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Synthesis of axially chiral bipyridine *N,N′*-dioxides and enantioselective allylation of aldehydes*

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Abstract: *N*-oxides possessing the pyridine framework are strong Lewis bases that can activate the C–Si bond of allylhalosilanes to such an extent that they catalyze reactions with aldehydes. *N*-oxides embedded in chiral scaffolds are usually capable of highly selective chirality transfer to the derived products. Our goal was to develop a general synthetic method allowing the preparation of structurally varied *N*,*N′*-dioxides suitable for enantioselective organocatalysis. The underlying synthetic strategy was based on [2 + 2 + 2]-cyclotrimerization of suitably substituted diynes with nitriles catalyzed by Co-complexes to generate the desired bipyridines, their further oxidation and resolution of which furnished the corresponding chiral *N*,*N′*-dioxides. The prepared compounds were used in catalytic allylation of aromatic aldehydes to homoallyl alcohols with high enantioselectivity (up to 96 % ee). Enantioselectivity, enantiodiscrimination, and the reaction mechanism are controlled by the choice of solvent.

Keywords: allylation; asymmetric synthesis; catalysis; cyclotrimerization; pyridine.

INTRODUCTION

Lewis base activation has not been used in organic synthesis as extensively as Lewis acid catalysis. Nonetheless, in the last decade this concept has been revived, especially in the area of enantioselective organocatalysis. One class of strong Lewis bases is pyridine *N*-oxides. During the past 10 years, a number of various chiral monodentate or bidentate compounds with the pyridine *N*-oxide moiety have been synthesized. Among them, the most efficient with respect to catalytic activity and enantioselectivity are those with axial chirality, developed by Nakajima et al. **I** and **II** [1], Hayashi et al. **III** [2], and Kočovský et al. **IV** [3] or those derived from natural compounds with chiral terpenoid scaffold, introduced by Kočovský et al. **V** [4] and **VI** [5] (Fig. 1). Catalysts with other frameworks have been developed as well [6].

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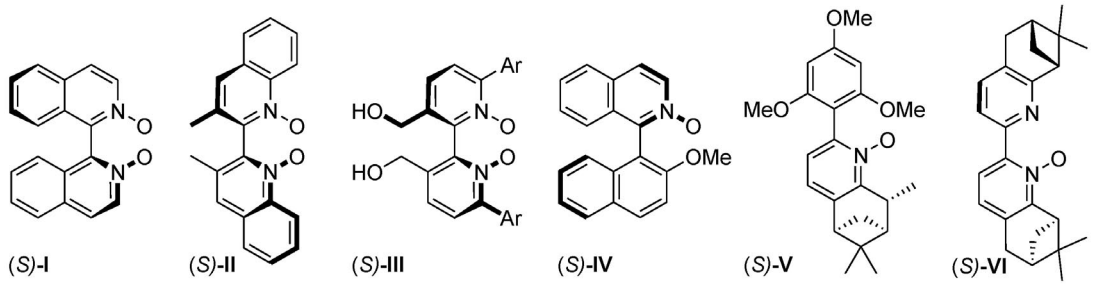
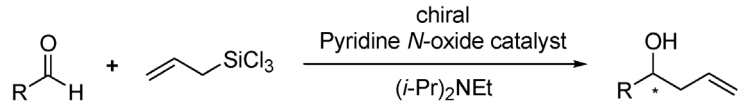


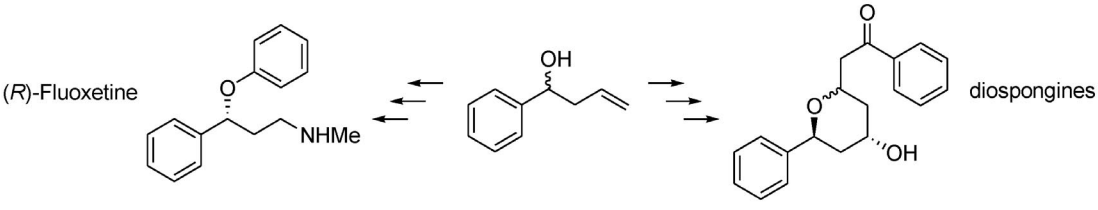
Fig. 1 Various pyridine *N*-oxides used for catalytic allylation of aldehydes.

Pyridine *N*-oxides are known to activate halosilanes in such a way that they react with carbonyl compounds and transfer the organyl moiety to the carbon atom, creating chiral alcohols. One of the most widely studied reactions is the allylation of aldehydes using allyltrichlorosilane, to form homoallylic alcohols (Scheme 1). This process is considered as a benchmark reaction, against which the catalytic activity and scope for asymmetric induction of potential catalysts is to be assessed. (Of course, reactions based on the transfer of other organyl moieties have been developed as well.) Allylation of aromatic and heteroaromatic aldehydes is probably the most widely studied class of reactions, whereas the study of allylation of aliphatic and α,β-unsaturated aldehydes has been relatively neglected.



Scheme 1 Catalytic allylation aldehydes.

Chiral homoallylic alcohols are important building blocks for synthesis of complex organic molecules. The syntheses of fluoxetine (Prozac, a known antidepressant) and diospongines (natural compounds with interesting antiosteoporotic activity) may serve as typical examples. The common chiral starting material for both the syntheses is 1-phenyl-4-buten-1-ol (Scheme 2).

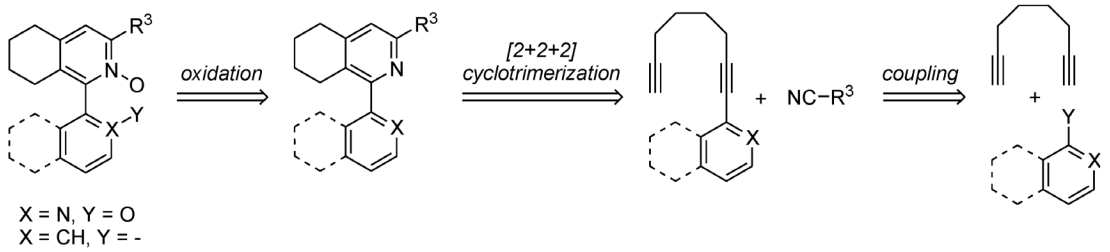


Scheme 2 Homoallyl alcohol as the starting material for the synthesis of diospongines and fluoxetine.

Despite the fact that the previously mentioned catalysts are often very active and give rise to homoallyl alcohols with a high degree of asymmetric induction, usually they must be prepared by using multi-step procedures. In addition, resolution of racemic catalysts or their precursors is often tedious and cumbersome.

The initial impetus to enter this area was provided by the synthesis of the catalyst **IV** (Kočovský et al. [3]). We then envisioned that similar compounds with the pyridine framework could be prepared by the catalytic cyclotrimerization of diynes with nitriles as the crucial synthetic step. We assumed that

the synthetic pathway to the pyridine base compounds could be shortened if the construction of the pyridine ring(s) is carried out with appropriately substituted alkynes (diynes) and nitriles. Moreover, structural variations within the alkyne and nitrile moieties would allow the synthesis of libraries of pyridines. Subsequent oxidation and resolution would yield pyridine *N*-oxide-based catalysts (Scheme 3).

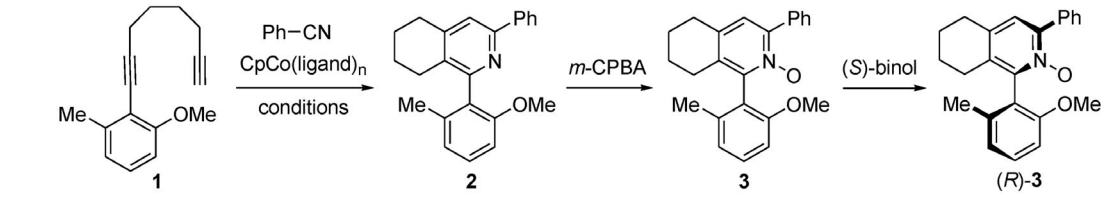


Scheme 3 General retrosynthetic analysis of the synthesis of compounds with pyridine or bipyridine framework.

RESULTS AND DISCUSSION

Synthesis of aryltetrahydroisoquinolines

In our first approach, we wanted to prepare analogs of **IV**. A series of variously substituted 1-aryl-1,7-octadiynes was prepared by the Sonogashira reaction of the corresponding aryl halides with 1,7-octadiyne [7]. Then, these compounds were subjected to the cyclotrimerization with benzonitrile under various catalytic conditions. The cyclotrimerization of 1-(1-methoxy-3-methyl-2-phenyl)octadiyne **1** under three different catalytic conditions (Scheme 4) may serve as a typical example. The highest yield of the desired aryltetrahydroisoquinoline **2** (62 %) was obtained with $CpCo(CH_2{=}CH_2)_2$ (Jonas catalyst) at 20 °C. The catalysis with the commercially available $CpCo(CO)_2$ gave **2** only in 30 % isolated yield. Similar results were obtained also with other 1-aryl-1,7-octadiynes. Oxidation of the prepared aryltetrahydroisoquinoline **2** by *m*-chloro peroxybenzoic acid (*m*-CPBA) yielded the expected *N*-oxide **3**, which was further resolved into enantiomers by co-crystallization with (*S*)-binol. The absolute configuration of the isolated chiral tetrahydroisoquinoline (*R*)-(+)-**3** was determined by single-crystal X-ray diffraction analysis of its co-crystal with (*S*)-binol (Fig. 2).



Scheme 4 Synthesis of pyridine *N*-oxide catalysts (*R*)-(+)-**3**.

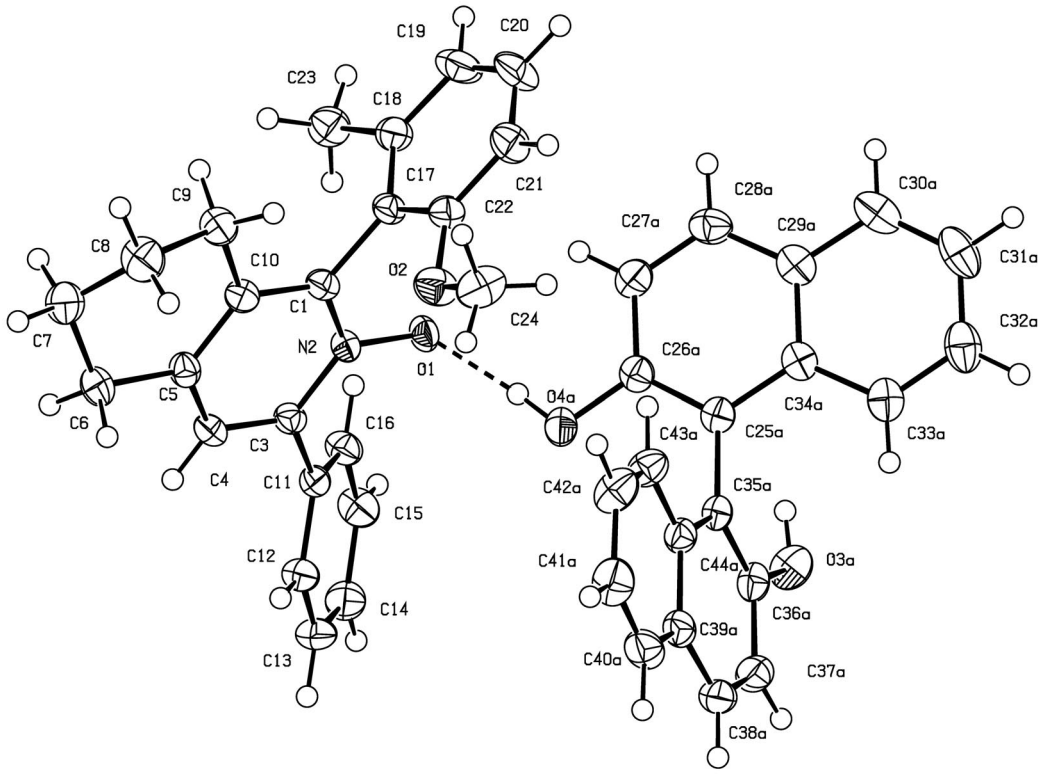
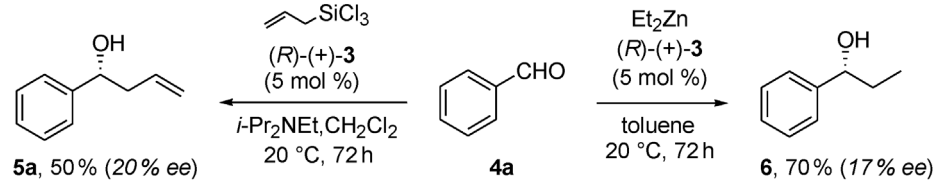


Fig. 2 X-ray structure of (*R*)-(+)-**3** co-crystal with (*S*)-binol.

The catalyst (*R*)-(+)-**3** obtained was tested in the allylation of benzaldehyde with allyltrichlorosilane. Unfortunately, its catalytic activity was surprisingly low as well as the asymmetric induction: the homoallyl alcohol **4** was formed only in about 50 % yield and 20 % ee (Scheme 5). Analogically, the addition of diethylzinc proceeded with similar efficacy.

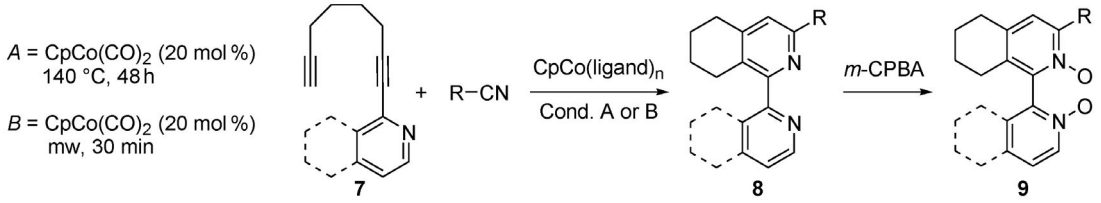


Scheme 5 Enantioselective allylation of benzaldehyde catalyzed by (*R*)-(+)-**3**.

Synthesis of pyridyl- and isoquinolinyltetrahydroisoquinolines

These results prompted us to look for a different kind of catalyst, and our attention shifted to synthesis of unsymmetrically substituted heteroaryl-tetrahydroisoquinolines. The starting material was substituted 1-pyridyl-1,7-octadiynes **7**, which were prepared by the Sonogashira reaction of 1,7-octadiyne with appropriately substituted halopyridines [8,9]. At the outset, the catalytic cyclotrimerization of **7** with benzonitrile in the presence of $CpCo(CO)_2$ was carried out under thermal conditions (conditions A, Scheme 6), but the yields of the desired heteroaryl-tetrahydroisoquinolines **8** were in many cases low

if any (Fig. 3). At that moment, we decided to try to run the reaction under microwave irradiation, hoping to increase yields of the cyclotrimerization reaction (conditions B, Scheme 6). Gratifyingly, the pyridyl-tetrahydroisoquinolines were obtained in higher yields in all cases (Fig. 3) than under the conditions A [13]. The formed compounds **8** were then oxidized to the corresponding *N*,*N*′-dioxides **9** with *m*-CPBA and resolved into enantiomers either by co-crystallization with (*S*)-binol or by using high-performance liquid chromatography (HPLC) with a chiral stationary phase.



Scheme 6 General approach to heteroaryl-tetrahydroisoquinolines.

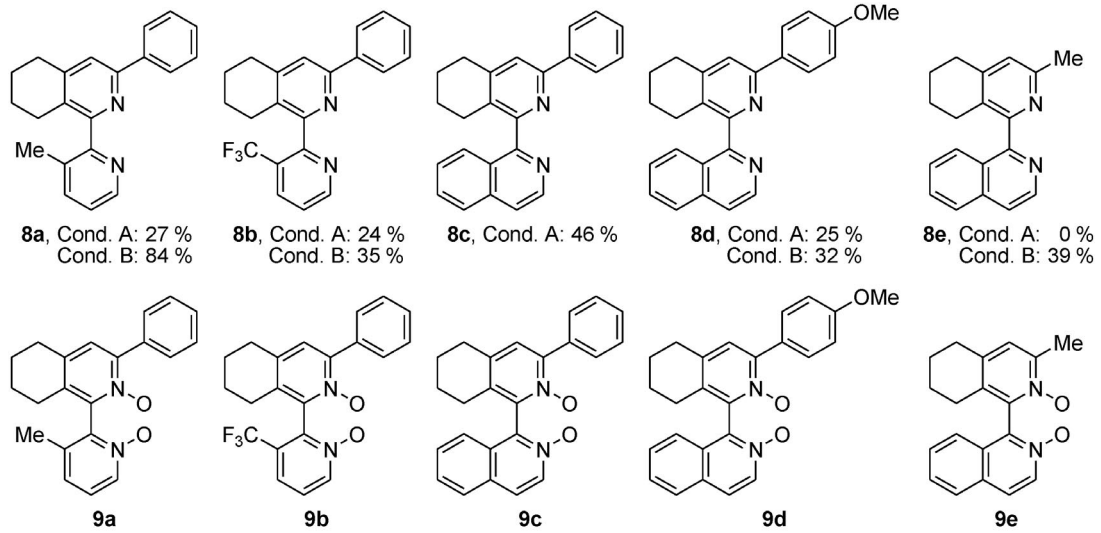
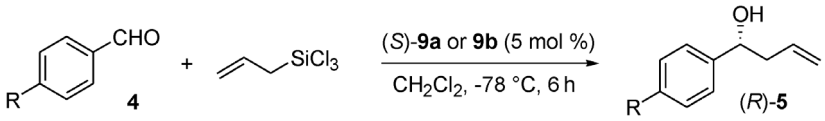


Fig. 3 Synthesized pyridyl and isoquinolilyltetrahydroisoquinolines **9a–e**.

The allylation of 4-methoxybenzaldehyde **4b**, benzaldehyde **4a**, and 4-trifluoromethylbenzaldehyde **4c** was carried out in the presence of a catalytic amount (5 mol %) of pyridyltetrahydroisoquinolines *N*,*N*′-dioxides **9a** and **b** [8]. The obtained results are summarized in Table 1. The catalyst **9a** bearing Me group gave the highest asymmetric induction (74 % ee) with the electron-rich benzaldehyde **4b**. On the other hand, the use of the catalyst **9b** gave comparable enantioselectivities in the allylation of **4b** (72 %) and the electron-poor benzaldehyde **4c** (68 % ee).

Table 1 Allylation of variously substituted benzaldehydes catalyzed by **9a** and **b**.

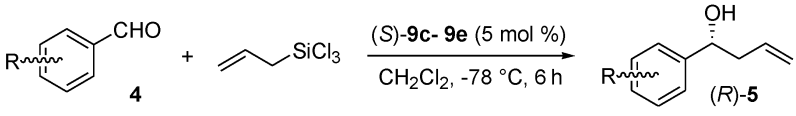


			ee (%)[a] yield (%)[b]	
Entry	R	Product	(*S*)-**9a**	(*S*)-**9b**
1	MeO	**5b**	74 (87)	72 (53)
2	H	**5a**	63 (82)	27 (36)
3	CF_3	**5c**	41 (79)	68 (30)

[a]Determined by GC.
[b]GC yields.

In the next stage, isoquinolyl-tetrahydroisoquinoline *N*,*N*′-dioxides **9c–e** were tested (Table 2) [9]. The catalytic allylation of a series of various *para*-, *meta*-, and *ortho*-substituted benzaldehydes in the presence of **9c** was tested. The highest asymmetric induction was observed during the allylation of the electron-rich 4-methoxybenzaldehyde (**5b**, 87 % ee), then it almost gradually decreased depending on the electron-withdrawing ability of the substituent hitting the lowest level in the case of 4-trifluorobenzaldehyde (**5c**, 54 % ee). The similar trends were observed in the *meta* and *ortho* series as well. The use of **9d** or **e** led to lower asymmetric induction in comparison with **9c**. Interestingly, the allylation of 4-methoxybenzaldehyde **5b** catalyzed by **9e** gave only the racemic product.

Table 2 Allylation of variously substituted benzaldehydes catalyzed by **9c–e**.

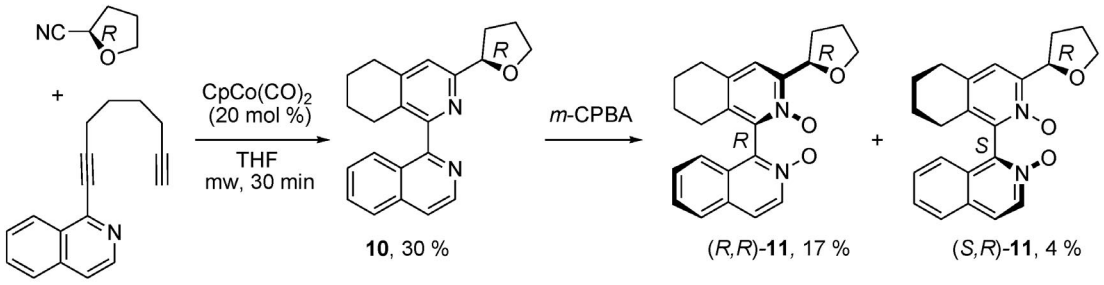


			ee (%)[a] yield (%)[b]		
Entry	R	Product	(*S*)-**9c**	(*S*)-**9d**	(*S*)-**9e**
1	4-MeO	**5b**	87 (62)	70 (72)	0 (78)
2	H	**5a**	80 (95)	76 (61)	61 (64)
3	4-Cl	**5d**	71 (88)		
4	4-F	**5e**	78 (48)		
5	4-CF_3	**5c**	54 (60)	58 (64)	21 (55)
6	3-MeO	**5f**	80 (53)		
7	3-Cl	**5g**	70 (46)		
8	2-MeO	**5h**	67 (61)		
9	2-Cl	**5i**	65 (66)		

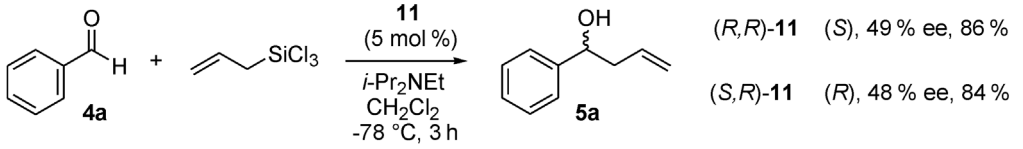
[a]Determined by GC.
[b]GC yields.

Then we assumed that perhaps the introduction of another chiral moiety into the molecular framework of the *N*,*N*′-dioxide could lead to better enantioselectivity. Thus, 1-(isoquinol-2-yl)-1,7-octadiyne was cyclotrimerized with chiral (*R*)-tetrahydrofurannitrile under the above-mentioned conditions [$CpCo(CO)_2$, microwave irradiation], affording the corresponding chiral isoquinolyl-tetrahydroisoquinoline **10**. Its oxidation with *m*-CPBA yielded a diastereoisomeric mixture of *N*,*N*′-dioxides that was readily separable to optically pure (*R*,*R*)-**11** and (*S*,*R*)-**11** by a simple column chromatography

(Scheme 7). Although the allylation of benzaldehyde **4a** yielded product **5a** with mediocre enantioselectivity, (*R*,*R*)-**11** gave the (*S*)-product in 49 % ee (86 %) and (*S*,*R*)-**11** gave the (*R*)-product in 48 % ee (84 %) (Scheme 8), this experiment confirmed that the configuration of the product is controlled by the axial chirality of the catalyst.



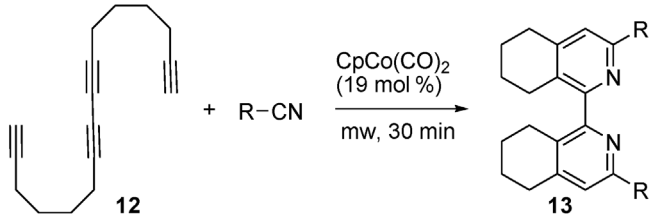
Scheme 7 Synthesis of diastereoisomeric isoquinolinyl-tetrahydroisoquinolines **11**.



Scheme 8 Asymmetric allylation of benzaldehyde catalyzed by **11**.

Synthesis of symmetrical bis(tetrahydroisoquinolines)

Then we decided to try to develop a new synthetic route to symmetrical bistetrahydroquinolines. We envisioned that the catalytic cyclotrimerization of a tetrayne with a nitrile could give rise to the desired compound with the bipyridine framework. Thus, 1,7,9,15-hexadecatetrayne **12** was prepared by an oxidative dimerization of 1,7-octadiyne in 15 % isolated yield. The low yield could be attributed to the starting material oligomerization. With the tetrayne **12** in hand, its cyclotrimerization with various nitriles was studied under the previously mentioned conditions (Scheme 9). Gratifyingly, in all cases desired bis(tetrahydroisoquinolines) **13** in up to 50 % isolated yields were obtained (some representative examples are displayed in Fig. 4) [10]. Taking into the account that six new bonds are formed in two catalytic cycles, the obtained yields are not bad. It should be emphasized that carrying out the reaction under the classical thermal conditions did not lead to the formation of the desired products. Bis(tetrahydroisoquinolines) **13a,d,f** were oxidized with *m*-CPBA to the corresponding *N*,*N*′-dioxides **14a,d,f**, and isolated in 46, 22, 76 % yields, respectively (Fig. 5). Compounds **14a,d** were resolved into enantiomers by HPLC with a chiral stationary phase. Owing to the presence of centers of chirality in the



Scheme 9 Synthesis of symmetrically substituted bis(tetrahydroisoquinolines) **13**.

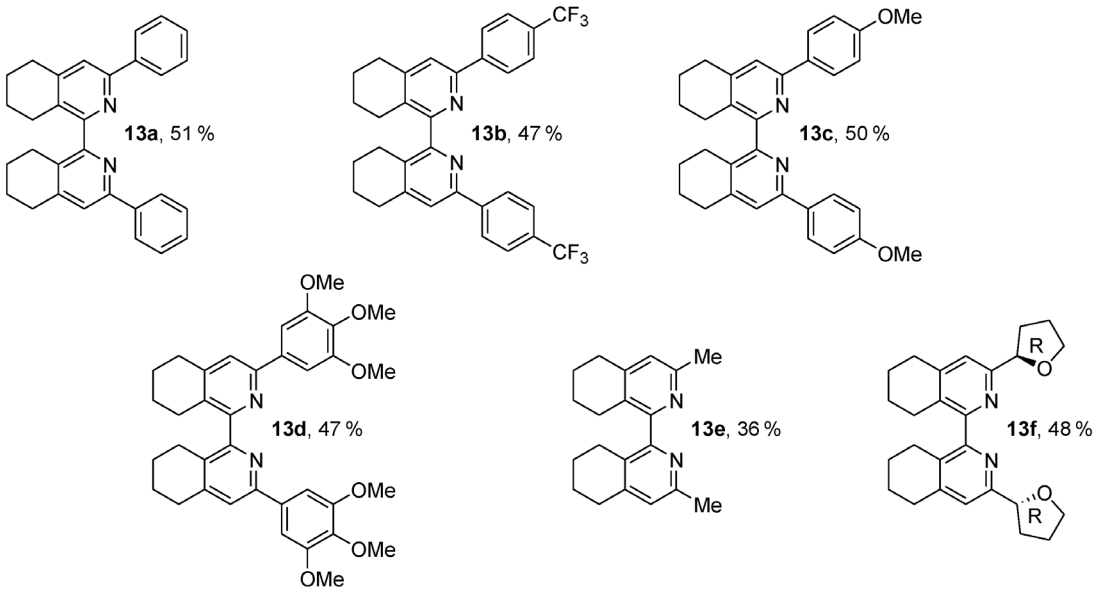


Fig. 4 Selected examples of symmetrically substituted bis(tetrahydroisoquinolines) **13a–f**.

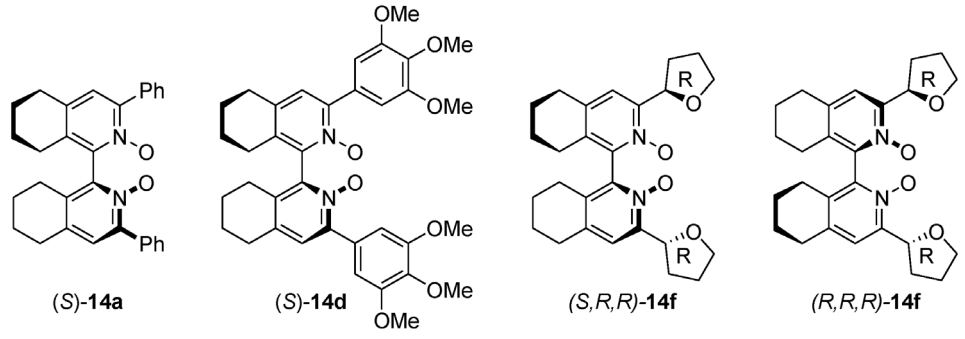
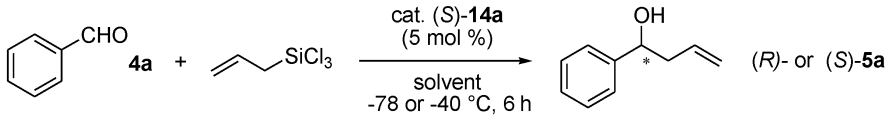


Fig. 5 Examples of symmetrically substituted bis(tetrahydroisoquinolines) *N-N′*-dioxides **14a,d,f**.

tetrahydrofuran (THF) rings in **14f**, the mixture of diastereoisomers was resolved by a simple column chromatography on silica gel.

Unlike in the previous cases where the allylation was carried out only in CH_2Cl_2 or MeCN, we decided to screen the solvent effect on asymmetric induction. Thus, the reaction of benzaldehyde **4a** with allyltrichlorosilane catalyzed by (*S*)-**14a** was carried out in a range of solvents. Nothing was as surprising as the outcome of this study that showed that the reaction medium indeed had a profound effect on the course of the reaction (Table 3) [10]. The reactions carried out in electrophilic solvents (CH_2Cl_2, MeCN, etc.) proceeded with mediocre enantioselectivity to yield (*R*)-homoallyl alcohol **5a** (it has been observed before that *R*-catalysts gave usually *S*-products and the opposite). On the other hand, the reactions carried out in the second group of solvents, non-electrophilic solvents (toluene, PhCl, THF, EtOAc, etc.), yielded (*S*)-homoallyl alcohol with high enantioselectivity (up to 83 % ee). This phenomenon was rather unexpected and also hitherto unobserved. In the next step, the allylation of benzaldehydes bearing electron-accepting and -donating groups by (*S*)-**14a**, (*S*)-**14d**, (*R*,*R*,*R*)-**14f**, and (*S*,*R*,*R*)-**14f** was studied in CH_2Cl_2 and chlorobenzene (Table 4). ((*S*,*R*,*R*)-**14f** was shown to be also a good catalyst for the allylation of aliphatic aldehydes [15].)

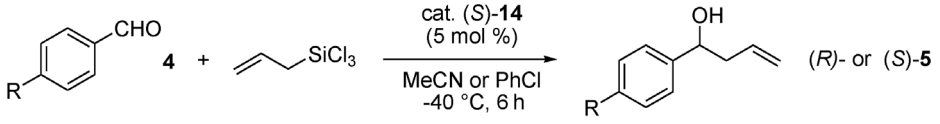
Table 3 Allylation of variously substituted benzaldehydes catalyzed by **14a**.



Solvent	*T* (°C)	ee (%)[a]	Yield (%)[b]	Solvent	*T* (°C)	ee (%)[a]	Yield (%)[b]
CH_2Cl_2	–78	55 (*R*)	100	PhMe	–78	83 (*S*)	45
MeCN	–40	65 (*R*)	100	PhF	–40	78 (*S*)	100
$CHCl_3$	–40	36 (*R*)	100	PhCl	–40	79 (*S*)	100
$EtNO_2$	–78	53 (*R*)	71	*m*-$C_5H_4F_2$	–40	73 (*S*)	100
				C_7F_8	–78	50 (*S*)	14
				$CFCl_3$	–78	40 (*S*)	14
				pentane	–78	44 (*S*)	1
				THF	–78	70 (*S*)	100
				EtOAc	–78	74 (*S*)	100
				C_6F_5OMe	–78	10 (*S*)	66

[a]Determined by GC.
[b]GC yields.

Table 4 Allylation of variously substituted benzaldehydes catalyzed by **14**.



				ee (%)[a] (yield (%))[b]			
Entry	Solvent	R	Product	(*S*)-**14a**	(*S*)-**14d**	(*R,R,R*)-**14f**	(*S,R,R*)-**14f**
1	MeCN	MeO	**5b**	30, *R* (100)	7, *R* (32)	15, *R* (82)	16, *R* (100)
2	MeCN	H	**5a**	65, *R* (100)	52, *R* (61)	48, *S* (100)	46, *R* (100)
3	MeCN	CF_3	**5c**	80, *R* (100)	68, *R* (24)	60, *S* (100)	0, *R* (100)
4	CH_2Cl_2	MeO	**5b**	61, *S* (83)	73, *S* (90)	0, 0	75, *S* (40)
5	CH_2Cl_2	H	**5a**	82, *S* (100)	70, *S* (100)	0, 0	62, *S* (100)
6	CH_2Cl_2	CF_3	**5c**	60, *S* (78)	33, *S* (96)	0, 0	56, *S* (47)

[a]Determined by GC.
[b]GC yields.

Reaction mechanism

Although the allylations have been previously carried out in different solvents, such a difference in *S* and *R* selectivity with respect to the solvent used either has not been observed (e.g., the reaction either did not proceed in toluene and THF with related axially chiral bipyridine *N,N'*-dioxide [12a]), or it was very small [16]). Theoretically, the aforementioned solvent effect is possible, if the key enantiodifferentiating steps proceed via modified transition states or if entirely different mechanisms are involved.

Since two allylation mechanisms of aldehydes proceeding via the ionic or neutral pathway had been proposed [1a,4,17], we envisioned that the crucial experiment to confirm their presence could rely on contactless conductivity analysis. The measurements of a mixture of **14a** with allyltrichlorosilane clearly showed a conductivity increase in MeCN and CH_2Cl_2, while in PhCl and EtOAc the conductivity remained at the same level (in comparison with the conductivity of individual compounds) [14].

Initially, the reaction of the catalyst **14a** with allyltrichlorosilane gave rise to the neutral hexa-coordinated silicon species **15**. However, then in MeCN and CH_2Cl_2 the formation of the cationic penta-coordinated silicon species **16** is suggested owing to the solvent acceptor properties (electrophilicity) (acceptor activity number (AN) [18]: MeCN = 18.9, CH_2Cl_2 = 20.4), which can stabilize (solvate) the chloride anion, providing thus the necessary driving force for the dissociation of the chloride anion from the neutral complex **15**. On the other hand, solvents such as PhCl, EtOAc, THF, etc. are much less electrophilic (AN: EtOAc = 9.3, THF = 8.0, benzene = 8.2) and cannot provide a sufficient stabilization for the chloride anion, preserving the neutral six-coordinated complex **15**. The computational study clearly supports the view that the catalyst and allyltrichlorosilane form ionic species in polar solvents, whereas they stay non-dissociated in less polar solvents (Fig. 6 and Table 5).

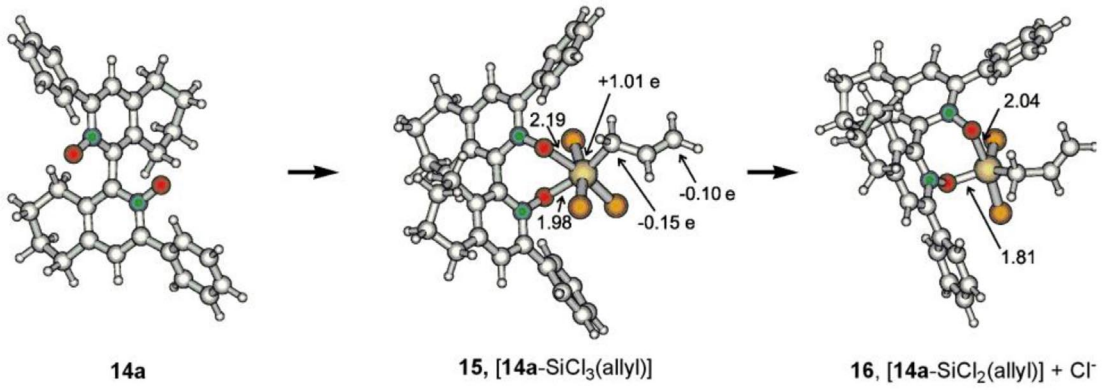


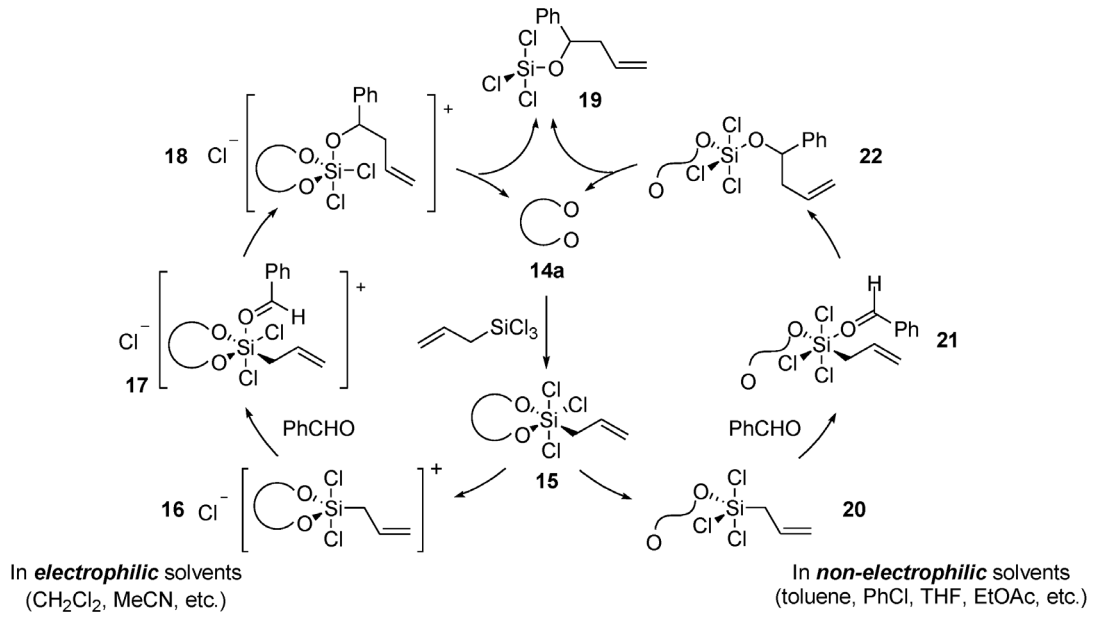
Fig. 6 Calculated intermediates **15** and **16** for allyltrichlorosilane activation by **14a**.

Table 5 Complex formation of **14a** with allyltrichlorosilane in various solvents.

Reaction	Reaction enthalpy (eV, 0 K)			
	MeCN	CH_2Cl_2	PhCl	Toluene
14a + $SiCl_3$(allyl) → **15**	0.01	0.07	0.13	0.28
15 → **16**	–0.29	0.02	0.27	1.24

Based on these findings, we proposed the existence of two different reaction mechanisms of the allylation depending on the solvent used (Scheme 10). The first intermediate in both mechanisms, a six-coordinated silicon species **15**, results from the reaction of *N*,*N*′-dioxide **14a** with allyltrichlorosilane. However, in MeCN or similarly electrophilic solvents, a cationic penta-coordinated silicon species **16** is formed. Its vacant coordination site at the silicon atom can be filled with the carbonyl group of benzaldehyde, leading to intermediate **17**. An intramolecular allylation via 6-membered cyclic transition state then yields the penta-coordinated silicon species **18** followed by its disintegration into trichlorosilylether **19**, and **14a** is released back into the catalytic cycle.

In less electrophilic solvents such as PhCl, etc., the free coordination site at the silicon atom is probably opened only after the dissociation of one of the *N*-oxide moieties, leading to the penta-coordinated species **20**. The dissociation is also supported by the calculations that indicate the non-equivalent bonding of the N–O moieties to the silicon atom in **16** (Fig. 6). In this regard, it cannot be excluded that the carbonyl group simply replaces the more weakly bound N–O moiety. The subsequent coordi-



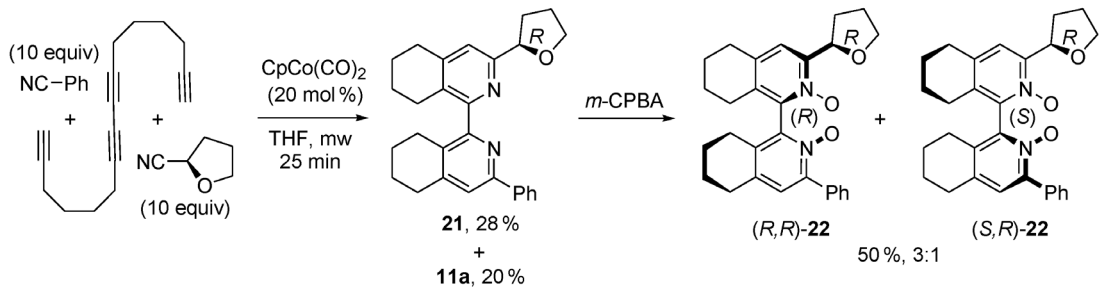
Scheme 10 Proposed reaction mechanism of aldehyde allylation in electrophilic or non-electrophilic solvents.

nation of the carbonyl moiety to the silicon atom results in the formation of the hexa-coordinated silicon species **21** followed by intramolecular allylation to yield the penta-coordinated-species **22**, which finally disintegrates to trichlorosilyl ether **19**, and **14a** is released back into the catalytic cycle.

Since the neutral complexes are less reactive than the ionic ones and the key intermediate **21** is sterically more crowded than the corresponding ionic intermediate **17**, it is reasonable to expect it to lead to higher selectivities. Indeed, higher enantiomeric excesses were observed in less electrophilic solvents such as toluene (83 %), PhCl (79 %), THF (70 %), and EtOAc (74 %) than in the more eletrophilic ones such as MeCN (65 %) and CH_2Cl_2 (55 %). Obviously, both the penta-coordinated silicon species **16** and **20** differ in the spatial arrangements. Thus, it is expected that the coordination of the aldehyde to the silicon atom will proceed via different trajectories, giving a rationale for the different signs of the obtained enantioselectivities.

Synthesis of unsymmetrical bis(tetrahydroisoquinolines)

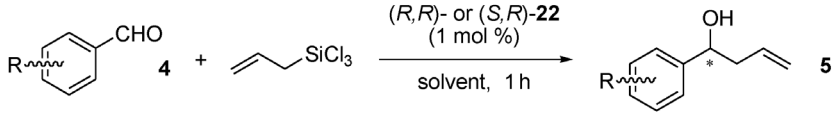
On the basis of the aforementioned results and calculations, synthesis of new potential catalysts was carried out. There were two objectives: (a) to synthesize an unsymmetrically substituted bis(tetrahydroisoquinolines) and (b) to develop a synthesis of chiral catalysts avoiding chiral resolution. With these objectives in mind, we envisioned that a catalytic cross-cyclotrimerization of diyne **10** with two different alkynes (one of them bearing a center of chirality) could give rise to desired compounds. Once again, cross-cyclotrimerization catalyzed by $CpCo(CO)_2$ under microwave irradiation proved to be the convenient method of choice. Thus, the reaction of **10** with excess of benzonitrile and (*R*)-tetrahydrofurannitrile yielded the desired unsymmetrically substituted bis(tetrahydroisoquinolines) **21** and symmetrically substituted **11a** in 28 and 20 % isolated yields, respectively [11]. The third possible product, **11f**, was not detected. This method works also for other combinations of various nitriles [12]. Oxidation of **21** with *m*-CPBA gave rise to a mixture of diastereoisomers (%) that were readily separated into optically pure (*R*,*R*)-**22** and (*S*,*R*)-**22** by a simple column chromatography (Scheme 11).



Scheme 11 Synthesis of unsymmetrically substituted diastereoisomeric bis(tetrahydroisoquinolines) **22**.

With these compounds in hand, the allylation of variously substituted benzaldehydes in different solvents was studied to find optimal conditions to achieve the highest possible asymmetric induction (Table 6). The reactions were carried out with 1 mol % of the catalyst at –78 °C for 1 h, and in all cases it proceeded in high yields of the corresponding homoallyl alcohols. Generally, the best results with respect to enantioselectivity were obtained in THF where the asymmetric induction was as high as 96 % ee. It is noteworthy that both catalysts gave rise to opposite enantiomers with approximately the same enantioselectivity, confirming the previous observation that enantiodiscrimination is controlled by axial chirality. Although a minor effect of the chiral THF moiety on the enantioselectivity could be observed in some cases, probably by the formation of matched and mismatched intermediates (e.g., entries 3, 6, 7, and 11), the THF moiety serves as a convenient chiral auxiliary for the separation of enantiomers. Moreover, by using one chiral nitrile it is possible to prepare two catalysts that give rise to products with different absolute configuration.

Table 6 Allylation of variously substituted benzaldehydes catalyzed by **22**.



Entry	R	Solvent	T (°C)	Product	(*R*,*R*)-**22** ee (%)[a]	Yield (%)[b]	(*S*,*R*)-**22** ee (%)[a]	Yield (%)[b]
1	H	MeCN	–40	**5a**	53, (*S*)	100	44, (*R*)	82
2	H	PhCl	–40	**5a**	93, (*R*)	100	94, (*S*)	100
3	H	THF	–78	**5a**	80, (*R*)	100	96, (*S*)	100
4	4-MeO	PhCl	–78	**5b**	85, (*R*)	83		
5	4-MeO	THF	–78	**5b**	86, (*R*)	100	91, (*S*)	100
6	4-Me	THF	–78	**5j**	85, (*R*)	99	94, (*S*)	100
7	4-F	THF	–78	**5e**	84, (*R*)	81	95, (*S*)	99
8	4-Cl	THF	–78	**5d**	89, (*R*)	89	93, (*S*)	91
9	4-CF_3	PhCl	–40	**5c**	67, (*R*)	76		
10	4-CF_3	THF	–78	**5c**	95, (*R*)	76	87, (*S*)	91
11	4-CN	THF	–78	**5k**	83, (*R*)	55	88, (*S*)	100
12	3-Cl	THF	–78	**5g**	87, (*R*)	75	92, (*S*)	100
13	2-Cl	THF	–78	**5i**	46, (*R*)	45	14, (*S*)	100

[a]Determined by GC.
[b]GC yields.

CONCLUSION

The Co-complex-catalyzed [2 + 2 + 2]-cyclotrimerization under microwave irradiation is a convenient method for the synthesis of pyridine rings with variously substituted substrates and is especially effective in cases where classical thermal conditions fail. This is mainly caused by shorter reaction times that can reduce the exposure of often sensitive starting material to high temperatures. This strategy was used to synthesize several new types of *N*,*N*′-dioxides with bipyridine scaffold, which were tested in enantioselective allylation of aldehydes.

The highest enantioselectivity was obtained with chiral unsymetrically 3,3'-substituted bis(tetrahydroisoquinoline) *N*,*N*′-dioxides that were prepared from commercially available compounds in just three steps and, owing to the presence of an additional centers of chirality, could be separated into enantiomers by a simple column chromatography.

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