Catalytic Enantioselective Aza-Diels–Alder Reactions of Imines—An Approach to Optically Active Nonproteinogenic α-Amino Acids

Sulan Yao, Steen Saaby, Rita G. Hazell, and Karl Anker Jørgensen*[a]

Abstract: A catalytic enantioselective aza-Diels–Alder reaction of imines has been developed. The reaction of *N*-tosyl α-imino ester with different dienes including activated, non-activated, cyclic, and acyclic dienes has been investigated in the presence of various chiral Lewis acids. A series of phosphino–oxazoline ligands have been synthesized and evaluated for the reaction. It was found that the combination of phosphino–oxazoline ligands with copper(I) salts gives the best results for the activated dienes, while BINAP-copper(I) complexes are good catalysts for all the dienes studied. In the case of activated acyclic dienes the aza-Diels–Alder products can be obtained in higher than 80% isolated yield and 96% *ee*, while for the unactivated cyclic dienes the *exo* diastereomer is formed as the major product in up to 95% *ee*. For an activated cyclic conjugated diene, 2-trimethylsilyloxy-1,3-cyclohexadiene, the reaction proceeds as a Mannich-type addition reaction giving optically active γ-oxo α-amino acid derivatives in good yields and up to 96% *ee*. The reaction of an unactivated acyclic diene, 2,3-dimethyl-1,3-butadiene, with the *N*-tosyl α-imino ester gives both the aza-Diels–Alder and aza-ene products, in a ratio of 9:1 favoring the aza-Diels–Alder product. Furthermore, a series of different imines have been synthesized and investigated as possible substrates for the present catalytic enantioselective aza-Diels–Alder reaction in order to obtain mechanistic insight. All imines studied gave moderate to high *ee*. Particularly, the reaction of the *N*-phenyl and *N*-*p*-methoxyphenyl substituted glyoxylate imines with Danishefsky's diene proceeded well affording the corresponding aza-Diels–Alder product in high yield with up to 91% *ee* at room temperature. The present catalytic enantioselective reaction of imines provided an effective route to optically active nonproteinogenic α-amino acids. The products of the catalytic enantioselective aza-Diels–Alder reaction of the cyclic dienes can be used for the preparation of key compounds such as natural products and compounds of pharmaceutical interest. The absolute configurations of five products have been solved by X-ray structural analysis, and it is found that the absolute configuration of the aza-Diels–Alder adduct is dependent on the substituent on the imine nitrogen atom. It turned out that the *N*-tosyl glyoxylate imine and *N*-*p*-methoxyphenyl glyoxylate imine give the aza-Diels–Alder adduct with opposite absolute configuration using the same enantiomer of the catalyst. On the basis of the results the mechanistic aspects for the reactions are discussed.

Keywords: asymmetric catalysis · cycloadditions · Diels–Alder reactions · enantioselective synthesis · Lewis acids

Introduction

The construction of optically active nitrogen containing compounds is a fundamental task in chemistry as they are key building blocks for the preparation of important compounds such as alkaloids, peptides and aza sugars. The aza-Diels–Alder reaction is among the most powerful methodologies for the construction of nitrogen containing compounds, particularly for the construction of piperidine and tetrahydroquinolidine derivatives.[1, 2] Not surprisingly, considerable attention has been paid to the development of diastereoselective aza-Diels–Alder reactions and their application in the synthesis of naturally occurring compounds.[3, 4]

Despite the potential advantages in using chiral Lewis acid complexes as catalysts and the great progress in the enantioselective reactions of carbonyl compounds catalyzed by chiral Lewis acid complexes,[5] the protocols for the analogous catalytic asymmetric reactions of imines are rarely found.[6, 7] Some of the common problems related to the imines as the substrates could be: i) The imine nitrogen atom is more Lewis basic than the oxygen atom of the carbonyl compounds. As a consequence, the coordination to the Lewis acids is much stronger leading to inhibition or decomposition of the chiral Lewis acid complexes. Thus stoichiometric amount of catalyst would be needed to achieve high asymmetric induction; ii) the flexible (*E*,*Z*)-conformational structure of the imine C=N double bond allows more possible transition species to exist in solution; iii) some imines are unstable and cannot be isolated,

[a] Prof. K. A. Jørgensen, S. Yao, S. Saaby, R. G. Hazell
Center for Metal Catalyzed Reactions
Department of Chemistry, Aarhus University
8000 Aarhus C (Denmark)
Fax: (+45) 86 19 61 99
E-mail: kaj@kemi.aau.dk

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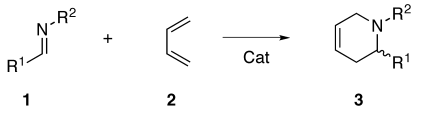
giving additional difficulties on precise investigation, and iv) the tendency of enolizable imines with an α-acidic proton to form enamines.

Within the last years, the first examples of the catalytic enantioselective aza-Diels–Alder,[7] ene[8] and Mannich-type,[9] allylation[10] and cyanation reactions[11] of imines have appeared. Yamamoto et al. showed that by using a stoichiometric amount of a chiral boron complex it was possible to catalyze enantioselective aza-Diels–Alder reactions of aldimines with activated dienes of the Danishefsky type.[6] By the use of a chiral zirconium complex as the catalyst Kobayashi et al. were able to develop the first catalytic enantioselective aza-Diels–Alder reaction of aldimines derived from for example 1-naphthaldehyde and 2-aminophenol as dienophiles with Danishefsky's diene.[7b] The highest *ee* obtained was 93% applying 20 mol% chiral zirconium catalyst. Recently, we communicated that a *N*-tosyl α-imino ester could react with activated dienes of the Danishefsky type in the presence of chiral BINAP-copper complexes to give optically active nonproteinogenic α-amino acids of the piperidine type in good yields with up to 80% *ee* for the unsubstituted Danishefsky's diene, and up to 96% *ee* for the dimethyl substituted Danishefsky's diene.[7c] However, it should be noted that these examples, according to our knowledge, are restricted to only activated dienes. In this paper we present the development of catalytic enantioselective aza-Diels–Alder reactions of different imines with both activated and unactivated cyclic dienes, as well as acyclic dienes, catalyzed by chiral BINAP and phosphino–oxazoline ligand copper(I) complexes [Eq. (1)]. The influence of different imines, dienes,



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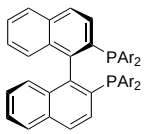
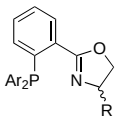
ligands, Lewis acids, and solvents on the reaction course will be presented. It is especially notable that the present enantioselective catalytic development gives access to optically active nonproteinogenic α-amino acid derivatives. These compounds can be used as versatile chiral building blocks for the synthesis of natural products and compounds of pharmaceutical interest. Furthermore, the mechanism for the reaction will also be discussed.

Results and Discussion

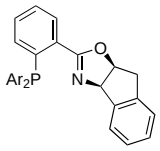
A series of BINAP- (P,P chelating) and C_2-symmetric bisoxazoline (N,N chelating) ligands in combination with different metal salts, such as $CuClO_4 \cdot 4MeCN$, $2CuOTf \cdot C_6H_6$, $CuPF_6 \cdot 4MeCN$, $Cu(OTf)_2$, AgOTf, $AgSbF_6$, $AgClO_4$, $Pd(SbF_6)_2$, $Pd(ClO_4)_2$, $Pd(OTf)_2$, $RuSbF_6$, and $Zn(OTf)_2$, were initially investigated[7c] as catalysts for the enantioselective aza-Diels–Alder reaction of the *N*-tosyl α-imino ester **1a** with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) (**2a**). It should be noted that Lectka et al. have used imine **1a** in ene- and alkylation reactions

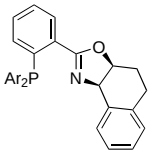


4a: Ar = Ph
4b: Ar = *p*-Tol



5a: Ar = Ph, R = Ph (*R*)
5b: Ar = Ph, = *i*Pr (*S*)
5c: Ar = Ph, R = *t*Bu (*S*)
5d: Ar = *p*-Tol, R = *t*Bu (*S*)



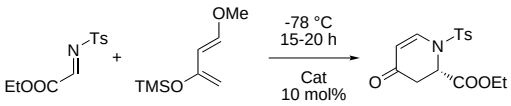


5e: (3a*R*,9b*S*), Ar = Ph
5f: (3a*R*,9b*S*), Ar = *p*-Tol
5g: (3a*R*,9b*S*), Ar = 2,4-xylene

5h: (3a*R*,9b*S*), Ar = Ph
5i: (3a*R*,9b*S*), Ar = *p*-Tol
5j: (3a*R*,9b*S*), Ar = 2,4-xylene

catalyzed by chiral copper(I)-BINAP complexes.[8a, 9c,f,g] We have found that the complex of the BINAP ligands with $CuClO_4$ as the Lewis acid is the best catalyst among the BINAP and bisoxazoline ligands investigated and we have therefore not investigated the use of the bisoxazoline ligands further for the present class of reactions. In view of the excellent performance of phosphino–oxazoline (P,N chelating) ligands in various reactions,[12] we rationalised that the phosphino–oxazoline ligands could be attractive for the present reaction, thus a series of phosphino–oxazoline ligands were synthesized[13] and evaluated for their enantioselective properties for the present reactions.

The examination of the ligands was performed using the aza-Diels–Alder reaction of imine **1a** with Danishefsky's diene **2a** [Eq. (2)]. The results for the reaction of **1a** with **2a**



1a **2a** **3a** (2)

in the presence of BINAP ligands **4a**,**b** and phosphino–oxazoline ligands **5a-j** with $CuClO_4$ as the Lewis acid in THF and CH_2Cl_2 as the solvents are given in Table 1.

It appears from the results in Table 1 that both the BINAP and phosphino–oxazoline ligands in combination with copper(I) as the Lewis acid can catalyze the enantioselective aza-Diels–Alder reaction of imine **1a** with diene **2a** giving the desired aza-Diels–Alder product **3a** in very high yield. The use of Tol-BINAP-(*R*)-**4b**-$CuClO_4$ as the catalyst in CH_2Cl_2 as the solvent gives the highest yield of the aza-Diels–Alder product for the BINAP ligands (*R*)-**4a**,**b** tested, as 89% isolated yield of **3a** is obtained, however, the *ee* was only 26% (entry 2). Changing the solvent to THF leads to a slightly lower yield of **3a** (80%) but in this solvent a significant increase to 79% *ee* is found (entry 2). The phosphino–oxazoline ligands in combination with $CuClO_4$ are attractive catalysts for the aza-Diels–Alder reaction of **1a** with **2a**. The phosphino–oxazoline ligands used in the present paper can be divided into three main classes based on their structural differences: the simple phosphino–oxazoline ligands **5a–d**,

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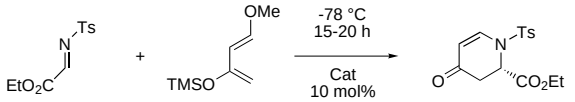
Table 1. The results for the aza-Diels–Alder reaction of the *N*-tosyl α-imino ester **1a** with Danishefsky's diene **2a** in the presence of BINAP ligands **4a**,**b** and phosphino–oxazoline ligands **5a**–**j** and $CuClO_4 \cdot 4MeCN$ (10 mol%) as the Lewis acid at $-78\,^{\circ}C$ in THF and CH_2Cl_2.



1a **2a** **3a**

Entry	Ligand	Yield[a]/*ee*[b] [%] (THF)	Yield[a]/*ee*[b] [%] (CH_2Cl_2)
1	(*R*)-**4a**	78/67 (*S*)	85/10 (*S*)
2	(*R*)-**4b**	80/79 (*S*)	89/26 (*S*)
3	(*R*)-**5a**	93/27 (*R*)	90/29 (*R*)
4	(*S*)-**5b**	97/77 (*S*)	73/71 (*S*)
5	(*S*)-**5c**	82/87 (*S*)	96/77 (*S*)
6	(*S*)-**5d**	74/87 (*S*)	91/71 (*S*)
7	(3a*R*,9b*S*)-**5e**	94/61 (*R*)	81/62 (*R*)
8	(3a*R*,9b*S*)-**5f**	97/62 (*R*)	93/62 (*R*)
9	(3a*R*,9b*S*)-**5g**	97/79 (*R*)	94/53 (*R*)
10	(3a*R*,9b*S*)-**5h**	49/80 (*R*)	92/75 (*R*)
11	(3a*R*,9b*S*)-**5i**	66/81 (*R*)	77/86 (*R*)
12	(3a*R*,9b*S*)-**5j**	90/66 (*R*)	70/45 (*R*)

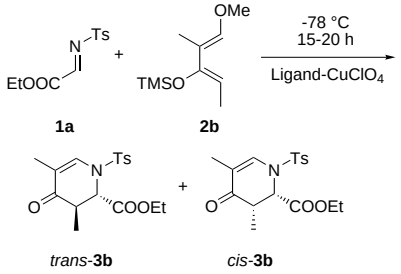
[a] Isolated yield. [b] *ee* determined by HPLC using a Chiralpak AD column.

the conformationally strained indane-derived, and 1,2,3,4-tetrahydronaphthanlene-derived phosphino–oxazoline ligands, **5e**–**g** and **5h**–**j**, respectively. The results for the use of these phosphino–oxazoline ligands are shown in entries 3–12 in Table 1. For the simple phosphino–oxazoline ligands **5a**–**d**, the highest *ee* of 87% is obtained in THF using either (*S*)-**5c** or (*S*)-**5d** with a bulky *tert*-butyl substituent in the oxazoline moiety (entry 5, 6). It is interesting to observe that the phenyl substituted oxazoline ligand **5a** gives much lower *ee* in both CH_2Cl_2 and THF (entry 3). For the indane-derived phosphino–oxazoline ligands **5e**–**g** the best results, 97% isolated yield and 79% *ee*, are obtained using the most bulky ligand (3a*R*,9b*S*)-**5g** in THF (entry 9). For the phosphino–oxazoline ligands **5h**–**j**, 86% *ee* is the highest enantioselectivity obtained by applying ligand (3a*R*,9b*S*)-**5i** in CH_2Cl_2 (entry 11). These results reflected the influence of extending the steric bulkiness of both the oxazoline moiety and the phosphino part on the asymmetric induction of the ligands.

The aza-Diels–Alder reaction of the *N*-tosyl α-imino ester **1a** with diene **2a** using the BINAPs, **4a**,**b** and phosphino–oxazoline ligands **5a**–**j** is very dependent on the Lewis acids and solvents. A variety of Lewis acids, including $Zn(OTf)_2$, $Cu(OTf)_2$, $AgSbF_6$, AgOTf, $AgClO_4$, $Pd(SbF_6)_2$, $Pd(ClO_4)_2$, $Pd(OTf)_2$, and $RuSbF_6$ can also catalyze this reaction giving good yield of **3a**, although the *ee* was significantly lower compared with the use of $CuClO_4$. The influence of the counterions is limited as the use of CuOTf and $CuPF_6$ instead of $CuClO_4$ led only to a slight difference in *ee* values. The reaction can also proceed in other solvents than THF and CH_2Cl_2; however, a lower *ee* for **3a** is obtained in solvents such as Et_2O, *tert*-butyl methyl ether, MeCN, DMF, toluene, and benzotrifluoride.

The aza-Diels–Alder reaction of the *N*-tosyl α-imino ester **1a** catalyzed by the BINAPs, **4a**,**b** and phosphino–oxazoline ligands **5a**–**j** in combination with $CuClO_4$ as the Lewis acid is not only restricted to Danishefsky's diene **2a**. The potential of the reaction will be shown in the following by presenting the reaction of **1a** with a variety of activated- and non-activated cyclic, as well as acyclic dienes catalyzed by both BINAP- and phosphino–oxazoline-$CuClO_4$ complexes.

The results for the reaction of the *N*-tosyl α-imino ester **1a** with *trans*-1-methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene, the dimethyl-substituted Danishefsky's diene, **2b** are presented in the following Equation:



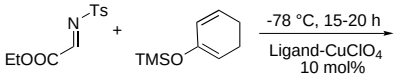
(3)

Ligand	Yield/*ee*	Yield/*ee*
4b-10 mol%/THF	83/94	8/rac
4b-1 mol%/THF	70/96	6/rac
5c-10 mol%/THF	71/66	23/15
5h-10 mol%/THF	64/79	32/15
5i-10 mol%/CH_2Cl_2	48/64	44/5

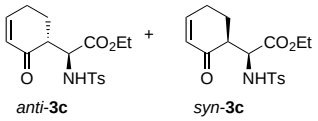
It appears from the results in Equation (3) that the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst gives the highest diastereoselectivity as a 10:1 ratio of *trans*-**3b**:*cis*-**3b** is obtained. The diastereomer *trans*-**3b** is formed in 83% isolated yield and with 94% *ee* applying 10 mol% of the catalyst, while the isolated yield is only slightly reduced to 70% by the use of only 1 mol% of the catalyst in THF and maintaining the high *ee*. In both cases a racemate of *cis*-**3b** is formed in very low yield. The results for the use of the phosphino–oxazoline ligands **5c**,**h**,**i** are also presented in Equation (3); the diastereoselectivity is reduced for example in the case of **5i** as the ligand and CH_2Cl_2 as solvent a nearly 1:1 mixture of the two diastereomers of **3b** is formed. The highest *ee* (79%) for *trans*-**3b** is obtained applying **5h** as the chiral ligand in THF, while only lower than 15% *ee* is found for diastereomer *cis*-**3b**. The Tol-BINAP-(*R*)-**4b**-$CuClO_4$ complex is thus the most effective catalyst regarding the diastereo- and enantioselectivity for the aza-Diels–Alder reaction of **1a** with **2b**. The formation of *trans*-**3b** as the major diastereomer indicated that the approach of diene **2b** to imine **1a** is *exo* relative to the ester group suggesting that the reaction proceeds via the (*E*)-form of imine **1a** with the tosyl substituent adopting the *endo* orientation relative to the diene (vide infra).

The results for the reaction of the *N*-tosyl α-imino ester **1a** with 2-trimethylsilyloxy-1,3-cyclohexadiene **2c** in the presence of various catalysts are presented in Equation (4).

Diene **2c** reacts with imine **1a** in the presence of the various chiral ligands **4b**,**5c**,**h**, and **i** in combination with $CuClO_4$ giving *not* the corresponding aza-Diels–Alder product, but the Mannich-type addition adducts **3c**. Very good isolated yields (80–85%) of *anti*-**3c** are obtained with a very high *ee* of up to 96% using Tol-BINAP-(*R*)-**4b**-$CuClO_4$ as the catalyst, and 94% *ee* applying the phosphino–oxazoline catalysts (*S*)-

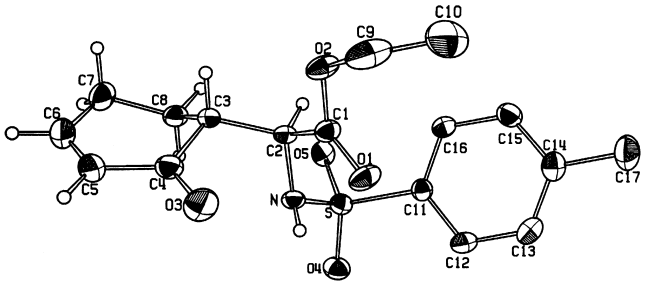


1a **2c**



anti-**3c** *syn*-**3c** (4)

Ligand	Yield/*ee*	Yield/*ee*
4b-THF	82/96	8/94
4b-CH_2Cl_2	80/75	8/15
5c-THF	85/94	-
5h-THF	85/94	-
5i-CH_2Cl_2	81/94	-

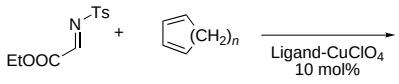


anti-**3c**

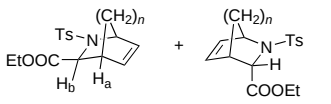
5c-,(3a*R*,9b*S*)-**5h**- and (3a*R*,9b*S*)-**5i**-$CuClO_4$ in THF as the solvent. The X-ray analysis revealed that the major diastereomer of **3c** is the *anti*-diastereomer with the absolute configuration of (1′*R*,2*S*). Initially we expected diene **2c** to undergo an aza-Diels–Alder reaction. However, under the present reaction conditions, the Mannich-type adducts *anti*-**3c** and *syn*-**3c** are formed exclusively. This result and others indicate that in a reaction which can proceed via either a Diels–Alder or a Mannich-type addition reaction, both substrates, chiral Lewis acids and reaction conditions can play an important role. Further discussion can be found in the Section dealing with the mechanistic aspects. Notably the Tol-BINAP-(*R*)-**4b**-copper(I) complex has been found to be a very effective enantioselective catalyst for ene[8] and alkylation addition reactions[9c,f,g, 10b] of **1a** with alkenes and enol silanes, respectively.

The *N*-tosyl α-imino ester **1a** reacts also with the unactivated cyclic dienes cyclopentadiene **2d** and 1,3-cyclohexadiene **2e** in the presence of the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ and phosphino–oxazoline ligand (*S*)-**5c**-$CuClO_4$ catalysts. The results are given in Equation (5).

It appears from Equation (5) that the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ complex can catalyze a highly diastereo- and enantioselective aza-Diels–Alder reaction of both cyclopentadiene **2d** and 1,3-cyclohexadiene **2e** leading to the formation of the *exo* adducts as the major diastereomer in all cases. In THF as the solvent *exo*-**3d** is isolated in 88% yield with 60% *ee*, while in CH_2Cl_2 similar high yield (85%) is obtained and the *ee* is improved to 83%. Noteworthy full conversion was observed within 15 min for the reaction of **1a** with **2d** in CH_2Cl_2 at $-20\,^{\circ}C$ using Tol-BINAP-(*R*)-**4b**-$CuClO_4$ as the catalyst.[14] By recrystallisation from *i*PrOH/hexane *exo*-**3d** can be obtained as an enantiomerically pure compound. The structure of the major diastereomer *exo*-**3d**



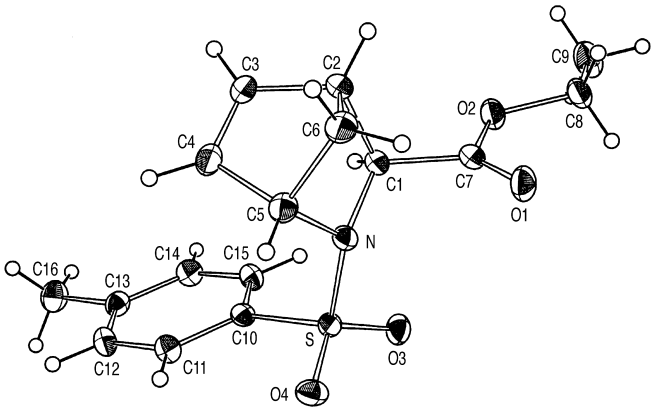
1a **2d**, *n* = 1 **2e**, *n* = 2



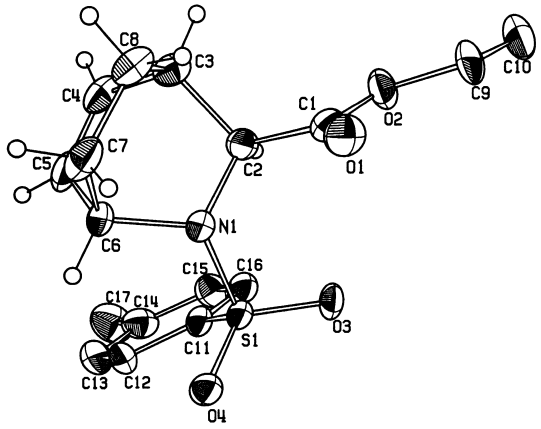
exo-**3d**, *n* = 1 *exo*-**3e**, *n* = 2 *endo*-**3d**, *n* = 1 *endo*-**3e**, *n* = 2 (5)

Ligand	Yield/*ee*	Yield/*ee*
4b-THF	88/60 (*n* = 1)	9/99 (*n* = 1)
4b-CH_2Cl_2	85/83 (*n* = 1)	7/83 (*n* = 1)
5c-THF	81/4 (*n* = 1)	9/- (*n* = 1)
4b-THF	31/91 (*n* = 2)	6/40 (*n* = 2)
4b-CH_2Cl_2	52/95 (*n* = 2)	7/37 (*n* = 2)
5c-THF	26/13 (*n* = 2)	10/10 (*n* = 2)

was assigned on the basis of ^{1}H-NMR spectroscopy as the coupling constant between H_a and H_b is found to be 1.1 Hz, and further confirmed by X-ray analysis. The X-ray structure of *exo*-**3d** shows its absolute configuration to be (1*S*,3*S*,4*R*) (Figure 1). The minor diastereomer *endo*-**3d** is formed in 9% isolated yield and with up to 99% *ee*. The phosphino–oxa-



exo-**3d**



exo-**3e**

Figure 1. X-ray structure of *exo*-**3d** and *exo*-**3e** showing the diastereochemistry and absolute configuration to be (1*S*,3*S*,4*R*) in both cases.

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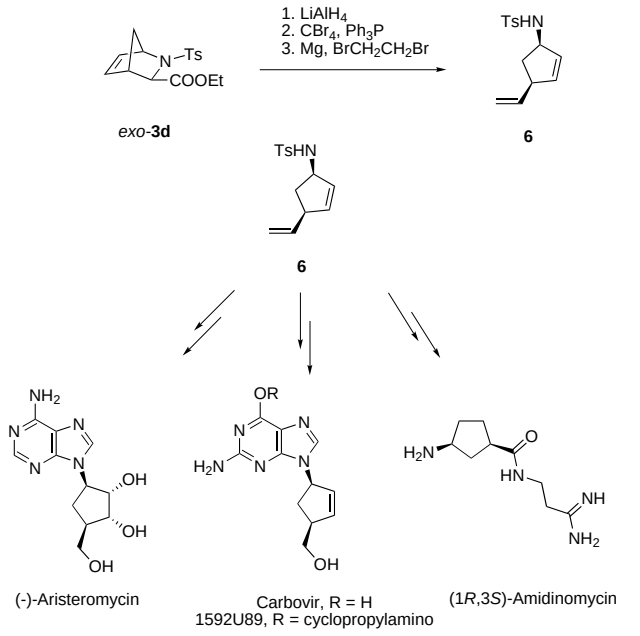
zoline catalyst (*S*)-**5c**-$CuClO_4$ is also a highly diastereoselective catalyst for the reaction since 81% isolated yield of *exo*-**3d** is obtained, however low enantioselectivity is found.

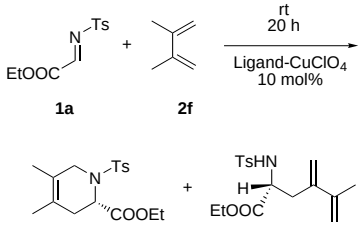
The catalytic enantioselective reaction of 1,3-cyclohexadiene **2e** with the *N*-tosyl α-imino ester **1a** proceeds also in a highly enantioselective fashion, albeit with a lower yield and diastereoselectivity applying the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst. In CH_2Cl_2 as the solvent up to 59% isolated yield of the *exo*- and *endo*-**3e** mixture is obtained with an *exo*-**3d**:*endo*-**3d** ratio of 7:1 and with 95% *ee* for *exo*-**3e**. The reaction of imine **1a** with diene **2e** catalyzed by Tol-BINAP-(*R*)-**4b**-$CuClO_4$ in THF was found to be slower with lower yield and diastereoselectivity compared with the reaction of cyclopentadiene **2d**, however, still high *ee* of 91% was obtained for *exo*-**3e**. With CH_2Cl_2 as a solvent, a higher yield and *ee* of *exo*-**3e** (52% yield, 95% *ee*) could be obtained. The X-ray structure of *exo*-**3e** shown in Figure 1 gives the absolute configuration as (1*S*,3*S*,4*R*). It is notable that the phosphino–oxazoline ligands give low asymmetric induction in the reaction of *N*-tosyl α-imino ester **1a** with the simple cyclic dienes **1d** and **e**.

The catalytic enantioselective aza-Diels–Alder reaction of the cyclic conjugated dienes **2d**,**e** with the *N*-tosyl α-imino ester **1a** outlined in Equation (5) can be used for the preparation of attractive molecules. The aza-Diels–Alder adducts *exo*-**3d** and *exo*-**3e** can be transformed into the chiral cyclopentenyl- and cyclohexenylamines in a few steps, via for example a procedure developed recently by Andersson et al.[15] as shown for the transformation of *exo*-**3d** to the chiral cyclopentenylamine **6** in Scheme 1. The highly functionalised amine **6** is the essential structural unit of the pharmaceutically active compounds (−)-aristeromycin, carbovir, 1592U89, and (1*R*,3*S*)-amidinomycin (Scheme 1). Thus, the catalytic enantioselective reaction of **1a** with cyclopentadiene **2d** provides a practical and efficient route for the enantioselective synthesis[16] of the carbocyclic nucleosides.



Scheme 1. Synthesis of highly functionalised amine **6** as an essential structural unit of the pharmaceutically active compounds.

The catalytic enantioselective aza-Diels–Alder reaction of the *N*-tosyl α-imino ester **1a** has also been investigated for non-activated acyclic dienes, such as 2,3-dimethyl-1,3-butadiene **2f**. The results for this reaction in the presence of Tol-BINAP-(*R*)-**4b**-$CuClO_4$ and the phosphino–oxazoline (*S*)-**5c**- and (3a*R*,9b*S*)-**5i**-$CuClO_4$ catalysts are outlined in Equation (6).



(6)

Ligand	Yield/*ee*	Yield/*ee*
4b-THF	64/65	7/86
4b-CH_2Cl_2	63/60	8/90
5c-THF	65/rac	not detected
5i-THF	71/rac	not detected

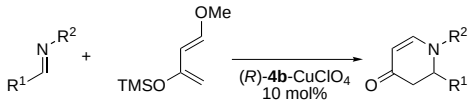
The reaction of the *N*-tosyl α-imino ester **1a** with diene **2f** in the presence of the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst leads to both the aza-Diels–Alder product **3f** and the ene product **3g** [Eq. (6)]. In THF as the solvent **3f** is formed in 64% yield with 65% *ee*, while **3g** is isolated in 7% yield with 86% *ee*. The phosphino–oxazoline ligands **5c** and **5i** in combination with $CuClO_4$ give only the aza-Diels–Alder adduct **3f**, but unfortunately as a racemate.

We have also tested the use of furan **2g** as the diene for the reaction of the *N*-tosyl α-imino ester **1a**. This reaction proceeds as a nucleophilic addition of the furan α-carbon atom to the imine carbon atom, instead of the expected aza-Diels–Alder reaction.[17]

The catalytic enantioselective aza-Diels–Alder reactions presented so far have been for the *N*-tosyl α-imino ester **1a** exclusively. Next, we aimed to broaden the synthetic scope of the reaction and to obtain mechanistic information of the present catalytic asymmetric reaction. Thus, we synthesized a series of imines **1b**–**f** with different substituents on the nitrogen- and carbon atom of the imine C=N double bond and evaluated their potential application as dienophiles for the aza-Diels–Alder reaction with Danishefsky's diene **2a** using Tol-BINAP-(*R*)-**4b**-$CuClO_4$ as the catalyst. The imines were constructed in a way to elucidate the mechanistic aspect of different possible binding modes. The results for the reactions are presented in Table 2.

The results in Table 2 show the synthetic scope of this catalytic enantioselective aza-Diels–Alder reaction as a variety of different substituted imines **1a**–**f** can be used as dienophiles reacting with Danishefsky's diene **2a** in the presence of Tol-BINAP-(*R*)-**4b**-$CuClO_4$ (10 mol%) as the catalyst giving moderate to high *ee*. Entry 1 shows the result for the aza-Diels–Alder reaction of the *N*-tosyl α-imino ester **1a** with diene **2a**, the aza-Diels–Alder adduct **3a** is formed in 80% yield with 79% *ee* at −78 °C in THF, and 89% yield with

Table 2. The results for the aza-Diels–Alder reaction of the different imines **1a–e** with Danishefsky's diene **2a** in the presence of Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ (10 mol%) as the catalyst.



1a: R^1 = COOEt, R^2 = Ts
1b: $R^1 = R^2$ = COOEt
1c: R^1 = COOEt, R^2 = *o*-MeO-Ph
1d: R^1 = COOEt, R^2 = Ph
1e: R^1 = COOEt, R^2 = *p*-MeO-Ph
1f: R^1 = Ph, R^2 = Ts

2a

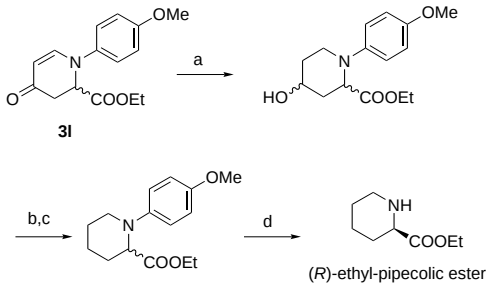
3a: R^1 = COOEt, R^2 = Ts
3i: $R^1 = R^2$ = COOEt
3j: R^1 = COOEt, R^2 = *o*-MeO-Ph
3k: R^1 = COOEt, R^2 = Ph
3l: R^1 = COOEt, R^2 = *p*-MeO-Ph
3m: R^1 = Ph, R^2 = Ts

Entry	Imine	Temp. [°C]	Product	Yield/*ee* [%] (THF)	Yield/*ee* [%] (CH_2Cl_2)
1	**1a**	−78	**3a**	80/79	89/26
2	**1b**	−78	**3i**	10[a]/79	23[b]/77
3	**1c**	rt	**3j**	25/60	23/58
4	**1d**	rt	**3k**	61/86	78/91
5	**1e**	rt	**3l**	93/15	89/72
6	**1e**	−78–rt	**3l**	82/16	75/78
7	**1f**	rt	**3m**	65[c]/46	65/48

[a] 56% Mannich-type addition product was isolated. [b] 50% Mannich-type addition product was isolated. [c] 16% Mannich-type addition product was isolated.

26% *ee* in CH_2Cl_2. Changing the *N*-substituent from a tosyl substituent to an ethyl ester group leads to substrate **1b** which reacts with **2a** at −78 °C in the presence of the same catalyst affording an enantioselective reaction with the same level of chiral induction as 79% *ee* and 77% *ee* of **3i** is obtained in THF and CH_2Cl_2, respectively. However, the yield for the aza-Diels–Alder adduct was only 23% (entry 2). It should be mentioned that for imine **1b** the reaction leads also to the formation of the Mannich-type addition product which was isolated in 56% and 50% yield in THF and CH_2Cl_2 as the solvent, respectively. However, the ring-open Mannich-type product was formed with low *ee* (≤37%). The *N*-*o*-methoxyphenyl glyoxylate imine **1c** reacts with **2a** at room temperature giving the aza-Diels–Alder product **3j** with reasonable *ee* (58–60%), however, the isolated yields were low (entry 3). The results from the first three entries in Table 2 indicate that the substituent at the nitrogen atom might be involved in the coordination of the imine to the catalyst as all three imines have functional groups (-SO_2-, -C(O)OEt, OMe), which can participate in the coordination to the catalyst. The same level of *ee* obtained by reaction of the imines **1a** and **1b** suggests that the *N*-ethyl ester and *N*-tosyl group attached to the imine nitrogen atom might have similar coordination mode to the catalyst, while the lower *ee* obtained for imine **1c** could indicate that the methoxy substituent attached to the phenyl ring coordinates less efficiently to the Lewis acid. However, the best result both in terms of yield and *ee* among these three imines is still obtained from the use of the *N*-tosyl α-imino ester **1a** as the dienophile. Changing the *N*-tosyl substituent in imine **1a** to a non-coordinating phenyl substituent leads to the *N*-phenyl glyoxylate imino ester **1d**, which reacts smoothly with **2a** at room temperature in the presence of 10 mol% Tol-BINAP-(*R*)-**4b**-$CuClO_4$ as the catalyst to give the aza-Diels–Alder adduct **3k** in 78% and 61% isolated yield in CH_2Cl_2 and THF, respectively. To our surprise 91% *ee* and 86% *ee* of **3k** were obtained in these solvents (entry 4). The imine **1e**, with an *N*-*p*-methoxyphenyl substituent, reacts also with **2a** in an enantioselective manner giving the corresponding aza-Diels–Alder adduct **3l** in high yields and with up to 78% *ee* in CH_2Cl_2 (entry 5,6). A change of the substituent on the imine carbon atom from an ethyl ester functionality to a non-coordinating phenyl group leads to imine **1f**. The reaction of **1f** with diene **2a** under the present catalytic conditions gives the aza-Diels–Alder adduct **3m** in reasonable yield and 48% *ee* in CH_2Cl_2 (entry 6). It appears from the results in Table 2 that a variety of imines with different possible coordination modes to the catalyst can be used for the present enantioselective aza-Diels–Alder reaction (vide infra).

The absolute configuration of the aza-Diels–Alder adduct **3a** has been assigned by X-ray analysis,[7c] while the aza-Diels–Alder adduct **3l** obtained by reaction of imine **1e** with Danishefsky's diene **2a** in the presence of Tol-BINAP-(*R*)-**4b**-$CuClO_4$ as the catalyst was determined to be (*R*) by correlating it to the commercially available optically active pipecolic acid by the transformations outlined in Scheme 2.



Scheme 2. a) H_2 (1 atm), PtO_2, EtOAc, room temperature. b) $CS(Im)_2$, toluene, reflux. c) Bu_3SnH, AIBN, toluene, 90 °C. d) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, H_2O, 0 °C. Yields: a)–c): 74%; d): 68%.

The transformation presented in Scheme 2 was carried out through hydrogenation of the alkene and carbonyl bond simultaneously with PtO_2/H_2 followed by deoxygenation of the hydroxyl group. Oxidative cleavage[19] of the *N*-*p*-methoxyphenyl substituent affords the (*R*)-ethyl pipecolic ester without loss of enantiopurity. This transformation shows the potential of the present reaction for the preparation of optically active α-amino acids of the piperidine type.

We have also tried to use a commercially available solid-supported chiral BINAP-ligand (*R*)-**4c**. The complex (*R*)-**4c**-$CuClO_4$ can catalyze the reaction of *N*-tosyl α-imino ester **1a** with Danishefsky's diene **2a** [Eq. (7)]. However, both the yield and *ee* of **3a** are significant lower compared with the other catalysts tested. Furthermore, a minor amount of the Mannich-addition adduct **3m** is also formed.

Mechanistic Aspects

***exo* Preference**: In the reaction of the *N*-tosyl α-imino ester **1a** with the dienes **2b**, **2d**, and **2e** where both *exo* and *endo* products can be formed, the *exo* products *trans*-**3b**, *exo*-**3d**, and *exo*-**3e** were obtained as the major products in all cases with a 10:1 *exo*:*endo* ratio for the dienes **2b** and **2d**, and a 7:1

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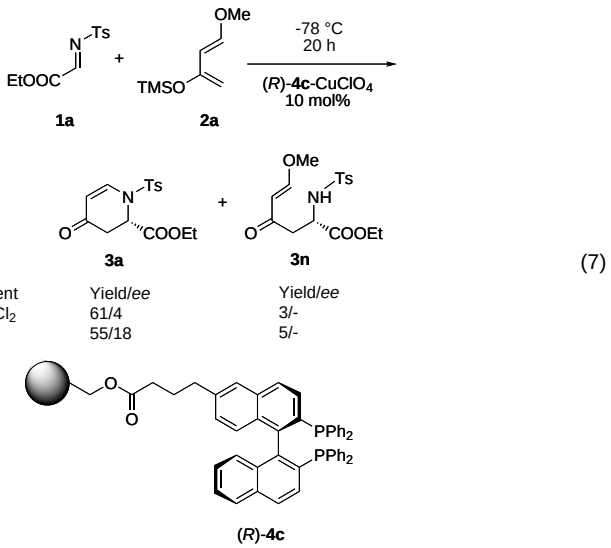
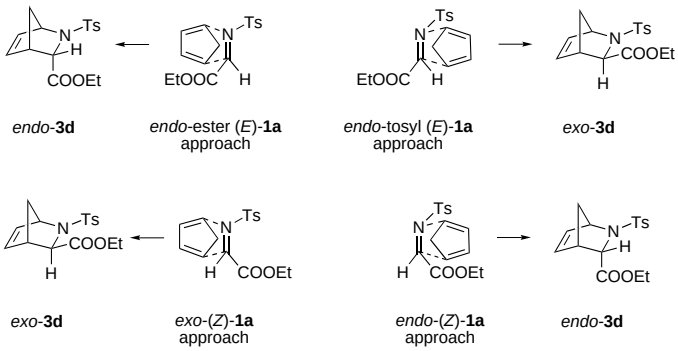


(7)

ratio for diene **2e**. This is in agreement with the common observation for aza-Diels–Alder reactions using imines with π-substituents (e. g. sulfonyl, carbonyl and aryl) on the nitrogen atom as the dienophiles.[20, 3a,d,h,i, 4c] To explain the *exo* preference one can not simply apply the "*cis*-addition principle" and "*endo*-rule" governing the *exo*/*endo* selectivity in a carbon-Diels–Alder reaction to an aza-Diels–Alder reaction of imino dienophiles unambiguously. However, with some reasonable assumptions, the preference for the formation of the *exo* product might be understandable.

The origin of the *endo* rule is believed to be a combination of effects such as steric, electronic, and secondary orbital interactions between the substituents on the diene and the dienophile.[21] For the present catalytic enantioselective reactions, it is expected, and postulated, that the reaction proceeds via the (*E*)-form of the *N*-tosyl α-imino ester **1a** with the *N*-tosyl substituent orienting *endo* relative to the diene. This hypothesis is supported by the following facts: The reaction of the *N*-tosyl α-imino ester **1a** with for example cyclopentadiene **2d** can in principle proceed via the *E*- or *Z* isomer, or both concomitantly (Scheme 3). If the reaction proceeded via the (*E*)-form of **1a**, an *endo* approach of **2d** relative to the imino ester substituent (*endo*-ester (*E*)-**1a** approach), would give the aza-Diels–Alder adduct *endo*-**3d**, while an approach *endo* relative to the imine tosyl substituent (*endo*-tosyl (*E*)-**1a** approach) gives the aza-Diels–Alder adduct *exo*-**3d**. However, if the reaction took place by the (*Z*)-form of **1a**, the *exo* approach relative to both the ester and tosyl substituents (*exo*-(*Z*)-**1a** approach) leads to the formation of *exo*-**3d**, while the *endo* approach relative to the ester and tosyl substituents (*endo*-(*Z*)-**1a** approach) leads to the formation of *endo*-**3d**. The (*Z*)-**1a** approaches would give predominantly the formation of *endo*-**3d** as the major product according to the *endo* rule. The major product *exo*-**3d** formed in the present reactions can thus be due to i) the reaction proceeds via the (*E*)-form of **1a** as proposed above for cyclopentadiene approaching *endo* relative to the tosyl substituent (*endo*-tosyl (*E*)-**1a** approach, Scheme 3) or ii) *endo*-**3d** is in equilibrium with *exo*-**3d** via a retro-aza-Diels–Alder reaction, favoring the thermodynamically more stable *exo*-**3d**. The latter aspect has been documented by the retro-aza-Diels–Alder reaction of cyclopentadiene with iminium dienophiles leading to a novel method for the *N*-methylation of amino acids derivatives.[22] We have tested this hypothesis in relation to the present results. *endo*-**3d** was added to a CH_2Cl_2 solution of the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst at −20 °C and stirred for 15 h. Under these reaction conditions, which are very similar to the conditions for which *exo*-**3d** is formed, no trace of *exo*-**3d** was observed and *endo*-**3d** was recovered, indicating that no retro-aza-Diels–Alder reaction occurs. Therefore the reaction most probably proceeds via the (*E*)-isomer of imine **1a** and the *N*-tosyl substituent adapting an endo orientation relative to the diene in the transition state.



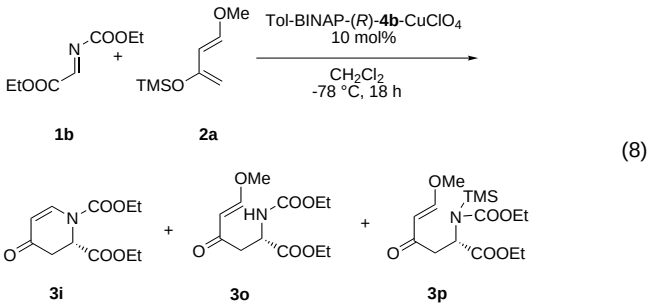
Scheme 3. Possible *exo*-/*endo*-**3d** transition pathways.

Let us continue with the reaction course. The hetero-Diels–Alder reaction of carbonyl compounds, and probably also the aza-Diels–Alder reaction of imino dienophiles can proceed via three possible courses: a concerted cycloaddition-, a step-wise-, and a Mannich-type process.[23, 24] It has been found that the reaction paths are very much depending on both diene, dienophile and reaction conditions.[23] For a specific reaction, the reaction courses can also vary from a Diels–Alder reaction to a Mannich-type addition reaction and solvents, temperature, and Lewis acids can have significant influence on the reaction courses.[24]

For the present catalytic enantioselective reactions, both the aza-Diels–Alder and Mannich-type addition (or ene) products were formed depending on the dienes and imines used. For the reaction of the *N*-tosyl α-imino ester **1a** with activated acyclic dienes such as Danishefsky's diene **2a** and the dimethyl-substituted Danishefsky's diene **2b**, only the aza-Diels–Alder products **3a** and **3b** are isolated in high yields under the standard reaction conditions for the activated dienes (BINAP- or phosphino–oxazoline $CuClO_4$-catalysts (10 mol %) at −78 °C in various solvents such as CH_2Cl_2, THF, Et_2O, *tert*-butyl methyl ether, toluene, and MeCN for 15–20 h followed by a TFA quench (2% TFA in CH_2Cl_2)). The reaction of imine **1a** with cyclopentadiene **2d** gives only the aza-Diels–Alder adduct **3d** in both THF and CH_2Cl_2 solvents. This reaction was also tested in the presence of Tol-BINAP-(*R*)-**4b**-$CuClO_4$ as the catalyst at a range of different temperature: −78, −40, −20, 0 °C, and room

temperature, and in all cases only the aza-Diels–Alder adducts **3d** were formed with *exo*-**3d** as the major product, besides the corresponding *endo* analogue. 1,3-Cyclohexadiene **1e** is much less reactive compared with cyclopentadiene. This reaction has to be performed at room temperature and also in this case only the aza-Diels–Alder adduct **3e** was isolated in both THF and CH_2Cl_2. However, the reaction of **1a** and 2-trimethylsilyloxy-1,3-cyclohexadiene (**2c**) at $-78\,^{\circ}C$ using the standard protocol, gives only the Mannich-type addition product **3c** which was isolated in high yields with a *anti*:*syn* ratio of about 10:1. Performing the reaction at different temperature and changing the solvents from THF, CH_2Cl_2 to nonpolar solvents did not affect the product distribution remarkably and the aza-Diels–Alder product was not detected in any case under the present Lewis acid catalytic conditions. Notably in contrast to the Lewis acid catalyzed reaction, under thermal conditions, the reaction of **1a** with **2c** gives mainly the aza-Diels–Alder adduct favoring the *exo* isomer. Holmes et al. investigated this reaction under a variety of conditions applying different solvents, temperatures, and Lewis acids.[24a,b] The general trend from their investigation was that an increased amount of the aza-Diels–Alder product was obtained with less polar solvent and increased temperature. From the present results, it appears that for the catalytic enantioselective reaction of diene **2c** with the *N*-tosyl α-imino ester **1a**, solvents and reaction temperature have a limited influence on the reaction course, while Lewis acids play a decisive part in determining the reaction paths.

The reaction of imines **1b**,**c** with Danishefsky's diene **2a** gave both the aza-Diels–Alder and Mannich-type addition products. For the reaction of imine **1b** [Eq. (8)] the aza-Diels–Alder adduct **3i** was formed with 79% *ee*, while the isolated yield was low. In contrast to this, the Mannich-type addition product **3o** (the ring-open product) was formed as the major product, however, with low *ee* (37%). A certain amount of the Mannich-type addition product **3p**, with a TMS-group attached to the nitrogen atom was also formed [Eq. (8)]. The transformation of the ring-open products **3o**

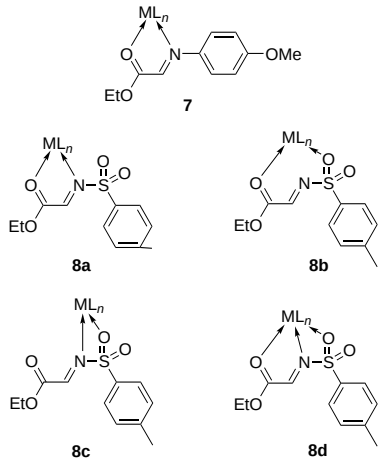


(8)

and **3p** to the aza-Diels–Alder product **3i** by treatment with diluted TFA in CH_2Cl_2 at room temperature was found to be slow and the aza-Diels–Alder product formed in this way was found to have low *ee*. These results could indicate that two different reaction paths are taking place simultaneously; one reaction path gives the aza-Diels–Alder product with a good chiral induction, while the other reaction path promotes the Mannich-type addition product **3o** with low *ee*. Further detailed investigations have to be performed in order to clarify the factors governing the reactions paths.

Coordination of the imines to the Tol-BINAP-(*S*)-4b-$CuClO_4$ and phosphino–oxazoline (*S*)-5d-$CuClO_4$ catalysts: In the following we will discuss the coordination of the imine to the Tol-BINAP-(*R*)-**4b** and phosphino–oxazoline (*S*)-**5d**-$CuClO_4$ catalysts in an attempt to account for the absolute configuration of the products formed. The coordination of the imines to the catalysts will be restricted to only include the *N*-tosyl glyoxylate imine **1a** and the *N*-*p*-methoxyphenyl glyoxylate imine **1e** as the absolute configurations of the aza-Diels–Alder adducts **3a** and **3l**, respectively, obtained by reaction Danishefsky's diene **2a** have been assigned. Most notably, the absolute configurations of the aza-Diels–Alder adducts **3a** and **3l** are opposite, *S* and *R*, respectively, at the formed chiral center. Furthermore, these two imines represent two different binding modes (vide infra). In the case of imine **1a**, the *N*-tosyl group can participate in the coordination to the chiral Lewis acid, while for imine **1e**, the *N*-*p*-methoxyphenyl substituent does not have this option.

For *N*-*p*-methoxyphenyl glyoxylate imine **1e**, the imine nitrogen atom and the glyoxylate carbonyl oxygen atom can coordinate to the Lewis acid leading to a bidentate coordination **7**, while for the *N*-tosyl glyoxylate imine **1a** several coordination modes are possible as outlined schematically in **8a–d**. The coordination modes are three bidentate, **8a–c**, and one tridentate, **8d**.



A bidentate coordination of the *N*-*p*-methoxyphenyl glyoxylate imine **1e** to the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst can lead to both a tetrahedral and a square planar structure at the copper(I) center. We have investigated[25] both types of intermediates and found that the tetrahedral intermediate[26] can account for the observed absolute configuration of the aza-Diels–Alder product **3k** obtained by reaction with Danishefsky's diene **2a**. This intermediate, **9**, is presented in Figure 2.

The intermediate **9** in Figure 2 is shown in two different perspectives, a side and an end view. The side view shows how the *N*-*p*-methoxyphenyl glyoxylate imine (**1e**) coordinates to

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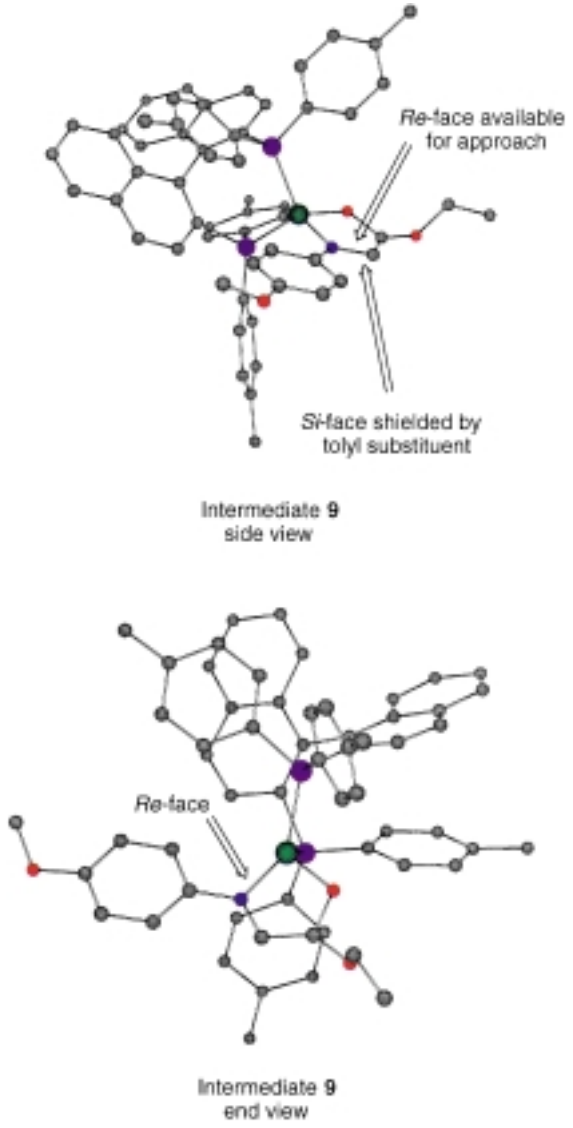

Figure 2. The proposed intermediate **9** in the Tol-BINAP-(*R*)-**4b**-Cu[I] catalyzed reaction. The intermediate is a bidentate coordination of the *N*-*p*-methoxyphenyl glyoxylate imine (**1e**) to the copper(I) center leading to a tetrahedral geometry at the metal center. The side view shows the two faces of the imine, the *Re*-face from the top and the *Si*-face from the bottom. The end view shows the face shielding of the *Si*-face. Hydrogen atoms are omitted for clarity.

the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst. In order to account for the absolute configuration of the aza-Diels – Alder adduct diene **2a** has to approach the *Re*-face of the imine in **9**. The *Si*-face shielding is not immediately obvious from the side view of intermediate **9**, however, the end view in Figure 2 nicely shows how the *Si*-face is shielded by one of the tolyl groups of the chiral BINAP ligand leaving the *Re*-face open for reaction. For the reaction of imine **1e** with diene **2a** catalyzed by the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ a tetrahedral intermediate can account for the stereochemical outcome of the reaction.

The *N*-tosyl α-imino ester **1a** has several possible coordination modes **8a** – **d** to the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst and the phosphino – oxazoline (*S*)-**5d**-$CuClO_4$ catalyst. Let us start with the reaction catalyzed by the former catalyst. Lectka et al. have observed changes in IR stretching frequencies of the glyoxylate carbonyl bond and imine bond by the presence of a Lewis acid.[9f] However, no results were presented for the sulfonyl bonds.[9f] We have also tried to investigate the changes in IR stretching frequencies for the coordination of imine **1a** to the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst, but no conclusive results were obtained. In the following we will therefore briefly present models for the catalytic intermediates which can account for the chiral induction.

The bidentate coordination of the glyoxylate carbonyl oxygen and imine nitrogen atoms of the *N*-tosyl α-imino ester to the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst (**8a**) gives an intermediate having a geometry similar to the one outlined in **9** in (Figure 2). This intermediate will by reaction with Danishefsky's diene **2a** give the opposite absolute configuration of the aza-Diels – Alder adduct **3a** as obtained experimentally. Studies of models for the bidentate coordination of **1a** by the imine nitrogen atom and one of the sulfonyl oxygen atoms as outlined in **8c** gives an intermediate with no obvious face-shielding. We are thus left with two coordination models, **8b** and **8d**, which both have the glyoxylate carbonyl oxygen atom and the sulfonyl oxygen atom coordinated to the chiral catalyst; furthermore, the model **8d** has also the imine nitrogen atom coordinated to the catalyst. Both models **8b** and **8d** can account for the absolute configuration of the addition products obtained. The proposed intermediate, **10**, obtained by a tridentate coordination of imine **1a** to the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst is outlined in Figure 3.

It appears from the proposed intermediate **10** in Figure 3, where both a side and an end view of **10** are presented, that the tridentate coordination of the *N*-tosyl α-imino ester **1a** to the Tol-BINAP-(*R*)-**4b**-$CuClO_4$ catalyst leads to a change in the face-shielding of the imine compared with the bidentate coordination outlined in Figure 2. With the two phosphorous atoms of the BINAP ligand coordinated *cis*, the remaining three sites at the copper(I) center are used for the coordination of the imine. Such a coordination leads to a shielding of the *Re*-face of the imine **1a** by one of the tolyl substituents of the BINAP ligand, leaving the *Si*-face available for an attack.

The different possible intermediates obtained by coordination of the *N*-tosyl α-imino ester **1a** to the phosphino – oxazoline (*S*)-**5d**-$CuClO_4$ catalyst have been investigated in a similar way and it is proposed that the tridentate coordination of the imine, intermediate **11** shown in Figure 4 can account for the stereochemical outcome of the reaction.

The proposed intermediate **11** in Figure 4, for the phosphino – oxazoline (*S*)-**5d**-$CuClO_4$ catalyzed reaction, shows why this ligand is also attractive for the present reactions. The chiral oxazoline, coordinated to the metal by the nitrogen lone pair, shields the *Re*-face of the imine. The steric reason for this shielding is that the tosyl and *tert*-butyl substituents are located opposite to each other to minimize steric repulsion. Intermediate **11** can also account for why the enantioselectivity of the reaction is indifferent for a change of the phenyl to tolyl substituent on the phosphorus atoms as these aryl substituents are not located in the proximity of the catalytic site (Table 1, entry 5 versus 6). But a change from isopropyl to a *tert*-butyl substituent on the chiral oxazoline causes a better

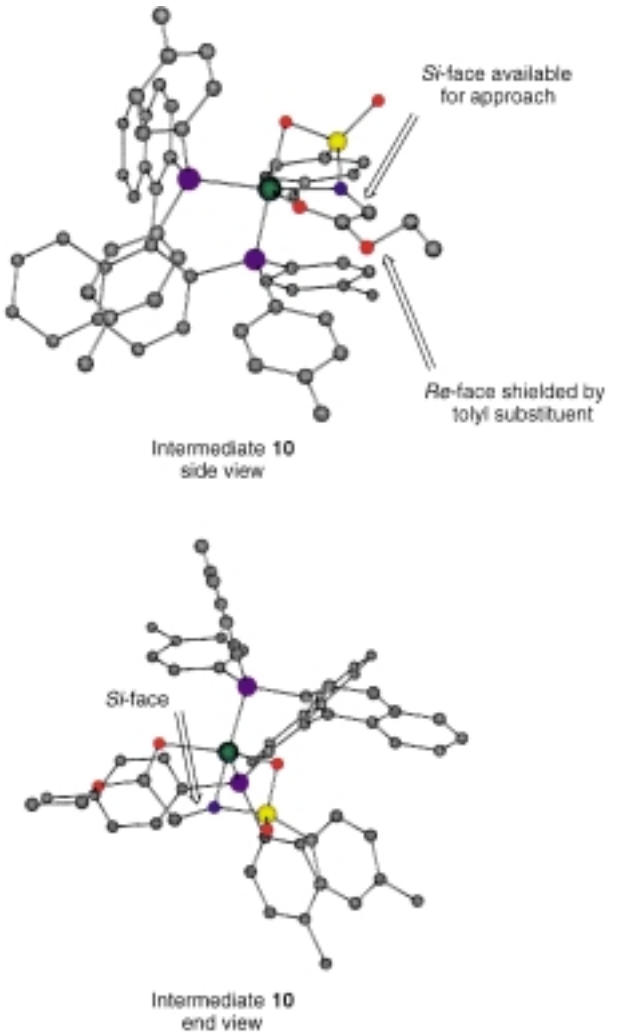

Figure 3. The proposed intermediate **10** in the Tol-BINAP-(*R*)-**4b**-Cu^{I} catalyzed reaction of *N*-tosyl α-imino ester **1a**. The intermediate is a trientate coordination of **1a** to copper(I). The side view shows the two faces of the imine, the *Si*-face from the top and the *Re*-face from the bottom. The end view shows the face shielding of the *Re*-face. Hydrogen atoms are omitted for clarity.

enantioselective induction (Table 1, entry 4 versus 5) which is apparent from intermediate **11**.

Conclusion

We have presented the development of a catalytic enantioselective aza-Diels–Alder reaction of various imines with activated and non-activated, cyclic, as well as, acyclic dienes catalyzed by chiral BINAP- and phosphino–oxazoline-copper(I) complexes. For the reaction of the *N*-tosyl α-imino ester with Danishefsky's diene, it was found that the phosphino–oxazoline ligands copper(I) catalysts gave the best results with up to 87% *ee* of the aza-Diels–Alder product and isolated yields up to 96%. The BINAP-copper(I) complexes are good catalysts for all classes of the dienes studied; for the dimethyl substituted Danishefsky diene up to 96% *ee* was obtained for the major diastereomer isolated in 71% yield, while an activated cyclic diene gave the Mannich-addition product, an

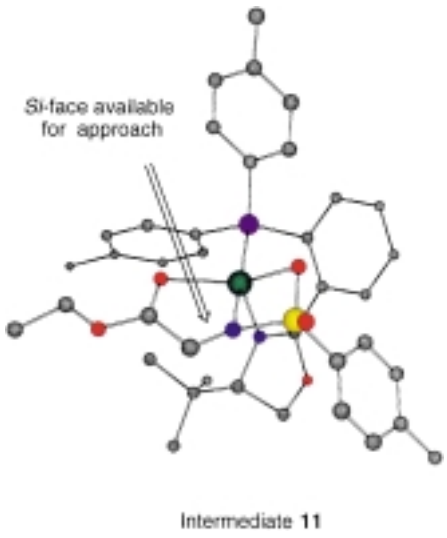

Figure 4. The proposed intermediate **11** in the phosphino–oxazoline (*S*)-**5d**-$CuClO_4$ catalyzed reaction of the *N*-tosyl α-imino ester **1a**. The intermediate is a tridentate coordination of **1a** to the copper(I) center. The view shows the face shielding of the *Re*-face of the imine by the oxazoline moiety. Hydrogen atoms are omitted for clarity.

γ-oxo α-amino acid derivative, in very high yield and enantioselectivity. The unactivated cyclic dienes cyclopentadiene and 1,3-cyclohexadiene react in a highly diastereo- and enantioselective aza-Diels–Alder reaction giving the *exo* diastereomer in up to 95% *ee*. The unactivated acyclic dienes also react with the *N*-tosyl α-imino ester leading to both the aza-Diels–Alder and aza-ene products in a ratio of 9:1 favoring the aza-Diels–Alder product formed in moderate yield and *ee*. The catalytic aza-Diels–Alder reaction is not restricted to only the *N*-tosyl α-imino ester as a series of different imines all reacted with Danishefsky diene giving the aza-Diels–Alder adduct in moderate to high *ee* and yield. Particularly, the reactions of the *N*-phenyl and *N*-*p*-methoxyphenyl substituted glyoxylate imines proceeded well affording the corresponding aza-Diels–Alder products in high yield with up to 91% *ee* at room temperature. It is shown that these reactions provided an effective route to optically active nonproteinogenic α-amino acids of the piperidine type. The *N*-tosyl α-imino ester and *N*-*p*-methoxyphenyl glyoxylate imines give the opposite configuration of the newly formed chiral center of the aza-Diels–Alder adduct using the same enantiomer of the catalyst. Based on the absolute configurations of the products of the catalytic enantioselective reactions it is proposed that the *N*-tosyl α-imino ester coordinates in a tridentate fashion to both the Tol-BINAP-(*R*)-**4b**-copper(I) and phosphino–oxazoline-copper(I) catalyst, while the *N*-*p*-methoxyphenyl glyoxylate imine coordinates in a bidentate fashion leading to a tetrahedral intermediate.

Experimental Section

General methods: All reactions were carried out under anhydrous conditions in flame-dried Schlenk tubes. Solvents were dried according to standard procedures and distilled prior to use. The ^{1}H- and ^{13}C-NMR spectra were recorded at 300 MHz and 75 MHz, respectively, using $CDCl_3$ as the solvent and were reported in ppm downfield from TMS ($\delta = 0$) for

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^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. Enantiomeric excess (*ee*) was determined by HPLC using a Chiralpack AD column or Chiracel OD or OJ columns as stated below and checked with corresponding racemic samples. Optical rotations were measured on a Perkin–Elmer 241 polarimeter using a sodium lamp and reported as follows: $[\alpha]_D^{rt}$ (*c* in g per 100 mL, solvent). Melting points were determined on an electrothermal metling point apparatus and were uncorrected. High resolution mass spectra were obtained on micromass LCT Q-TOF instrument.

Materials: (*R*)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl ((*R*)-BINAP, **4a**), (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl ((*R*)-Tol-BINAP, **4b**) were purchased from Strem and (*R*)-polymer bound BINAP [(*R*)-**4c**] was purchased from Oxford Asymmetry. All the phosphino–oxazoline ligands (**5a–j**) were prepared using literature or modified procedures.[13] *N*-Tosyl α-imino ester **1a** was prepared from ethyl glyoxylate and *p*-toluenesulphonyl isocyanate.[27] *N*-Ethyloxycarbonyl α-imino ester **1b** was formed in situ via an aza-Wittig reaction through *N*-ethoxycarbonylimino triphenylphosphane with ethyl glyoxylate.[28] Imines **1c–e** were prepared by direct condensation from corresponding amines and ethyl glyoxylate in the presence of molecular sieves, and imine **1f** was prepared with $Si(OEt)_4$ as dehydrating reagent as reported by Love et al.[29] The dienes *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) (**2a**), 1,3-cyclohexadiene **2e** and 2,3-dimethyl-1,3-butadiene **2f** were obtained from Aldrich and were all used as received. Cyclopentadiene **2d** was cracked from its dimer and redistilled prior to use, furan **2f** was distilled before use. *trans*-1-Methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene (**2b**) and 2-trimethylsilyloxy-1,3-cyclohexadiene (**2c**) were prepared as described in literature.[30] $CuClO_4 \cdot 4MeCN$ was prepared according to the literature procedure.[31]

General procedure for the catalytic reactions: $CuClO_4 \cdot 4MeCN$ (13 mg, 0.04 mmol) and Tol-BINAP-(*R*)-**4b** (30 mg, 0.044 mmol) were added under N_2 to a flame-dried Schlenk tube. The mixture was dried for 1 h under vacuum and freshly distilled anhydrous solvent (1.5 mL) was added with a syringe under N_2 and the light yellow solution was stirred for 0.5 h. *N*-Tosyl α-imino ester **1a** (104 mg, 0.4 mmol) was added at room temperature and stirred for 3–5 min, then the solution was placed at the required temperature before diene (1.1–2.0 equiv) was added. The reaction mixture was kept stirring at that temperature for stated reaction time. For reactions using trimethylsilyloxy-containing dienes **2a–c**, the reactions were quenched by addition of TFA (0.1 mL) in CH_2Cl_2 (10 mL) at $-78\,^\circ$C and stirred at room temperature for 20 min. Evaporation of the solvent gave the crude product which was purified by flash chromatography (FC) to give the product.

***N*-Tosyl-4-oxo-1,2,3,4-tetrahydro-pyridine-2-carboxylic acid ethyl ester (3a)**: According to the general procedure, the reaction of the *N*-tosyl α-imino ester **1a** with diene **2a** in the presence of 10 mol% catalyst (*S*)-**5c**-$CuClO_4 \cdot 4MeCN$ in THF at $-78\,^\circ$C for 20 h produced aza-Diels–Alder adduct **3a**, after purification by FC (30% EtOAc in pentane), as a light yellow oil (82%). The *ee* was found to be 87% according to HPLC using a Chiralpak AD column (*i*PrOH/hexane 15:85, 0.5 mL min^{-1}). The product can be recrystallized using *i*PrOH/hexane to give colorless crystals and the *ee* of the crystals is $\geq$98.5%. M.p.: 70–71 °C; $[\alpha]_D^{rt} = -96.0$ ($c = 0.50$ in $CHCl_3$); ^{1}H NMR: $\delta = 7.75$ (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$), 7.72 (d, $J = 9.4$ Hz, 1H, =CHN), 7.37 (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$), 5.37 (d, $J = 9.4$ Hz, 1H, HC=), 4.99–4.95 (m, 1H, NC*H*$CO_2CH_2CH_3$), 4.11–3.95 (m, 2H, $CO_2CH_2CH_3$), 2.83–2.71 (m, 2H, C(O)CH_2), 2.45 (s, 3H, ArCH_3), 1.15 (t, $J = 7.1$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 189.14$, 167.86, 145.44, 142.53, 134.89, 130.18, 127.41, 107.71, 62.43, 56.22, 38.11, 21.65, 13.85; HRMS: exact mass calcd for $C_{15}H_{17}SNO_5$ $[M+Na]^+$: 346.0725; found: 346.0741.

***N*-Tosyl-3,5-dimethyl-4-oxo-1,2,3,4-tetrahydro-pyridine-2-carboxylic acid ethyl ester (3b)**: According to the general procedure, the reaction of the *N*-tosyl α-imino ester **1a** with diene **2b** using 10 mol% Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ as the catalyst in THF at $-78\,^\circ$C for 20 h afforded *trans*-**3b** (83%) and *cis*-**3b** (8%) as light yellow oils. The FC condition was 15–20% EtOAc in pentane. The *ee* of the major product *trans*-**3b** was determined as 94% using HPLC with a Chiralpak AD column (*i*PrOH/hexane 15:85, 1.0 mL min^{-1}), and the minor product *cis*-**3b** was found racemic. Suitable crystals of *cis*-**3b** for X-ray structure analysis was obtained from *i*PrOH/hexane and the *cis* relationship of this minor product was confirmed by the X-ray crystallographic analysis.[7c] *trans*-**3b**: $[\alpha]_D^{rt} = -91.9$ ($c = 0.67$ in $CHCl_3$); ^{1}H NMR: $\delta = 7.76$ (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$), 7.53 (br s, 1H, =C*H*N), 7.34 (d, $J = 7.6$ Hz, 2H, $C_6H_2H_2$), 4.60 (m, 1H, NC*H*$CO_2CH_2CH_3$), 3.98–4.10 (m, 2H, $CO_2CH_2CH_3$), 2.88 (q, $J = 7.7$ Hz, 1H, C(O)C*H*CH_3), 2.45 (s, 3H, ArCH_3), 1.71 (br s, 3H, CH=CCH_3), 1.16 (t, $J = 7.1$ Hz, 3H, $CO_2CH_2CH_3$), 0.99 (d, $J = 7.7$ Hz, 3H, C(O)CHCH_3); ^{13}C NMR: $\delta = 193.93$, 168.16, 145.12, 137.46, 135.07, 130.04, 127.47, 113.10, 62.26, 62.22, 42.35, 21.66, 17.06, 13.91, 12.95; HRMS: exact mass calcd for $C_{17}H_{21}SNO_5$ $[M+Na]^+$: 374.1038; found: 374.1026. *cis*-**3b**: m.p.: 109–110 °C; ^{1}H NMR: $\delta = 7.72$ (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$), 7.48 (br s, 1H, =CHN), 7.34 (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$), 4.77 (m, 1H, NC*H*$CO_2CH_2CH_3$), 3.91–3.77 (m, 2H, $CO_2CH_2CH_3$), 2.89–2.80 (m, 1H, C(O)C*H*CH_3), 2.43 (s, 3H, ArCH_3), 1.73 (br s, 3H, =CCH_3), 1.13–1.04 (m, 6H, C(O)CHCH_3, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 192.54$, 167.04, 145.04, 136.73, 134.88, 130.00, 127.32, 114.43, 61.48, 61.23, 40.73, 21.58, 13.76, 12.92, 10.44; HRMS: exact mass calcd for $C_{17}H_{21}SNO_5$ $[M+Na]^+$: 374.1038; found: 374.1041.

***N*-Tosylamino-2-(2′-oxo-cyclohex-3′-enyl)-acetic acid ethyl ester (3c)**: According to the general procedure, the reaction of the *N*-tosyl α-imino ester **1a** with diene **2c** in the presence of 10 mol% catalyst Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ in THF at $-78\,^\circ$C for 20 h produced after purification by FC (EtOAc/pentane 10:90) *anti*-**3c** as a colorless solid (82%) and *syn*-**3c** (8%). The *ee* of the major product *anti*-**3c** is 96% *ee* according to HPLC using a Chiralpak AD column (*i*PrOH/hexane 15:85, 0.5 mL min^{-1}), and the *ee* of the minor product *syn*-**3c** is 94% detected by HPLC using a Chiralcel OD column (*i*PrOH/hexane 2:98, 0.5 mL min^{-1}). *anti*-**3c**: m.p.: 137–138 °C; $[\alpha]_D^{rt} = +5.8$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR: $\delta = 7.73$ (d, $J = 8.3$ Hz, 2H, $C_6H_2H_2$), 7.29 (d, $J = 8.3$ Hz, 2H, $C_6H_2H_2$), 7.03–6.97 (m, 1H, HC=), 5.98 (d, $J = 9.9$ Hz, 1H, =CHC(O)), 5.34 (d, $J = 8.8$ Hz, 1H, NH), 4.03–3.86 (m, 3H, NC*H*$CO_2CH_2CH_3$), 3.29–3.20 (m, 1H, CHC(O)), 3.54–2.14 (m, 4H, CH_2CH_2), 2.41 (s, 3H, ArCH_3), 1.03 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 198.48$, 169.99, 151.35, 143.49, 136.98, 129.53, 129.33, 127.30, 61.89, 56.59, 50.37, 26.19, 25.95, 21.53, 13.71; HRMS: exact mass calcd for $C_{17}H_{21}SNO_5$ $[M+Na]^+$: 374.1038; found: 374.0988. *syn*-**3c**: ^{1}H NMR: $\delta = 7.75$ (d, $J = 8.3$ Hz, 2H, $C_6H_2H_2$), 7.29 (d, $J = 8.3$ Hz, 2H, $C_6H_2H_2$), 7.00–6.96 (m, 1H, =CH), 5.99 (d, $J = 9.9$ Hz, 1H, =CH), 5.60 (d, $J = 9.3$ Hz, 1H, NH), 4.15 (dd, $J = 9.3$, 4.4 Hz, 1H, C*H*NH), 3.92 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 2.84–2.77 (m, 1H, C(O)CH), 2.46–2.06 (m, 4H, CH_2CH_2), 2.41 (s, 3H, ArCH_3), 1.05 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 197.62$, 170.34, 150.72, 143.55, 136.95, 129.53, 129.28, 127.34, 61.76, 55.80, 51.17, 25.84, 25.62, 21.53, 13.77; HRMS: exact mass calcd for $C_{17}H_{21}SNO_5$ $[M+Na]^+$: 374.1038; found: 374.1021.

***N*-Tosyl-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid ethyl ester (3d)**: According to the general procedure, the reaction of the *N*-tosyl α-imino ester **1a** with cyclopentadiene **2d** in the presence of 10 mol% catalyst Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ at $-20\,^\circ$C for 0.5 h in CH_2Cl_2 produced after purification by FC (10%–15% EtOAc in pentane) *exo*-**3d** (85%) and *endo*-**3d** (8%) as colorless solids. The *ee* of the major diastereomer *exo*-**3d** was 83% detected by HPLC using a Chiralcel OD column (*i*PrOH/hexane 5:95, 0.5 mL min^{-1}), and the *ee* of the minor diastereomer *endo*-**3d** was found to be 83% accoding to HPLC using a Chiralpak AD column (*i*PrOH/hexane 10:90, 0.2 mL min^{-1}). *exo*-**3d**: m.p.: 102–103 °C; $[\alpha]_D^{rt} = -195.7$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR: $\delta = 7.74$ (d, $J = 8.3$ Hz, 2H, $C_6H_2H_2$), 7.26 (d, $J = 8.3$ Hz, 2H, $C_6H_2H_2$), 6.25–6.14 (m, 2H, CH=CH), 4.56 (d, $J = 1.1$ Hz, 1H, =CHC*H*NTs), 4.12 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 3.46 (s, 1H, TsNC*H*CO_2Et), 3.29 (br s, 1H, =CHC*H*), 2.40 (s, 3H, ArCH_3), 2.03 (d, $J = 8.8$ Hz, 1H, CH_aH_b), 1.45 (d, $J = 8.8$ Hz, 1H, CH*a*H*b*), 1.24 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 170.73$, 143.52, 136.52, 136.18, 135.90, 129.37, 127.87, 64.42, 61.40, 59.74, 49.62, 46.15, 21.50, 14.04; HRMS: exact mass calcd for $C_{16}H_{19}SNO_4$ $[M+Na]^+$: 344.0933; found: 344.0926. *endo*-**3d**: m.p.: 74—79 °C; ^{1}H NMR: $\delta = 7.82$ (d, $J = 8.3$ Hz, 2H, C_6H_4), 7.31 (d, $J = 8.3$ Hz, 2H, C_6H_4), 6.50–6.47 (m, 1H, =CH), 6.19–6.16 (m, 1H, =CH), 4.60 (d, $J = 1.1$ Hz, 1H, =CHC*H*NTs), 4.28 (d, $J = 3.3$ Hz, 1H, C*H*CO_2Et), 4.14 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 3.51 (br s, 1H, =CHC*H*), 2.43 (s, 3H, ArCH_3), 1.53 (d, $J = 8.8$ Hz, 1H, CH_aH_b), 1.27 (br d, $J = 12.2$ Hz, 1H, CH_aCH_b), 1.24 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 170.0$, 143.62, 137.10, 136.44, 136.01, 129.67, 127.83, 65.58, 61.21, 58.91, 48.39, 47.83, 21.57, 14.17; HRMS: exact mass calcd for $C_{16}H_{19}SNO_4$ $[M+Na]^+$: 344.0933; found: 344.0904.

***N*-Tosyl-2-aza-bicyclo[2. 2.2]oct-5-ene-3-carboxylic acid ethyl ester (3e)**: According to the general procedure, the reaction of the *N*-tosyl α-imino ester **1a** with 1,3-cyclohexadiene **2e** in the presence of 10 mol% catalyst

Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ in CH_2Cl_2 at room temperature for 50 h produced after purification by FC (20% EtOAc in pentane) a mixture of *exo*-**3e** and *endo*-**3e** as a colorless solid (59%) with a ratio of 7:3 according to ^1H NMR. The *ee* for *exo*-**3e** was found to be 95% and for the *endo*-**3e** 37% according to HPLC using a Chiralcel OD column (*i*PrOH/hexane 5:95, 1.0 mL min^{-1}). M. p.: 122—123 °C; $[\alpha]_D^{rt} = -216.5$ ($c = 0.57$ in $CHCl_3$); ^1H NMR δ 7.87 (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$, *endo*-**3e**), 7.75 (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$, *exo*-**3e**), 7.29 (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$, *endo*-**3e**), 7.27 (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$, *exo*-**3e**), 6.53–6.48 (m, 1H, HC=, *endo*-**3e**), 6.23–6.05 (m, 1H, HC=, *endo*-**3e**; 2H, HC=CH, *exo*-**3e**), 4.31–4.10 (m, 3H, =CHC*H*N, $CO_2CH_2CH_3$, *exo*-**3e**; 2H, =CHC*H*N, NC*H*CO_2Et, *endo*-**3e**), 4.12 (q, $J = 7.1$ Hz, 2H, $CO_2CH_2CH_3$, *endo*-**3e**), 3.77 (br s, 1H, NC*H*CO_2Et, *exo*-**3e**), 3.18–3.13 (m, 1H, =CHC*H*CH, *endo*-**3e**), 2.98–2.93 (m, 1H, =CHC*H*CH, *exo*-**3e**), 2.42 (s, 3H, ArCH_3), 2.20–2.12 (m, 1H, CH_aH_b, *exo*-**3e**), 2.05–1.94 (m, 1H, CH_aCH_b, *endo*-**3e**), 1.74–1.06 (m, 3H, CH_aCH_b, $CH'_aCH'_b$, *endo*-**3e** + exo-**3e**), 1.32 (t, $J = 7.1$ Hz, 3H, $CO_2CH_2CH_3$, *exo*-**3e**), 1.25 (t, $J = 7.1$ Hz, 3H, $CO_2CH_2CH_3$, *endo*-**3e**); ^{13}C NMR for *exo*-**3e**: $\delta = 170.73$, 143.52, 135.75, 132.80, 132.75, 129.47, 128.05, 61.36, 59.77, 48.36, 33.78, 25.84, 21.57, 17.96, 14.23; HRMS: exact mass calcd for $C_{17}H_{21}SNO_4$ $[M+Na]^+$: 358.1089; found: 358.1034.

***N*-Tosyl-4,5-dimethyl-1,2-dihydro-pyridine-2-carboxylic acid ethyl ester (3f) and 5-methyl-2-tosylamino-4-methylene-hex-5-enoic acid ethyl ester (3g)**: According to the general procedure, the reaction of the *N*-tosyl α-imino ester **1a** and 2,3-dimethyl-1,3-butadiene **2f** in the presence of 10 mol% catalyst Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ in CH_2Cl_2 at room temperature for 24 h produced after purification by FC (10% EtOAc in pentane) **3f** (64%) and **3g** (7%) as light yellow oils. The *ee* of the major product (aza-Diels–Alder product) **3f** was found to be 65% according to HPLC using a Chiralcel OJ column, and the *ee* of the aza-ene product **3g** was determined as 86% using a Chiralcel OD column. Product **3f**: $[\alpha]_D^{rt} = +17.4$ ($c = 0.40$ in $CHCl_3$); ^1H NMR: $\delta = 7.69$ (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$), 7.27 (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$), 4.80 (dd, $J = 1.6$ Hz, 7.1 Hz, 1H, NC*H*$CO_2CH_2CH_3$), 4.05–3.61 (m, 4H, =CCH_2N, $CO_2CH_2CH_3$), 2,41 (s, 3H, ArCH_3), 2.55–2.32 (m, 2H, =CCH_2CH), 1.60 (s, 3H, =CCH_3), 1.58 (s, 3H, =CCH_3), 1.06 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 170.95$, 143.12, 136.43, 129.33, 127.26, 122.25, 121.87, 60.97, 53.33, 45.94, 33.43, 21.48, 18.66, 15.59, 13.88; HRMS: exact mass calcd for $C_{17}H_{23}SNO_4$ $[M+Na]^+$: 360.1246; found: 360.1252. **3g**: ^1H NMR: $\delta = 7.69$ (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$), 7.27 (d, $J = 8.2$ Hz, 2H, $C_6H_2H_2$), 5.14–4.97 (m, 5H, =CH_2, =CH_2, NH), 4.07 (q, $J = 7.9$ Hz, 1H, C*H*NHTs), 3.90 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 2.70–2.60 (m, 2H, =CCH_2), 2.40 (s, 3H, ArCH_3), 1.82 (s, 3H, =CCH_3), 1.10 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR, δ 171.41, 143.55, 141.81, 141.50, 136.84, 129.53, 127.29, 116.52, 113.54, 61.46, 54.97, 38.15, 21.50, 21.04, 13.92; HRMS: exact mass calcd for $C_{17}H_{23}SNO_4$ $[M+Na]^+$: 360.1246; found: 360.1278.

***N*-Ethoxycarbonyl-4-oxo-1,2,3,4-tetrahydro-pyridine-2-carboxylic acid ethyl ester (3i) and 2-ethoxycarbonylamino-6-methoxy-4-oxo-hex-5-enoic acid ethyl ester (3o)**: According to the general procedure, the reaction of the *N*-ethyloxycarbonyl glyoxylate imine (**1b**) and diene **2a** in the presence of 10 mol% catalyst Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ in THF was stirred at −78 °C for 20 h. The reaction mixture was quenched by TFA (0.1 mL) in CH_2Cl_2 (15 mL) at −78 °C and stirred at room temperature for 0.5 h, followed by evaporation of the solvent. Purification of the crude product by FC (gradual eluent from 20% to 35% EtOAc in pentane) afforded aza-Diels–Alder product **3i** (10%) and Mannich-type product **3o** (56%). The *ee* of **3i** was found to be 79% according to HPLC using a Chiralcel OD column (hexane/*i*PrOH 99:1, 0.3 mL min^{-1}), and the *ee* for **3o** was determined as 37% using a Chiralcel OD column. Compound **3i**: $[\alpha]_D^{rt} = +26.3$ ($c = 1.0$ in $CHCl_3$); ^1H NMR: $\delta = 7.88$ (br d, $J = 7.7$ Hz, 1H, =CHN), 5.33 (br d, $J = 7.7$ Hz, 1H, =CH(CO)), 5.14 (br d, $J = 7.6$ Hz, 1H, NC*H*$CO_2CH_2CH_3$), 4.38–4.30 (q, $J = 7.3$ Hz, 2H, $NCO_2CH_2CH_3$), 4.20 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 3.03–2.85 (m, $J = 15.6$, 7.3 Hz, 2H, $C(O)CH_2$), 1.35 (d, $J = 7.3$ Hz, 3H, $NCO_2CH_2CH_3$), 1.25 (t, $J = 7.2$ Hz, $CHCO_2CH_2CH_3$); ^{13}C NMR: $\delta = 190.60$, 168.90, 152.49, 143.47, 142.81, 107.73, 107.15, 64.00, 62.37, 55.18, 54.79, 37.48, 14.26, 14.00; HRMS: exact mass calcd for $C_{11}H_{15}NO_5$ $[M+Na]^+$: 264.0848; found: 264.0844. **3o**: ^1H NMR: $\delta = 7.61$ (d, $J = 13.0$ Hz, 1H, =C*H*OCH_3), 5.71 (d, $J = 8.2$ Hz, 1H, NH), 5.56 (d, $J = 13.0$ Hz, 1H, =CHC(O)), 4.57–4.52 (m, 1H, C*H*NH$CO_2CH_2CH_3$), 4.23–4.10 (m, 4H, $2 \times CO_2CH_2CH_3$), 3.72 (s, 3H, =CHOCH_3), 3.26 (dd, $J = 17.5$, 4.4 Hz, 1H, $C(O)CH_aH_b$), 3.01 (dd, $J = 17.5$, 3.9 Hz, $C(O)CH_aH_b$), 1.29–1.19 (m, 6H, $2 \times CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 196.48$, 171.31, 163.50, 156.37, 156.37, 105.11, 61.61, 61.14, 57.61, 50.05, 42.47, 14.54, 14.09; HRMS: exact mass calcd for $C_{12}H_{19}NO_6$ $[M+Na]^+$: 296.1110; found: 296.1103.

***N*-o-methoxyphenyl-4-oxo-1,2,3,4-tetrahydro-pyridine-2-carboxlic acid ethyl ester (3j)**: According to the general procedure, the *N*-*o*-methoxyphenyl glyoxylate imine (**1c**) was reacted with diene **2a** in the presence of 10 mol% catalyst Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ in CH_2Cl_2 at rt. After stirred for 40 h, the reaction mixture was directly loaded on the column and seperated by FC (40% EtOAc in pentane) to give the title compund as a light yellow oil (25%). The *ee* of the product **3j** was found to be 55% according to HPLC using a Chiralcel OJ column (hexane/*i*PrOH 94:6, 0.5 mL min^{-1}). $[\alpha]_D^{rt} = +34.6$ ($c = 0.5$ in $CHCl_3$); ^1H NMR: $\delta = 7.30$–7.21 (m, 5H, =CHN, C_6H_4), 5.14 (dd, $J = 1.1$, 7.7 Hz, 1H, =CH(CO)), 4.77–4.74 (m, 1H, NC*H*$CO_2CH_2CH_3$), 4.23 (dq, $J = 1.7$, 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.11 (dd, $J = 7.1$, 17.0, 1H, $C(O)CH_aCH_b$), 2.86 (dd, $J = 2.2$, 17.0, 1H, $C(O)CH_aCH_b$), 1.19 (t, $J = 7.2$ Hz, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 189.33$, 169.98, 153.06, 152.30, 133.31, 128.05, 126.25, 121.12, 111.77, 100.56, 61.65, 60.45, 55.65, 38.01, 13.96; HRMS: exact mass calcd for $C_{15}H_{17}NO_4$ $[M+Na]^+$: 298.1056; found: 298.1058.

***N*-Phenyl-4-oxo-1,2,3,4-tetrahydro-pyridine-2-carboxylic acid ethyl ester (3k)**: According to the general procedure, the reaction between *N*-phenyl glyoxylate imine (**1d**) and diene **2a** in the presence of 10 mol% catalyst Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ in CH_2Cl_2 was performed at rt. After stirred for 20 h, the reaction was then quenched by TFA (0.1 mL) in CH_2Cl_2 (15 mL), purification by FC (60% EtOAc in pentane) gave **3k** (78%) with 91% *ee* according to HPLC using a Chiralpak AD column (hexane/*i*-PrOH 99:1, 0.4 mL min^{-1}). $[\alpha]_D^{rt} = +36.7$ ($c = 0.1$ in $CHCl_3$); ^1H NMR: $\delta = 7.52$ (d, $J = 7.7$ Hz, 1H, =CHN), 7.41–7.08 (m, 5H, Ph), 5.27 (d, $J = 7.7$ Hz, 1H, =CH), 4.77–4.74 (dd, $J = 1.6$, 7.1 Hz, 1H, NC*H*$CO_2CH_2CH_3$), 4.23 (q, $J = 7.2$ Hz, 2H, $CO_2CH_2CH_3$), 3.03 (ddd, $J = 7.1$, 17.0, 2H, $C(O)CH_aH_b$), 1.25 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 189.34$, 169.76, 148.94, 144.56, 129.68, 124.91, 119.05, 102.97, 62.34, 60.52, 38.46, 14.10; HRMS: exact mass calcd for $C_{14}H_{15}NO_3$ $[M+Na]^+$: 268.0950; found: 268.0919.

***N*-p-Methoxyphenyl-4-oxo-1,2,3,4-tetrahydro-pyridine-2-carboxylic acid ethyl ester (3l)**: According to the general procedure, the reaction between *N*-*p*-methoxyphenyl imine **1e** with diene **2a** in the presence of 10 mol% catalyst Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ in CH_2Cl_2 was stirred at room temperature for 20 h. Purification by FC (50% EtOAc in pentane) afforded product **3l** (89%) with 72% *ee* according to HPLC using a Chiralpak AD column (hexane/*i*PrOH 90:10, 1.0 mL min^{-1}). $[\alpha]_D^{rt} = +181.7$ ($c = 0.82$ in $CHCl_3$); ^1H NMR: $\delta = 7.40$ (d, $J = 7.7$ Hz, 1H, =CHN), 7.07 (d, $J = 8.8$ Hz, 2H, $C_6H_2H_2$), 6.89 (d, $J = 8.8$ Hz, 2H, $C_6H_2H_2$), 5.19 (d, $J = 7.7$ Hz, 1H, =CHC(O)), 4.66 (br d, $J = 6.8$ Hz, 1H, NC*H*$CO_2CH_2CH_3$), 4.22 (q, $J = 7.1$ Hz, $CO_2CH_2CH_3$), 3.19 (s, 3H, ArOCH_3), 2.03 (ddd, $J = 6.8$, 16.5 Hz, $C(O)CH_aH_b$), 1.24 (t, $J = 7.1$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR: $\delta = 189.12$, 169.81, 157.35, 150.20, 138.21, 121.90, 114.75, 101.78, 62.23, 61.25, 55.57, 14.07; HRMS: exact mass calcd for $C_{15}H_{17}NO_4$ $[M+Na]^+$: 298.1056; found: 298.1041.

2-Phenyl-1-tosyl-2,3-dihydro-1*H*-pyridin-4-one (3m): According to the general procedure, the reaction between *N*-tosyl benzaldimine (**1f**) and diene **2a** in the presence of 10 mol% catalyst Tol-BINAP-(*R*)-**4b**-$CuClO_4 \cdot 4MeCN$ in CH_2Cl_2 was stirred at room temperature for 60 h. Purification by FC (30% EtOAc in pentane) gave product **3m** (63%) with 48% *ee* according to HPLC using a chiralcel OD column (hexane/*i*PrOH 95:5, 0.8 mL min^{-1}). $[\alpha]_D^{rt} = -54.0$ ($c = 0.50$ in $CHCl_3$); ^1H NMR δ 7.81 (dd, $J = 8.2$ Hz, 1H, =CHN), 7.60 (d, $J = 8.4$ Hz, 2H, $SO_2C_6H_2H_2$), 7.24–7.14 (m, 7H, C_6H_5, $SO_2C_6H_2H_2$), 5.52 (d, $J = 7.2$ Hz, 1H, NC*H*Ph), 5.42 (dd, $J = 8.2$ Hz, 1H, =CHC(O)), 2.84 (dd, $J = 7.2$, 16.5 Hz, 1H, $C(O)CH_aH_b$), 2.65 (dd, $J = 1.6$, 16.5 Hz, 1H, $C(O)CH_aH_b$), 2.41 (s, 3H, ArCH_3); ^{13}C NMR: $\delta = 190.49$, 145.01, 142.48, 136.97, 135.56, 130.05, 128.70, 128.09, 127.04, 126.25, 108.33, 57.61, 41.76, 21.60; HRMS: exact mass calcd for $C_{18}H_{17}SNO_3$ $[M+Na]^+$: 350.0827; found: 350.0838.

Reaction with solid-supported chiral BINAP: According to the general procedure of the catalytic reaction, the catalyst solution was prepared by adding THF (1.5 mL) to a mixture of (*R*)-polymer-bound BINAP **4c** (68 mg, ≥ 0.022 mmol) and $CuClO_4 \cdot 4MeCN$ (6.5 mg, 0.022 mmol) under N_2, and shaken for 0.5 h. The reaction between the *N*-tosyl α-amino ester **1a** and *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**2a**) was kept at −78 °C for 18 h, MeOH/CH_2Cl_2 3:7 (10 mL) was added, and the suspension was centrifugalized for 10 min. The clear upper solution phase was

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transferred to another flask, followed by evaporation of the solvents to give the crude products. The solid phase ((*R*)-**4c**) was dried and collected for reuse. The crude products were purified by FC to give the aza-Diels – Alder product **3a** (36.2 mg, 55 % yield) and Mannich-type product **3n** (3.5 mg, 5 %). The *ee* of **3a** was determined as 18 % according to the HPLC analysis using a Chiralpak AD column.

Transformation of *N*-*p*-methoxyphenyl-4-oxo-1,2,3,4-tetrahydro-pyridine-2-carboxylic acid ethyl ester (3l) into ethyl pipecolic ester. Assignment of absolute configuration of product (3l) (Scheme 2): a) A solution of **3l** (173 mg, 0.67 mmol) in EtOAc (5 mL) was stirred under H_2 (1 atm) for 80 h at room temperature in the presence of 20 % PtO_2 (30.3 mg, 0.13 mmol). The catalyst was removed by filtration and the filtrate was concentrated. The product alcohol was obtained as a diastereomeric mixture of two alcohols in a ratio of 4:1 and used as such. b) Dry toluene (15 mL) and thiocarbonyl diimidazole (358 mg, 2.0 mmol) were added to the crude product obtained in step a), and the solution was stirred for 6 h at 110 °C under N_2. Evaporation of the solvent gave the crude product, purification by FC (60 % EtOAc in pentane) afforded the diastereomeric mixture of products in an overall yield of 74 % from **3l**. Satisfactory spectroscopic data were obtained. c) The products from reaction b) (184 mg, 0.49 mmol) were then dissolved in dry toluene (15 mL), Bu_3SnH (199 μL, 0.74 mmol), and a catalytic amount of AIBN were added. The reaction mixture was heated to 90 °C and stirred under N_2 for 4 h. Purification by FC (30 % EtOAc in pentane) gave *N*-*p*-methoxyphenyl pipecolic ester (121 mg, 99 %) as a white solid. d) An aqueous solution of CAN (232 mg, 0.42 mmol) in H_2O (1.5 mL) was added dropwise over 3 min to a solution of the *N*-*p*-methoxyphenyl pipecolic ester (35 mg, 0.14 mmol) in CH_3CN (3 mL) at 0 °C. The reaction mixture was stirred for another 20 min at 0 °C and then diluted with H_2O (5 mL). The acidic solution was washed with EtOAc (2 × 10 mL), followed by the addition of saturated aqueous $NaHCO_3$ (3 mL). The pH of the solution was adjusted to about 10 by addition of 2 M NaOH, then the solution was extracted with EtOAc (6 × 10 mL). Combined organic layers were washed with 2 M NaOH, dried (Na_2SO_4), and concentrated in vacuo to afford the ethyl pipecolic ester (15 mg, 68 %) as a bright yellow oil. The spectroscopic data were in good agreement with the data obtained from an ethyl pipecolic ester synthesized from (±)-pipecolic acid. The absolute configuration of the product was assigned to be *R* by correlation with commercially available optically active pipecolic acid by chiral GC-MS analysis and checked with racemic sample. The enantiopurity of the (*R*)-ethyl pipecolic ester was found to have the same high level of *ee* as **3l** before the transformations (a – d).

X-ray structure determination of *anti*-3c, *exo*-3d, and *exo*-3e, racemic and chiral form: All formed colorless crystals, and at least a hemisphere of data were collected at 120 K on a SIEMENS SMART diffractometer using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods (SIR97)[32] and refined by least-squares methods including a parameter to decide the absolute configuration[33] using all significant reflections; the results and the structures are given in the text.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-137173 – 137176. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

The data are for *anti*-**3c**: orthorhombic, $P2_12_12_1$, $a = 9.5231(5)$ Å, $b = 9.6565(5)$ Å, $c = 19.148(1)$ Å, 21521 reflexions measured, 5415 unique, 3963 with $I > 3\sigma(I)$ used in refinement of 303 parameters, final $R = 0.033$, $Rw = 0.035$.

exo-**3d**: monoclinic, $P2_1$, $a = 7.5383,(6)$ Å, $b = 12.403(1)$ Å, $c = 8.3480(7)$ Å, $\beta = 93.229(2)°$, 7202 reflexions measured, 4090 unique, 3693 with $I > 3\sigma(I)$ used to refine 276 parameters, $R = 0.028$, $Rw = 0.033$.

The sample of *exo*-**3e** contained two sorts of crystals: the racemic form (needles) crystallizes first, the chiral form (parallelepipeds) not till the minor isomer is used up.

exo-**3e**-rac: orthorhombic, *P*bca, $a = 13.114(2)$ Å, $b = 14.771(2)$ Å, $c = 16.706(3)$ Å, 36415 reflexions measured, 5315 unique, 2360 with $I > 3\sigma(I)$ used to refine 293 parameters, $R = 0.038$, $Rw = 0.039$.

exo-**3e**-chiral: monoclinic, $P2_1$, $a = 11.074(1)$ Å, $b = 11.207(1)$ Å, $c = 13.527(2)$ Å, $\beta = 92.971(3)°$, $Z = 4$, 16439 reflexions measured, 8570 unique, 5529 with $I > 3\sigma(I)$ used to refine 418 parameters; $R = 0.048$, $Rw = 0.060$.

In all these structures the geometry around the nitrogen atom is a very flat pyramid, in between sp^2 and sp^3 hybridization: The sum of the three angles at the nitrogen atom are in the range 347.4° to 350.6°, the distance of the nitrogen atom from the plane through the neighbours is 0.3 – 0.27 Å compared with 0.5 Å if the nitrogen atom had tetrahedral shape.

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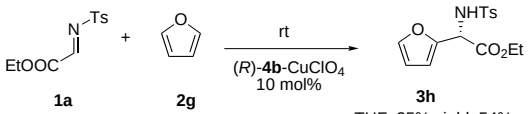

1a **2g** **3h**

THF: 25% yield, 54% *ee* CH_2Cl_2: 30% yield, 45% *ee*

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