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Chiral Unsymmetrically Substituted Bipyridine *N,N*'-Dioxides as Catalysts for Allylation of Aldehydes

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Dedicated to Professor Pavel Kočovský on the occasion of his 67th birthday.

Abstract: A series of unsymmetrically substituted diastereoisomeric (R_a, R) and (S_a, R) bipyridine N, N'-dioxides was synthesized by using of corresponding oxidative coupling the metallated tetrahydroisoquinoline N-oxides in the presence of iodine. The N,N'dioxides possessed substituted aryls with electron-donating or electron-accepting groups in the near vicinity of the N,N'-dioxide moiety. Their catalytic activity was tested in a series of reactions of allyltrichlorosilane with variously substituted benzaldehydes, thiophenecarbaldehyde, and cinnamaldehyde. It proceeded with enantioselectivity up to 98% ee with as low catalyst loading as 0.5 mol%. On top of that, allylations of (E)-3-iodomethacrylaldehyde to give chiral (E)-1-iodo-2-methylpenta-1,4-dien-3-ol, a convenient building block for synthesis of natural compounds, were carried out as well. Allylations proceeded with enantioselectivity up to ~99% ee with a catalyst loading of 2.5 mol%.

Introduction

In the last several decades has been seen a rapid growth and advances in design and development of new catalysts and (or) catalytic systems for enantioselective synthesis. This pertains to both, transition metal catalysis as well as organocatalysis. In this respect a considerable attention has been dedicated to development of various catalytic methods for enantioselective allylation (crotylation, etc.) of aldehydes and ketones to produce the corresponding chiral homoallylic alcohols. This interest stemmed from the fact that the arising chiral homoallylic alcohols can serve as interesting and useful chiral building blocks for syntheses of more complex compounds.^[11] Much interest was concentrated on development of organocatalytic methods based on the use of various chiral Brønsted and Lewis acids and bases

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with special attention to chiral catalysts possessing the pyridine *N*-oxide moiety. Among these compounds bipyridine *N*,*N'*-dioxides are a distinguished group that have been tested as potential catalysts for allylation reaction of aldehydes with allyltrichlorosilane. A number of bipyridine *N*,*N'*-dioxides catalysts have been prepared and they can be divided into three classes according to chirality elements present in their basic molecular frameworks: those possessing the elements of axial or central chirality, and a small group of those possessing both elements. These catalysts (Figures 1-3) and their performance regarding allylation of benzaldehyde (taken as the model reaction) are displayed in Table 1.

Historically the first chiral bipyridine *N*,*N*'-dioxide **1a** possessing the element of axial chirality was prepared and resolved into enantiomers by Fujii *et al.*,^[2] but it was Nakajima and Hashimoto *et al.*^[3] who reported the first use of **1a** and **1b** as catalysts for the enantioselective allylation of aldehydes. As for other axially chiral bipyridine *N*,*N'*-dioxides, compounds **1c**,^[4] **1d-1g**,^[5] **1i**,^[6] and **1j-1k**^[7] and (*R*)-**1h**^[8] were synthesized (Figure 1). Typical examples of bipyridine *N*,*N'*-dioxides possessing elements of central chirality are **2a**,⁹ **2b**,**c**,^[10] **2d**,^[11] (Figure 2). The last group comprises chiral bipyridine *N*,*N'*-dioxides **3** (MAKDIOX),^[12] **4** and **5** bearing the chiral tetrahydrofuranyl moiety (Figure 3).^[13]



Figure 1. N,N'-dioxides 1 with the element of axial chirality.



Figure 2. N,N'-dioxides 2 with the element of central chirality.



Figure 3. N,N'-dioxides 3-5 with the element of central and axial chirality.

The solvent of choice is usually MeCN or dichloromethane, in which the catalysts are well soluble even at low reaction temperatures (-40 or -78 °C) and the allylations proceed with a reasonable rate and conversion. Another feature of the enantioselective allylations catalysed by the pyridine N-oxide catalysts is a rule of thumb that says that a catalysts with R_a configuration gives rise to a homoallylic alcohol with S configuration and vice versa. The best asymmetric induction (>90% ee) was achieved with catalysts 1j and 5 as can be judged from comparison of allylation reactions (Table 1). Catalyst 3 was tested only in crotylation, where asymmetric induction is in general higher in comparison with simple allylation. As for the reaction mechanism it is generally assumed that ionic and neutral mechanisms may take place. There is evidence that the ionic mechanism takes place in MeCN or dichloromethane and similar solvents whereas the neutral one is assumed to be typical for reactions in THF and similar solvents.^[14]

Interestingly, allylation experiments have shown that N.N'dioxides catalysts $4^{[15]}$ and $5^{[5e,16]}$ developed in this laboratory (it should be appreciated that their design was inspired by the elegant synthesis and use of QUINOX (a mono N-oxide possessing the element of axial chirality) by Kočovský and Malkov)^[17] give the best results in terms of asymmetric induction and yields in THF and other non-polar solvents. The R-catalysts in this instance give rise to homoallylic R-alcohols and Scatalysts give rise to homoallylic S-alcohols. It was demonstrated that the configuration around the chiral axis dictates the stereoinduction.^[5c] However, when the reactions were carried out in MeCN or dichloromethane the above mentioned rule of thumb was found not to be generally applicable. This and other hints indicate that the course of the reaction could proceed via a different reaction mechanism, which has not been elucidated yet.

Last but not least, a number of chiral mono *N*-oxides with the pyridine scaffold has been developed and applied in enantioselective allylation as well. In this respect, the pioneering works of Kočovský with Malkov,^[17] and others^[10,18] deserve to be mentioned. However, catalytic activity, reaction mechanisms, and application of the chiral mono *N*-oxides have their own distinct characteristics and exhibit features different and not comparable with *N*,*N*²-dioxides such as **4** and **5**.

Table cataly	1. Repres sed by 1-5 .	entative	enantios	selecti	ve ally	lations of	benzald	ehyde
Entry	Catalyst	mol-%	Solvent	t (h)	T (°C)	Yield (%) ^[a]	ee (%)	Ref.
1	(S)- 1a	10	CH ₂ Cl ₂	24	-90	82	52	3
2	(S)- 1b	10	CH_2CI_2	6	-78	85	88(<i>R</i>)	3
3	(<i>R</i>)-1c	0.1	CH₃CN	2.5	-45	95	84(S)	4
4	(S)-1d	5	CH_2CI_2	6	-78	87	74(<i>R</i>)	5a
5	(S)-1e	5	CH_2CI_2	6	-78	53	72(<i>R</i>)	5a
6	(S)-1f	5	CH_2CI_2	3	-78	95	80(<i>R</i>)	5b
7	(<i>R</i>)-1g	1	CH₃CN	1	-40	100	65(S)	5c
8	(<i>R</i>)-1g	1	PhCl	1	-40	100	82(<i>R</i>)	5c
9	(<i>R</i>)-1h	7	CH_2Cl_2	18	-80	95	81(S)	8
10	(R)-1j	1	CH_2CI_2	16	-80	88	95(S)	7a
11	(<i>R</i>)-1k	1	CH_2CI_2	20	-80	85	87(S)	7b
12	(-)-2a	7	CH_2CI_2	48	-90	18	84(<i>R</i>)	9
13	2b	10	CH₃CN	40	-45	60	60(S)	10a
14	2c	10	CH₃CN	67	-40	37	85(S)	10b
15	2d	10	CH_2CI_2	18	-78	64	26(<i>R</i>)	11
16	(R _a ,R,R)- 4	1	CH₃CN	1	-40	95	45(S)	5c
17	(R _a ,R,R)- 4	1	PhCl	1	-40	0	0	5c
18	(S _a ,R,R)- 4	1	CH₃CN	1	-40	95	46(<i>R</i>)	5c
19	(S _a ,R,R)- 4	1	PhCl	1	-40	95	62(S)	5c
20	(R _a ,R)- 5	1	THF	1	-78	95	93(<i>R</i>)	13
21	(R _a ,R)- 5	1	PhCl	1	-40	95	93(<i>R</i>)	13
22	(S _a ,R)- 5	1	THF	1	-78	95	96(<i>S</i>)	13
23	(S _a ,R)- 5	1	PhCl	1	-40	95	94(S)	13

[a] Isolated yields.

Results and Discussion

Synthesis of chiral N,N'-dioxides

Most chiral bipyridine N,N'-dioxides (with exception of those prepared from chiral terpenes) require a resolution step using stoichiometric amounts of chiral resolution agents or other methods. On the other hand, catalysts **5** have an inbuilt resolution handle (chiral tetrahydrofuranyl moiety) that allows

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separation of the atropoisomeric diastereoisomers by a simple column chromatography at the end of their preparation route. Although catalysts **5**, which catalysed allylation as well as crotylation of various aldehydes with a high asymmetric induction (up to 99% ee), could be prepared by a rather simple three step procedure, we were looking for a more modular and general synthetic method allowing to prepare these compounds. In this respect, we wanted to address the following goals: i) development of a procedure allowing to prepare variously substituted bipyridine *N*,*N'*-dioxides, ii) to find a more effective *N*,*N'*-dioxide based catalyst(s) that would allow to reduce the catalyst's load without compromising asymmetric induction, and iii) to shed more light on the probable course of the reaction and substituent effects that control it.

In this respect, the importance of substituted aryl groups in the basic scaffold of various ligands and catalysts has been demonstrated previously. For example, Kočovský et al. in his inspiring work clearly showed that appropriate substitution of the aromatic ring in a catalyst can profoundly change the level of the asymmetric induction in the allylation of aldehydes.^[19] Also we observed a similar effect when 1d and 1e were used in the allylation reaction.^[5b] In addition, a positive effect of the phenyl group vicinal to the nitrogen atom of the bipyridine scaffold on the asymmetric induction was observed in enantioselective Michael addition.^[20] For the sake of fairness it should be noted that Hayashi et al. did not observed any effect when catalysts 1c with substituted aromatic rings were used.^[4b] Nonetheless, the aforementioned provided us with necessary impetus to undertake synthesis of a series of substituted N.N'-dioxides bearing variously substituted aromatic rings and check their catalytic activity and asymmetric induction in the allylation of selected aromatic, heteroaromatic and α , β -unsaturated aldehydes.

First, we resolved to develop an alternative synthetic pathway to these compounds that would circumvent the cyclotrimerization of tetraynes with nitriles.^[21] To this end, we used the method developed by Denmark^[22] based on the oxidative dimerization of metallated *N*-oxides. Our three-step procedure relied on cyclotrimerization of 1,7-octadiyne with various nitriles **6** catalysed by CpCo(CO)₂ under irradiation with a 250W halogen lamp, followed by oxidation to give the corresponding *N*-oxides, and oxidative coupling.



Thus, cyclotrimerization 1,7-octadiyne of with (R)tetrahydrofuran-2-carbonitrile 6a provided (R)-3-(tetrahydrofuran-2-yl)-tetrahydroisoquinoline 7a in 28% isolated yield. Then 7a was oxidized with m-chloroperoxobenzoic acid in (R)-3-(tetrahydrofuran-2-yl)dichloromethane to yield tetrahydroisoquinoline-N-oxide 8a (40% isolated yield). Tetrahydroisoquinolines 7b-7h (31-58%) and the corresponding N-oxides 8b-8h (43-71%) were prepared starting from 6b-6h by using the same methodology.

With the N-oxides 8 in hand we proceeded with their oxidative coupling to unsymmetrically substituted N,N'-dioxides 9. Lithiation of equimolar mixtures of 8a with 8b-8h in THF was carried out with TMP-Li at -78° for 3 h. Then a dropwise addition of a THF solution of iodine into the reaction mixture resulted in oxidative coupling to produce mixtures of the desired unsymmetrically substituted N,N'-dioxides 5, 9a-9f and the undesired symmetrically substituted N.N'-dioxides 1g, 10a-10f and **4**. A rather tedious isolation of analytically pure (R_a, R) - and (S_a, R) -5, 9a-9f from 1q, 10a-10f and 4 was achieved by repeated column chromatography on silica gel (Scheme 2). Problems associated with separation and purification of compounds 5 and 9 were reflected in rather low isolated yields, but these correspond to chemically and enantiomerically pure substances. Actually, total amounts of the N,N'-dioxides 5 and 9 in the reaction mixtures were much higher (~40-50%). Despite of that the N,N'-dioxides 5 and 9 were obtained in sufficient amounts to proceed with tests pertaining to their catalytic activity.



Scheme 2. Synthesis of unsymmetrically substituted *N*,*N'*-dioxides 5 and 9a-9f.

It is worth mentioning that both diastereoisomers of N,N'dioxides **9f** are at 20 °C 1/1 mixture of rotamers as could be judged from ¹H and ¹³C NMR spectra (all signals were doubled).

In order to prove it, ¹H NMR spectra of a C₆D₆ solution of (R_a ,R)-**9f** were recorded at various temperatures. The signals of the H atom on the pyridine rings were taken as the reference peaks: at 25 °C two singlets at δ 8.16 and 8.18, and 7.73 and 7.76 ppm were observed. At ~70 °C both signals collapsed into one broad peak (coalescence). The calculated rotation barrier ($\Delta G^{\#}$ ~72-74 kJ/mol, ~17 kcal/mol),^[23] which is too low for a potential isomer separation. After cooling back to 20 °C the same two singlets were seen again.

Allylation of aldehydes

The catalytic activity of the unsymmetrically substituted N,N'dioxides (R_a, R) - and (S_a, R) -5, 9a-9f was evaluated in the allylation of aldehydes 11 with allyltrichlorosilane (Scheme 3). As the model compounds five aldehydes were chosen: benzaldehyde 11a, electron-rich 4-methoxybenzaldehyde 11b, electron-poor 4-trifluoromethylbenzaldehyde 11c. cinnamaldehyde **11d** (a representative of α , β -unsaturated aldehydes), and thiophene-2-carbaldehyde 11e (a representative of heteroaromatic aldehydes). Allylations were carried out with 0.25 mmol of the aldehyde, 0.375 mmol of allyltrichlorosilane, 0.5 mol% of the catalyst, and 0.375 mmol of DIPEA at -78 °C for 2 h. The allylations were carried out in two commonly used solvents: dichloromethane and THF. The results are presented in Tables 2-5.

Scheme 3. Allylation of various aldehydes 11 with 5 and 9a-9f.

In general, allylation of benzaldehydes **11a-11e** with allyltrichlorosilane catalysed by (R_a ,R)-**5**,**9a-9f** in THF provided the corresponding homoallylic alcohols **12** with good enantioselectivity and the expected *R* configuration (Table 2). The highest asymmetric induction was observed for electron-poor aldehyde **11c** (4-trifluoromethylbenzaldehyde) and for α , β -unsaturated aldehyde **11d** (cinnamaldehyde) that were in the range of 90-96% ee and 92-98% ee, respectively. Asymmetric induction in case of allylation of 4-methoxybenzaldehyde, benzaldehyde, and thienyl aldehydes were lower in the range of 70-81, 83-90, and 33-78% ee, repectively. Among the catalysts, the best results in terms of the enantioselectivity were obtained with **9d** (80-98% ee). Reactions carried out in dichloromethane gave rise to products with a rather low asymmetric induction in the range of 1-81% ee (Table 3).



Table 2. Allylation of aldehydes 11a-11e catalysed by $\textit{N,N'-dioxides}~(\textit{R}_a,\textit{R})-5,9$ in THF.^[a]

	A	12 , ee (%), ^[b] yield (%) ^[c]						
Catalyst	R (in 5 or 9)	12b	12a	12c	12d	12e		
(<i>R_a,R</i>)- 9a	4-MeOC ₆ H ₄	70, 74	83, 78	90, 55	94, 82	66, 2		
(<i>R_a</i> , <i>R</i>)- 9b	4-MeC ₆ H ₄	76, 76	89, 49	93, 45	95, 74	33, 2		
(R _a ,R)- 5	Ph	81, 74	90, 75	95, 30	96, 82	47, 3		
(<i>R_a</i> , <i>R</i>)- 9c	4-CIC ₆ H ₄	77, 81	87, 90	92, 56	92, 75	45, 2		
(<i>R_a</i> , <i>R</i>)- 9d	4-CF ₃ C ₆ H ₄	80, 62	94, 72	96, 43	97, 76	59, 2		
(<i>R_a</i> , <i>R</i>)- 9e	$4-MeO_2CC_6H_4$	72, 54	88, 74	93, 43	95, 76	52, 3		
(<i>R_a</i> , <i>R</i>)- 9f	2-Naphthyl	71, 48	88, 66	95, 57	98, 76	78, 3		

[a] Reaction conditions: (R_{a} ,R)-catalyst (0.5 mol%), DIPEA, -78 °C, 2 h. [b] Determined by HPLC. In all case products with R configuration. [c] Determined by ¹H NMR. Mesitylene was used as an internal standard.

Table 3. Allylation of aldehydes 11a-11e catalysed by N,N'-dioxides (R_a,R)-5,9 in CH₂Cl₂.^[a]

	r -	12 , ee (%), ^[b] yield (%) ^[c]							
Catalyst	R (in 5 or 9)	12b	12a	12c	12d	12e			
(R _a ,R)- 9a	4-MeOC ₆ H ₄	7, 74	11, 41	51(<i>R</i>), 50	15(<i>R</i>), 11	37, 1			
(R _a ,R)- 9b	$4-\text{MeC}_6\text{H}_4$	10, 16	17, 59	51(<i>R</i>), 55	27(<i>R</i>), 27	46, 1			
(R _a ,R)- 5	Ph	53, 52	17, 23	57(<i>R</i>), 60	35(<i>R</i>), 72	46, 6			
(R _a ,R)- 9c	4-CIC ₆ H ₄	17, 31	1(<i>R</i>), 60	66(<i>R</i>), 63	38(<i>R</i>), 70	51, 1			
(R _a ,R)- 9d	$4-CF_3C_6H_4$	22, 58	32(<i>R</i>), 91	81(<i>R</i>), 68	45(<i>R</i>), 81	25, 1			
(R _a ,R)- 9e	4-MeO ₂ CC ₆ H ₄	31, 51	11 ,86	69(<i>R</i>), 67	31(<i>R</i>), 75	52, 1			
(R _a ,R)-9f	2-Naphthyl	38, 58	12(<i>R</i>), 86	47(<i>R</i>), 56	28(<i>R</i>), 70	49, 2			

[a] Reaction conditions: (R_{a} ,R)-catalyst (0.5 mol%), DIPEA, -78 °C, 2 h. [b] Determined by HPLC. In all case products with *S* configuration unless mentioned. [c] Determined by ¹H NMR. Mesitylene was used as an internal standard.

In a similar manner proceeded allylations catalyzed by *N*,*N'*-dioxides (S_{a} ,*R*)-**5**,**9a-9f** (Table 4). The highest asymmetric induction was observed with benzaldehyde **11a** (92-94% ee) followed by cinnamaldehyde **11d** (87-95% ee), and 4-trifluoromethylbenzaldehyde **11c** (88-93% ee). Regarding the catalyst, the highest asymmetric induction was obtained with catalyst (S_{a} ,*R*)-**9a** that provided products with enantioselectivity in the range of 89-95% ee. As in the previous instance, reactions

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carried out in dichloromethane gave rise to homoallylic alcohols 12a-12e with a rather low asymmetric induction in the range of 0-40% ee and the expected R configuration (Table 5).

Table 4. Allylation of aldehydes 11a-11e catalysed by N,N'-dioxides (Sa,R)-5,9 in THF.^[a]

		12 , ee (%), ^[b] yield (%) ^[c]					
Catalyst	R (in 5 or 9)	12b	12a	12c	12d	12e	
(<i>S_a,R</i>)- 9a	4-MeOC ₆ H ₄	91, 43	94, 83	93, 77	95, 77	89, 2	
(S _a ,R)- 9b	4-MeC ₆ H ₄	88, 49	93, 89	91, 62	93, 86	79, 2	
(S _a ,R)- 5	Ph	90, 90	94, 97	93, 75	94, 80	79, 5	
(S _a ,R)- 9c	4-CIC ₆ H ₄	90, 97	93, 98	93, 53	93, 84	89, 5	
(<i>S_a</i> , <i>R</i>)- 9d	$4-CF_3C_6H_4$	86, 84	94, 95	88, 71	82, 78	58, 4	
(S _a ,R)- 9e	4-MeO ₂ CC ₆ H ₄	75, 66	93, 94	91, 64	85, 66	63, 5	
(S _a ,R)- 9f	2-Naphthyl	92, 87	92,92	91, 64	87, 78	70, 4	

[a] Reaction conditions: (S_a,R)-catalyst (0.5 mol%), DIPEA, -78 °C, 2 h. [b] Determined by HPLC. In all case products with S configuration unless mentioned. [c] Determined by ¹H NMR. Mesitylene was used as an internal standard.

 (S_a, R) -5 (1-5 mol%) were carried out (Table 6). The reactions were run for 15 h at -78 °C. The results indeed confirmed that asymmetric induction depended on the catalyst concentration: asymmetric induction was greatly improved already from 63% ee to 83% ee when (S_a, R) -5 concentration rose from 0.5 mol% to 1 mol% and reached 90% ee with 5 mol%. In addition, prolonged reaction time (15 h) had a beneficial effect on the reaction yield. In order to assess the influence of the catalyst/allyltrichlorosilane ratio on the asymmetric induction, allyltrichlorosilane (0.156 mmol) was sequentially added in 12 portions (totally 1.875 mmol) every 30 minutes into the reaction mixture containing 1 mol% of (R_a, R) - or (S_a, R) -5 (thiophenecarbaldehyde 11e 1.25 mmol, catalyst 0.0125 mmol, THF 5 mL). However, in both instances the asymmetric induction turned out to be disappointingly low of 30 or 41% ee, respectively. Although these results did not provide clear-cut answers, they indicate that there exist also other aspects of the allylation reaction yet to be discovered, at least in this instance.

Table 6. Allylation of 11e catalysed by N,N'-dioxides 5 in THF.^[a]

	12e , ee (%)	^[b] yield (%) ^[c]
Catalyst (mol-%)	(R _a ,R)- 5	(S _a ,R)- 5
0.5	52(<i>R</i>), 2	63(S), 3
1	56(<i>R</i>), 28	83(S), 42
2	76(<i>R</i>), 60	88(S), 80
5	74(<i>R</i>), 80	90(<i>S</i>), 88

Table 5. Allylation of aldehydes 11a-11e catalysed by N,N'-dioxides (S_a, R)-5,9 in CH₂Cl₂.

			12 , ee (%), ^[b] yield (%) ^[c]				
Catalyst	R (in 5 or 9)	12b	12a	12c	12d	12e	
(S _a ,R)- 9a	4-MeOC ₆ H ₄	12, 8	28, 42	1, 43	17, 12	31, 1	
(S _a ,R)- 9b	4-MeC ₆ H ₄	7, 8	33, 82	15, 28	4(S), 36	12, 1	
(S _a ,R)- 5	Ph	7, 23	30, 87	5(S), 54	20, 30	16, 1	
(S _a ,R)- 9c	4-CIC ₆ H ₄	18, 36	0, 87	30(<i>S</i>), 68	33, 62	37, 1	
(S _a ,R)- 9d	$4-CF_3C_6H_4$	4, 22	5, 74	30(<i>S</i>), 54	35, 48	28, 1	
(S _a ,R)- 9e	4-MeO ₂ CC ₆ H ₄	0, 5	24, 81	12(S), 59	31, 38	4, 1	
(S _a ,R)- 9f	2-Naphthyl	1, 40	19, 70	11(<i>S</i>), 62	40, 68	30, 1	

[a] Reaction conditions: (Sa,R)-catalyst (0.5 mol%), DIPEA, -78 °C, 2 h. [b] Determined by HPLC. In all case products with R configuration unless mentioned. [c] Determined by ¹H NMR. Mesitylene was used as an internal standard

Rather puzzling were the results obtained in allylations of thiophenecarbaldehyde 11e that did not match those previously obtained for (Sa,R)-5, which reached 97% ee at 1 mol% (-40 °C).^[24] In order to shed light on this discrepancy, further screening of allylations with a different amount of catalysts

[a] Reaction conditions: DIPEA, -78 °C, 15 h, THF. [b] ¹H NMR. [c] Determined by ¹H NMR. Mesitylene was used as an internal standard.

In a similar manner a set of N, N'-dioxides (S_a, R) - and (R_a, R) -5 and 9 was used to evaluate allylation of (E)-3iodomethacrylaldehyde 13. The interest behind allylation of 13 stems from the fact that the allylation product 14 (or the crotylation product) could be used as a convenient chiral building block for synthesis of natural products such as pteroenone, callyspongiolide, antillatoxin and potentially others.^[25,26] The allylations were carried out with 0.2 mmol of aldehyde 13 (1 mL of 0.2M solution in toluene), 0.4 mmol of allyltrichlorosilane, 2.5 mol% of the catalyst 9, 0.6 mmol of DIPEA, and in THF (1 mL) at -40 °C for 22 or 45 h. In case of catalysis with (R_a, R) -5 and 9, the product (R)-14 was obtained with high enantioselectivity when (R_a, R) -9b (96% ee) and (R_a, R) -9c (97% ee) were used. Gratifyingly, the use of (S_a,R)-5,9a-e provided the allylation product (S)-14 with excellent enantioselectivity of ≥98% ee in all instances.

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Table	7.	Allylation	of	aldehyde	(<i>E</i>)- 13	catalysed	by	N,N'-dioxides	(R_a,R) -
(S_a,R)	- 5 c	or 9. ^[a]							

ا را	Me O + Cl ₃ Si]-13	cat. 5 or 9 (2.5 m DIPEA toluene/THF, -44 22 h	Me → ○ ℃ OH (E)-14	/
	ee	(%), ^[a] yield (%)) ^[b] ee (%), ^[a] yield (%) ^[b]
R (in 5 or 9)	Catalyst	14	Catalyst	14
4-MeOC ₆ H ₄	(S _a ,R)- 9a	85(<i>R</i>), 58	(S _a ,R)- 9b	98(S), 66
4-MeC ₆ H ₄	(S _a ,R)- 9b	96(<i>R</i>), 72	(S _a ,R)- 9b	98(S), 77
Ph	(S _a ,R)- 5	57(<i>R</i>), 71	(S_a, R) - $5^{[c]}$	98(S), 49
4-CIC ₆ H ₄	(S _a ,R)- 9c	97(<i>R</i>), 71	(S _a ,R)- 9c	98(<i>S</i>), 79
$4-CF_3C_6H_4$	(S _a ,R)- 9d	94(<i>R</i>), 85	(S _a ,R)- 9d	99(<i>S</i>), 89
4-MeO ₂ CC ₆ H ₄	(S _a ,R)- 9e	80(<i>R</i>), 70	(S _a ,R)- 9e	98(S), 76
2-Naphthyl	(<i>S_a</i> , <i>R</i>)-9f	88(<i>R</i>), 74	(S _a ,R)- 9f	_[d]

[a] Determined by HPLC. Configuration assignment is in agreement with the previous published data, see ref. 25. [b] solated yields. [c] Reaction time: 45 h. Only incomplete conversion was observed after 22 h. [d] Not tested.

Thoughts on the reaction mechanism.

Although numerous studies have been carried out by us (vide infra) and others,[27,28] the true course of activation has not yet been clarified. Regarding the reaction mechanism of allylation in dichloromethane or acetonitrile, there is a general agreement that it proceeds via the chair-like six-membered transition state possessing hexa-coordinated silicon species^[27] presumably formed by a reaction of an aldehyde with the penta-coordinated anionic silicon species. Its formation was indirectly proved by contactless conductivity measurements for solution of allyltrichlorosilane and N,N'-dioxide 1g in dichloromethane and acetonitrile, respectively, which confirmed the formation of the pentacoordinated anionic silicon species. These results were in agreement with calculations supporting dissociation of hexacoordinated silicon species to the pentacoordinated ones in these solvents.^[14]

On the other hand, the course of the reaction in THF and related solvents remains to be elucidated. The previous studies based on ¹H NMR experiments indicated the formation of 1:1 and 2:1 complexes depending on the allyltrichlorosilane to N,N'dioxide 1g ratio.[5d] Furthermore, density functional theory calculations, regarding the N,N'-dioxide catalyzed allylation of crotonaldehyde with allyltrichlorosilane, identified an intermediate where the N,N'-dioxide moiety interacts with the allyl moiety of trichloroallylsilane, but not coordinating to the silicon atom, as species of the lowest energy.[16a,29] It also indicated that the most stable arrangement in the transition state corresponds to the structure that is stabilized by $\pi-\pi$ stacking between crotonaldehyde and the phenyl substituent of (S_a, R) -5. The formation of the (S)-product was in agreement with experimental results and the transition state (*S*)-TS1 was favored by the corresponding energy barrier of 3 kJ·mol⁻¹ over the one leading to the (*R*)-product (for details see ref. 16a). Disappointingly, further intensive as well as extensive ¹H, ¹³C, and ²⁹Si NMR studies trying to confirm the presence of penta- or hexa-coordinated species in dichloromethane or THF, as it was done for other hypervalent silicon species,^[30] did not provide any useful information that could help to confirm the presence of the species predicted by calculations or cast light on the intermediate structure and a probable course of the reaction.

Conclusions

With respect to set goals the following conclusion can be drawn. First, a new 3-step procedure allowing synthesis of variously substituted N,N'-dioxides have been developed, albeit separation of the unsymmetrically substituted N,N'-dioxides from the homodimers remains a problem resulting in lower isolated yields.

Second, the (S_a ,R)-catalysts **9a**, **5**, and **9c** bearing 4-MeOC₆H₄, Ph and 4-ClC₆H₄ groups provided the best asymmetric induction. Moreover, reaction times are generally shorter (1-3 h) in comparison with the other methods (see Table 1). In addition, catalyst's loads within the 0.5-2.5 mol% range are sufficient to achieve a reasonably high enantioselectivity. In general, *N*,*N'*-dioxides catalysed allylations proceed with a high asymmetric induction comparable to that obtained by some of the previously developed *N*-oxide catalysts.³¹ Especially high enantioselectivity up to 99% ee were observed in allylations of α , β -unsaturated aldehyde **13**.

Third, as far as the reaction mechanism is concerned, a number of questions remain. The previously observed phenomenon showing that the level of asymmetric induction is systematically much higher in THF then in dichloromethane is kept also for structurally modified catalysts. There is no clear-cut relationship between the asymmetric induction in allylation of benzaldehydes **11** and the structural features of the catalysts **5**, **9a-9f**. The presence of electron–withdrawing or –donating substituents on the aromatic ring in **5**, **9a-9f** affect enantioselectivity only negligibly. In a similar manner the presence of electron–withdrawing or –donating substituents in aromatic aldehydes **11** does not have, except a few cases, a significant effect on enantioselectivity of allylation as well.

Although a very nice work regarding predictability of asymmetric induction in the *N*-oxide catalyzed allylations and propargylations have been proposed and designed,³² the present results clearly show that fine tuning of the catalysts properties may not be as straightforward and simple as expected and non-covalent interactions should be also taken into the account.³³ With this in mind, it is obvious that this field is far from matured and will remain to be a challenging task offering new opportunities for further development.

Experimental Section

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Experimental details can be found in the Supporting information section.

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Keywords: chiral Lewis bases • organocatalysis • asymmetric allylation • aldehydes • catalyst design

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A series of unsymmetrically substituted diastereoisomeric (R_a, R) and (S_a, R) bipyridine N, N'-dioxides were tested as catalyst for enantioselective allylation of various aldehydes. Homoallylic alcohols were obtained with enantiopurity up to 99% ee.

Enantioselective organocatalysis

J. Ulč, D. Nečas, P. Koukal, V. Havlíček, Z. Tošner, S. Hybelbauerová, and M. Kotora*

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Chiral Unsymmetrically Substituted Bipyridine *N*,*N*'-Dioxides as Catalysts for Allylation of Aldehydes