 1, entries 9 and 10). The allylation of β,β-disubstituted aldehyde **4d** gave **5d** also with high asymmetric induction (Table 1, entry 11). However, in the case of α-methylacrolein **4e** high enantioselectivity was achieved with the (*S*,*R*)-**1** catalyst, whereas its stereoisomer (*R*,*R*)-**1** resulted in a diminished selectivity (Table 1, entry 12). The same effect was also observed in the allylation of α,β-disubstituted aldehydes **4f** and **4g**: the reaction catalyzed by (*R*,*R*)-**1** proceeded with low enantioselectivity, whereas the use of (*S*,*R*)-**1** gave excellent asymmetric induction (Table 1, entries 13 and 14).

To rationalize the high selectivity of the title reaction, the reaction mechanism has been approached by means of density functional theory calculations.[13,20] The (*S*,*R*)-**1** base is considered here. The interaction between (*S*,*R*)-**1** and allyltrichlorosilane leads to two types of complexes, and the most stable isomers, **6a** and **6b**, are shown in Figure 2. The interaction between the reactant and the catalyst can either be due to the coordination of the oxygen atom of (*S*,*R*)-**1** to the silicon atom (**6a**) or be mediated by the interaction between the oxygen atoms of (*S*,*R*)-**1** and hydrogen atoms of the allyl group (**6b**). Both intermediates are further stabilized by weak interactions between the backbones of the catalyst and the substrate.[14,15] Accordingly, it is necessary to account for the dispersion interactions in the calculations. To this end, we used the B97D functional, which contains a semiempirical correction for the dispersion interactions.[16]

Starting with the formation of intermediate **6a**, several transition structures for the coupling with crotylaldehyde have been found (all structures can be found in the Supporting Information). The most stable arrangement corresponds to the structure that is stabilized by π-π stacking between crotylalde-

Table 1. Allylation of α,β-unsaturated **2** and **4** to homoallylic alcohols **3** and **5** catalyzed by (*R*,*R*)-**1** or (*R*,*S*)-**1**.



Entry	Aldehyde	R^1	R^2	R^3	Alcohol	Catalyst (*R*,*R*)-**1**		Catalyst (*S*,*R*)-**1**	
						Yield [%][a]	e.r. (*R*:*S*)[b]	Yield [%][a]	e.r. (*R*:*S*)[b]
1	**2a**	H	H	–	**3a**	92	98.7:1.3	95	3.5:96.5
2	**2b**	H	Me	–	**3b**	90	94.3:5.7	99	1.4:98.6
3	**2c**	H	Cl	–	**3c**	35	96:4	35	3.2:96.8
4	**2d**	F	H	–	**3d**	74	97.7:2.3	75	4.5:95.5
5	**2e**	Br	H	–	**3e**	80	99.3:0.7	85	2.6:97.4
6	**2f**	NO2	H	–	**3f**	60	93.3:6.7	60	30.4:69.6
7	**2g**	MeO	H	–	**3g**	80	85.3:14.7	80	18.5:81.5
8	**4a**	Me	H	H	**5a**	40	92.9:7.1	90	7.4:92.6
9	**4b**	Et	H	H	**5b**	85	99.1:0.9	90	2:98
10	**4c**	*n*Bu	H	H	**5c**	90	99.1:0.9	95	1.9:98.1
11	**4d**	Me	Me	H	**5d**	30	95.6:4.1	35	7:93
12	**4e**	H	H	Me	**5e**	20	69.3:30.7	25	2.7:97.3
13	**4f**	Me	H	Me	**5f**	35	59.7:40.3	80	1.8:98.2
14	**4g**	Et	H	Me	**5g**	70	59.6:40.4	90	1.9:98.1

[a] Yield determined by ^{1}H NMR spectroscopy. [b] Determined by GC; the values are average of three measurements.

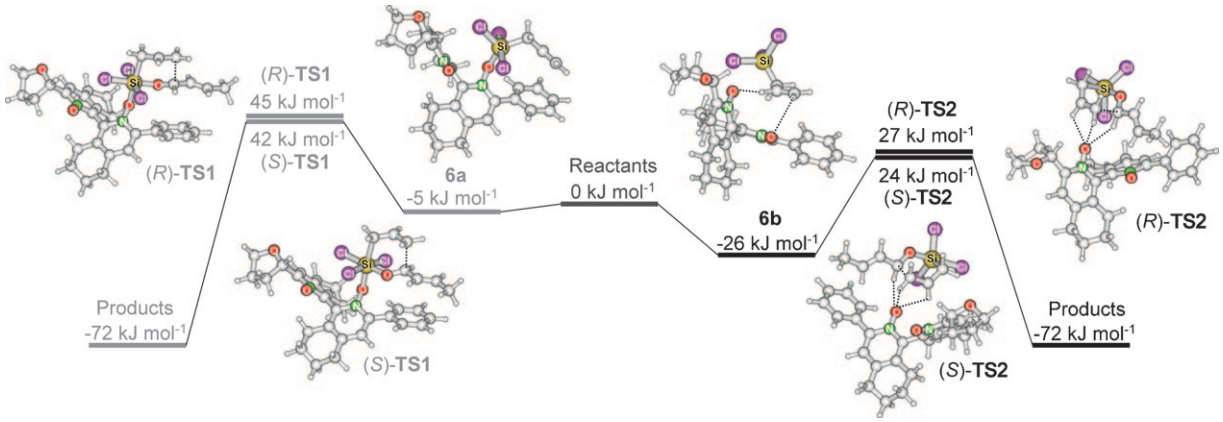


Figure 2. B97D/cc-pVTZ//B97D/6-31g* potential energy diagram for the coupling of allyltrichlorosilane ($C_3H_5SiCl_3$) with crotylaldehyde (C_3H_5CHO) catalyzed by (*S*,*R*)-**1** in THF. Structures **6a** and **6b** show the optimized geometries of complexes between (*S*,*R*)-**1** and $C_3H_5SiCl_3$. Structures (*S*)-**TS1**, (*R*)-**TS1**, (*S*)-**TS2**, and (*R*)-**TS2** show the optimized geometries of the transition structures. Energies are given relative to the sum of the enthalpies of the reactants ($C_3H_5SiCl_3 + C_3H_5CHO + (S,R)$-**1**) at 298 K in THF (for details see the Supporting Information).

hyde and the phenyl substituent of (*S*,*R*)-**1**. In agreement with the experimental results, the formation of the (*S*) product is favored (via (*S*)-**TS1**) in that the corresponding energy barrier is 3 kJ mol^{-1} lower than that for the formation of the (*R*) product (the grey reaction pathway in Figure 2, Table 2).

Table 2. B97D/cc-pVTZ energetics[13] of the coupling between crotylaldehyde and allyltrichlorosilane.

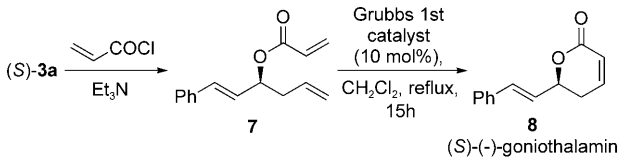
	B97D/cc-pVTZ//B97D/6-31G*[12]			
	$\Delta E^{0\,K}$[a]		$\Delta H^{298\,K}$[b]	$\Delta G^{298\,K}$[c]
	Gas phase	THF	THF	THF
(*S*)-**TS1**	54	45	42	168
(*R*)-**TS1**	55	48	45	170
(*S*)-**TS2**	17	26	24	140
(*R*)-**TS2**	20	29	27	146
6a	10	−6	−5	56
6b	−35	−29	−26	17

[a] Energies are given relative to the sum of energies of the reactants at 0 K (for details see the Supporting Information). [b] Energies are given relative to the sum of enthalpies of the reactants (for details see the Supporting Information). [c] Energies are given relative to the sum of Gibbs energies of the reactants (for details see the Supporting Information).

An alternative mechanism can be found if intermediate **6b** is considered (the black reaction pathway in Figure 2). This transition structure is stabilized by a number of weak interactions.[14] Besides the interaction between the oxygen atoms of the catalyst and the hydrogen atoms of allyltrichlorosilane and crotylaldehyde, π–π interactions and the interaction between the hydrogen atoms of the saturated rings of the catalyst and the chlorine atoms should be considered. Formation of the (*S*) product again proceeds via an energy barrier that is 3 kJ mol^{-1} lower than the formation of the (*R*) product.

The calculations also clearly show why the chirality of the THF substituent of (*S*,*R*)-**1** plays a minor role. In all types of transition structures found, the interaction of the phenyl substituent with the reactants plays an important role. The transition structures in which the reactants are placed in the vicinity of the THF substituent lie higher in energy that those in which the reactants are more stabilized by the interaction with phenyl (for all structures, see the Supporting Information). This effect is most evident for transition structures with the O–Si bond because the THF group is completely remote.

Finally, the efficiency of the above-mentioned asymmetric allylation was demonstrated by a short enantioselective synthesis of (*S*)-(−)-goniothalamin (Scheme 1). The allylation



Scheme 1. Synthesis of (*S*)-(−)-goniothalamin **8**.

of cinnamaldehyde **2a** (3.78 mmol) catalyzed by (*S*,*R*)-**1** (1 mol%) in THF (−78 °C, 1 h) gave desired homoallyl alcohol (*S*)-(−)-**3a** in 97% isolated yield (97% *ee*). Esterification of **3a** with acryloyl chloride gave ester (*S*)-(−)-**7** in 86% yield without loss of chirality (95% *ee*, GC). Ring-closing metathesis of **7** catalyzed by Grubbs 1st generation complex [$RuCHPhCl_2(PCy_3)_2$] (10 mol%) was carried out. Metathesis in dichlormethane (reflux, 15 h) gave (*S*)-(−)-goniothalamin **8** in 70% isolated yield (95% *ee*, HPLC). The reaction in toluene gave only 30% of (*S*)-(−)-**8** with identical enantioselectivity. It is important to stress that it was necessary to keep the concentration of the reactants low (0.01 M) to maintain a high yield of **8**. When the metathesis was carried out at higher concentrations (≈0.1 M), the yields did not exceed 20%. These results are in agreement with previously reported results[17] and a recent study regarding

concentration effect on the ring-closing metathesis of acrylic esters.[18]

In conclusion, the easy preparation of (*R*,*R*)-**1** and (*R*,*S*)-**1** and their high catalytic activity enables the efficient allylation of α,β-unsaturated aldehydes to the corresponding homoallyl alcohols to be carried out with high enantioselectivities of up to 99% *ee*. This method could serve as an alternative to the Keck allylation.[19]

Experimental Section

Cinnamaldehyde (0.4 mmol, 53 mg), diisopropylethylamine (0.6 mmol, 104 μL, 77 mg), and allyltrichlorsilane (0.6 mmol, 85 μL, 51 mg) were added to a solution of bipyridine-*N*,*N*′-dioxide (*R*,*R*)-**1** (0.004 mmol, 2 mg) in THF (1 mL) at −78 °C. The mixture was stirred for 1 h, then quenched with brine (4 mL), and the organic layer was separated, dried over $MgSO_4$, and filtered on silica gel. The *ee* was determined by using GC (HP-Chiral ß column, 30 m × 0.25 mm; oven: 80 °C for 1 min, then 1 °C min^{-1} to 160 °C, 5 min): t_R = 71.09 min, t_S = 71.78 min; e.r.: 98.7:1.3 (97% *ee*).

Characterization data for ***3a***: 90% yield as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.25–7.42 (m, 5H; Ar), 6.64 (d, ^3J(H,H) = 16 Hz, 1H; CH), 6.27 (dd, ^3J = 16, 6.3 Hz, 1H; CH), 5.84–5.92 (m, 1H; CH), 5.19–5.26 (m, 2H; CH_2), 4.37–4.42 (m, 1H; CHO), 2.38–2.50 (m, 2H; CH_2), 2.05 (s, 1H; OH). The spectral characteristics of **3a** are in agreement with previously reported data.[17b]

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Keywords: allylation · asymmetric synthesis · lewis bases · organocatalysis · nitrogen oxides

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