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Transition Metal Catalysis |*Hot Paper*|

Ni-Catalyzed Asymmetric Cycloisomerization of Dienes by Using TADDOL Phosphoramidites**

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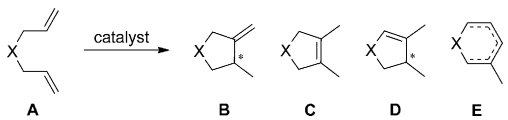
Dedicated to Professor Günther Wilke on the occasion of his 90th birthday

Abstract: A library of α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL)-based phosphoramidites has been synthesized and applied in the Ni-catalyzed cycloisomerization of different dienes. Through the systematic variation of the three structural motifs of the lead structure, that is, the amine moiety, the protecting group, and the aryl substituents, the ligand features could be optimized for the asymmetric cycloisomerization of the model substrate diethyl diallylmalonate. The substrate scope of the new catalytic system was extended to other diallylic substrates, including unsymmetrical dienes. Overall remarkably high activities of up to approximately 13500 h^{-1}, very high selectivities toward five-membered *exo*-methylenecyclopentanes, and enantioselectivities of up to 92% *ee* have been achieved.

Introduction

Transition-metal-catalyzed carbon-carbon bond formations belong to the most intensively studied transformations in organic synthesis.[1] In this regard, the catalytic cycloisomerization of α,ω-dienes provides a powerful and atom-efficient tool for the construction of carbo- and heterocyclic molecules from readily available olefinic substrates.[2] These fundamental constituents of natural products, pharmaceutical compounds, and functional materials could be in principle prepared through a cycloisomerization step. A number of achiral transition-metal catalyst systems based on Pd,[3] Ni,[3j,4] Rh,[3h,5] Ru,[6] Pt,[7] and Ti[8] are known to deliver the individual five-membered ring products **B**–**D** with high levels of regio- and chemoselectivities (Scheme 1).

However, only very few examples for enantioselective catalysts have been reported so far. The main challenge is the design of catalytic systems that combine high chemo-, regio-, and enantioselectivities for the formation of the thermodynamically least favored chiral products of type **B**, thus providing an exocyclic methylene group for subsequent transformations.



Scheme 1. Cycloisomerization of 1,6-dienes (X = CH_2, $C(CO_2R)_2$, O, N–R, etc.).

A first example of asymmetric diene cycloisomerization was reported by Bogdanović in the 1970s. A cationic Ni complex containing a *P**-stereogenic menthyl-based phosphane ligand selectively catalyzed the cycloisomerization of 1,6-heptadiene (X = CH_2) and diallyl ether (X = O), albeit with low optical yields of up to 37% *ee*.[9] Wilke described the asymmetric cycloisomerization of 1,6-heptadiene (X = CH_2) with the *P**-stereogenic azaphospholene ligand *all*-(*R*)-**1**[10] to give the corresponding *exo*-methylenecyclopentane of type **B** in 94% yield and high enantioselectivity (93% *ee* at −30 °C).[11] In 1998, Heumann and Moukhliss[3i] reported the asymmetric cycloisomerization of diethyl diallylmalonate (X = $C(CO_2Et)_2$). By using a catalyst system based on [$Pd(CH_3CN)_2Cl_2$], 2 equivalents of $AgBF_4$, and either (*R,R*)-4,4′-dibenzylbisoxazoline or (−)-sparteine, enantiomeric excesses up to 60% were achieved, albeit with low conversions and poor regioselectivities.[3c,i,12]

More recently, we have investigated the scope of Ni-based catalysts involving the Wilke azaphospholene *all*-(*R*)-**1** and 1,1′-bi-2-naphthol (BINOL)-based phosphoramidites **2**[13] and **3**[14,15] as ligands for inter- and intramolecular olefin dimerization reactions (Figure 1).[16] Systems based on these ligands and the [Ni(allyl)(cod)]$^+$ (cod = 1,5-cyclooctadiene) precursor afforded active catalysts for the asymmetric cycloisomerization of diethyl diallylmalonate (X = $C(CO_2Et)_2$) and *N,N*-diallyltosylamide (X = NTs; Ts = tosyl). By using the Wilke azaphospholene *all*-(*R*)-**1**, the corresponding five-membered ring products of type **B** were formed in moderate-to-high enantioselectivities (up to 80 and 54% *ee* for X = $C(CO_2Et)_2$ and NTs, respectively), thus providing the best currently found values for these substrates.[17] Furthermore, we reported the highly chemo- and regioselective cycloisomerization of unsymmetrically substituted

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[**] *TADDOL = α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol.*

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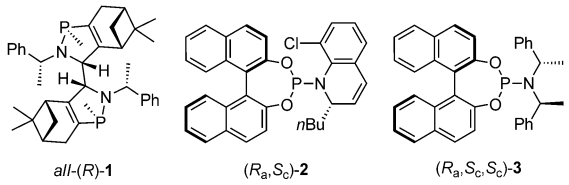


Figure 1. Ligands used in previous studies.

1,6-dienes and bis-allylamines with this catalytic system.[18] The possibility of tandem sequences that involve asymmetric cycloisomerization as an initial C–C bond-forming step was also shown. Although the utilization of monodentate BINOL phosphoramidites **2** and **3** led to moderate enantioselectivities (up to 46% *ee* for $X=C(CO_2Et)_2$) and low catalyst activities (turnover frequency (TOF) $\approx 37\ h^{-1}$),[16a,c,17a] the structural diversity of this ligand type, achievable through a modular and straightforward synthesis, suggested phosphoramidites as attractive lead structures for further development.

Encouraged by the past and recent work of Alexakis,[19] Rovis,[20] Suginome,[21] Fürstner,[22] and others,[23] who showed that α,α,α,α-tetraaryl-1,3-dioxolane-4,5- dimethanol (TADDOL)-based ligands may lead to more active and selective catalysts than their BINOL-based analogues in several transformations, we started a detailed study on the use of TADDOL-derived phosphoramidite ligands[24] in the Ni-catalyzed asymmetric cycloisomerization of 1,6-dienes.

Herein, we describe an iterative variation sequence of the TADDOL phosphoramidite lead structure that comprises the amine moiety, the protecting group, and the aryl substituents (Figure 2). Fine tuning of the electronic, steric, and chiral cooperative effects led eventually to an optimized catalyst for the cycloisomerization of the model substrate diethyl diallylmalonate, thus setting a new benchmark for this transformation.

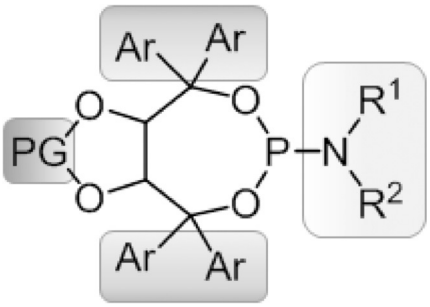
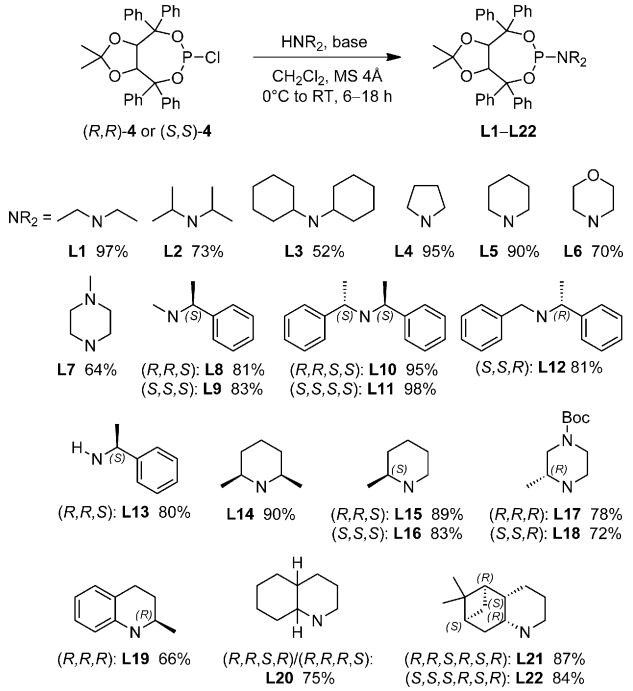


Figure 2. TADDOL-based phosphoramidite ligands and the three structural motifs that allow the systematic optimization of the catalytic performances.

The substrate scope of the new catalytic system was extended to other diallylic substrates, also including the asymmetric cycloisomerization of unsymmetrical dienes for the first time. Overall, remarkable high activities, very high selectivities toward *exo*-methylenecyclopentanes of type **B**, and enantioselectivities of up to 92% *ee* have been achieved.



Scheme 2. Synthesis of monodentate TADDOL phosphoramidites with different amine moieties. Boc = *tert*-butoxycarbonyl, MS = molecular sieves.

Results and Discussion

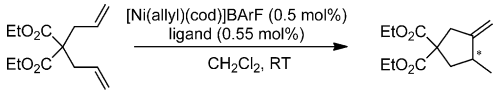
As the first structural motif, variation of the amine moiety was investigated. A broad variety of amines that possess different steric properties was evaluated, including cyclic, acyclic, achiral, and chiral amines (Scheme 2). In the latter case, additional cooperative effects may occur that contribute to enhanced stereocontrol in catalysis.

The first set of ligands **L1**–**L7** was synthesized from an achiral amine with acyclic and cyclic structures by using diethylamine, diisopropylamine, dicyclohexylamine, pyrrolidine, piperidine, morpholine, and *N*-methylpiperazine with (*R*,*R*)-TADDOL as building blocks. For the synthesis of ligands **L1**–**L7**, the respective amine was dissolved in CH_2Cl_2 in the presence of triethylamine. The solution was cooled to 0 °C and a solution of the (*R*,*R*)-TADDOL chlorophosphite **4**[25] was added dropwise within 15 minutes. Afterwards, the reaction mixture was allowed to reach room temperature and stirred for 6–18 hours, thus resulting in full conversion of the chlorophosphite. After filtration through a pad of basic alumina, the ligands were obtained in sufficient purity (91–99% based on ^{31}P and ^{1}H NMR spectroscopic analysis) for catalytic application and in moderate-to-high yields (52–97%; Scheme 2).

The ligands were tested in the asymmetric cycloisomerization with diethyl diallylmalonate (**5a**) as a model substrate with a catalyst loading of 0.5 mol%. The catalytically active species was generated in situ from the respective ligand and [Ni(allyl)(cod)]BArF[17a] (the results are summarized in Table 1).

A high conversion was observed after 6 hours in almost all cases with good-to-high selectivities toward the desired *exo*-

Table 1. Cycloisomerization of diethyl diallylmalonate by using monodentate TADDOL-based ligands.



5a 6a

Ligand	*t* [h]	Cv. [%]	Sel. [%][a]	*ee* [%][b]
L1	6	>99	69	32 (−)
L2	6	78	71	16 (−)
L3	6	74	84	9 (−)
L4	6	92	97	10 (+)
L5	6	>99	92	43 (−)
L6	6	93	93	36 (−)
L7	6	66	91	52 (−)
L8	6	99	91	45 (−)
L9	6	99	90	30 (+)
L10	6	98	94	22 (−)
L11	6	85	81	19 (+)
L12	6	50	40	2 (−)
L13	6	92	96	1 (−)
L14	6	85	58	9 (−)
L15	1	95	89	55 (−)
L16	1	>99	96	57 (+)
L17	1	99	95	56 (−)
L18	1	99	91	35 (+)
L19	1	95	92	53 (−)
L20	1	96	83	66 (−)
L21	6:1	99:97	92:94	67 (−):67 (−)
L22	6	92	73	32 (+)

[a] Selectivity toward **6a**. [b] Determined by means of chiral HPLC analysis.

methylenecyclopentane (**6a**). Low enantioselectivities toward the (−) enantiomer were achieved with **L1–L3**, in which increasing steric demand of the amine part resulted in a decrease of activity and enantioselectivity. In the case of the five-membered pyrrolidine-based ligand **L4**, the opposite product enantiomer was obtained preferentially with a low level of enantioselectivity (i.e., 10% *ee*). Most promising was the result achieved with **L5**, which incorporated piperidine, thus leading to full conversion, 92% selectivity, and 43% *ee* (+ enantiomer). Thus, two other ligands with a six-membered-ring amine moiety were applied in catalysis. Morpholine-based **L6** showed a lower activity and enantioselectivity relative to **L5**, whereas the new *N*-methylpiperazine-based ligand **L7** achieved 66% conversion and higher enantioselectivity (52% *ee*).

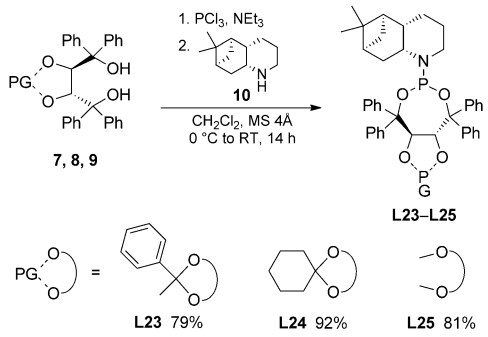
Next, a series of ligands based on chiral amines were synthesized and evaluated in catalysis. By using the same procedure as above, phosphoramidites **L8** and **L9** were prepared in good yields from (*S*)-*N*-methyl-1-phenylethylamine and (*R,R*)- or (*S,S*)-TADDOL, respectively. For the synthesis of the ligands **L10** and **L11**, (*S,S*)-bis(1-phenylethyl)amine was dissolved in THF, treated with *n*BuLi, and then added to a solution of (*R,R*)- or (*S,S*)-TADDOL chlorophosphite **4**, respectively, in THF at −60 °C. Again, the resulting phosphoramidites were purified by filtration over basic alumina and obtained in preparatively useful purity and excellent yields (i.e., 95–98%).

Both **L8** and **L9** led to active and selective nickel catalysts, whereby (*R,R,S*)-**L8** resulted in higher enantioselectivity (45% *ee*) than the diastereomeric (*S,S,S*)-**L9** (30% *ee*). Ligands **L8** and **L9** promoted the preferential formation of opposite enantiomers, thus indicating that the chirality of the diol backbone is the dominating control factor, whereas moderate cooperative effects of the different chiral elements were observed. The same behavior was also observed with **L10** and **L11** bearing a bulky C_2-symmetric chiral amine moiety, which gave quite poor enantioselectivities of 22 and 19% *ee* for the + and − enantiomers, respectively.

The outcome obtained so far with **L1**–**L11** indicates that further optimization of the ligand structure should concentrate on amines with a cyclic structure that contain small substituents and a C_1 symmetry. The catalytic results achieved with ligands **L12**–**L16** fully corroborated this assumption. Ligand **L12**, based on (*R*)-*N*-benzyl-1-phenylethylamine, led to low conversion, poor selectivity, and an almost racemic mixture, thus confirming that an increase in steric bulk relative to **L9** is unfavorable for the reaction under investigation. Also, **L13**, derived from the primary amine (*S*)-1-phenylethylamine, resulted in a racemic mixture of **6a**. The use of **L14**, based on *cis*-2,6-dimethylpiperidine, a ligand sterically more demanding than **L5**, gave poor (enantio)selectivity. In contrast, both diastereomers of the related ligands **L15** and **L16**, prepared from C_1-symmetric (*S*)-2-methylpiperidine and (*R,R*)- or (*S,S*)-TADDOL, resulted in the highest enantioselectivities hitherto with 55 and 57% *ee* for the − and + enantiomers, respectively. Remarkably, full conversion was obtained with both ligands within one hour, which corresponds to a lower limit of the TOF of 200 h^{-1}.

Finally, the best ligands **L15** and **L16**, combining a cyclic piperidine and a C_1-symmetric amine fragment with additional chiral information, provided the basis for further manipulation of the ligand structure. To this aim, C_1-symmetric piperidine derivatives, such as (*R*)-*N*-Boc-3-methylpiperazine, (*R*)-2-methyl-1,2,3,4-tetrahydroquinoline, (*rac*)-*trans*-decahydroquinoline, and pinene-piperidine derivative **10**[26] were selected and the corresponding new ligands **L17–L22** were synthesized (Scheme 2) and applied in the cycloisomerization of **5a**.[27] In this set of experiments, good results were obtained with almost all the ligands based on a six-membered nitrogen heterocycle. The diastereomeric ligands **L17** and **L18** derived from (*R*)-*N*-Boc-3-methylpiperazine gave results similar to the outcome achieved with **L15** and **L16**. By using ligand **L19**, synthesized from (*R*)-2-methyl-1,2,3,4-tetahydroquinoline and (*R,R*)-TADDOL, an enantiomeric excess of 53% was achieved. A significantly higher enantioselectivity of 66% was obtained with **L20** based on *trans*-decahydroquinoline,[27] albeit with a moderate isomer selectivity toward **6a** of 83%. The best ligand of the series was the pinene-piperidine/(*R,R*)-TADDOL-based ligand **L21** with a conversion of 97% within one hour, selectivity of 94% toward the desired *exo*-methylenecyclopentane (**6a**), and an enantioselectivity of 67% *ee*. The diastereomeric ligand **L22**, based on (*S,S*)-TADDOL, led to considerably lower (enantio)selectivity.

Thus, the pinene-piperidine-based TADDOL-phosphoramidite **L21**, which led to the best results so far, was selected as the most suitable amine for optimization of the TADDOL fragment of the ligand. Both the variation of the acetonide protecting



Scheme 3. Synthesis of TADDOL phosphoramidites with different diol protecting groups.

group and the phenyl substituents were subsequently addressed.

First, TADDOL derivatives **7**, **8**,[28] and **9**[22a] with different protecting groups for the peripheric diol moiety were used for the synthesis of the novel ligands **L23–L25**, respectively, with pinene-piperidine **10** as the amine part (Scheme 3). For the methylphenyl-protected ligand **L23**, two diastereomers ($\delta_P = 138.3$ and 138.6 ppm (60 and 40%, respectively)) were obtained and used without further separation in catalysis.[29]

In general, the diol protecting group had almost no effect on activity, selectivity, or enantioselectivity (Table 2, entries 1–4). The same enantiomeric excess of 67% (− enantiomer) was

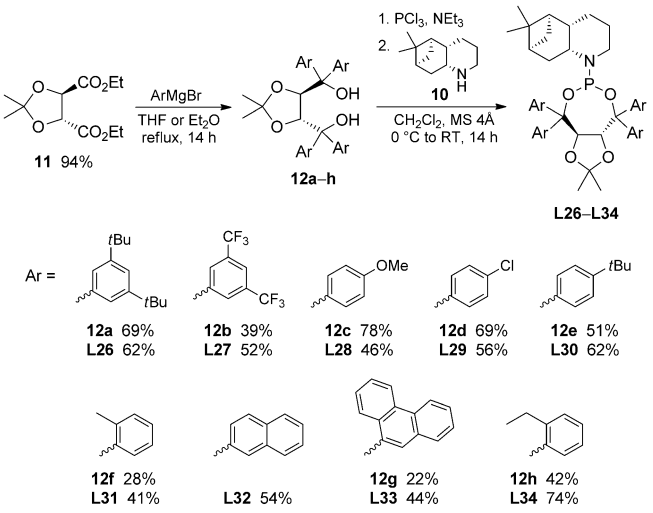
Table 2. Cycloisomerization of diethyl diallylmalonate by using TADDOL phosphoramidites **L21**–**L34**.[a]

Entry	Ligand	Ar	Cv. [%]	Sel. [%][b]	*ee* [%][c]
1	**L21**	Ph	97	94	67 (−)
2	**L23**	Ph	91	94	67 (−)
3	**L24**	Ph	96	91	67 (−)
4	**L25**	Ph	97	94	62 (−)
5	**L26**	3,5-(tBu)$_2$-Ph	62	15	36 (−)
6	**L27**	3,5-(CF_3)$_2$-Ph	75	38	23 (−)
7	**L28**	4-OMe-Ph	63	46	7 (−)
8	**L29**	4-Cl-Ph	89	79	34 (−)
9	**L30**	4-tBu-Ph	92	85	64 (−)
10	**L31**	2-Me-Ph	93	96	73 (−)
11	**L32**	2-naphthyl	90	91	71 (−)
12	**L33**	9-phenanthryl	41	48	76 (−)
13	**L34**	2-Et-Ph	98[d]	96	80 (−)
14[e]	**L34**	2-Et-Ph	92	95	88 (−)

[a] Reaction conditions: 0.5 mol% [Ni(allyl)(cod)]BArF, 0.55 mol% ligand, 1 h, CH_2Cl_2, RT. [b] Regioselectivity toward **6a**. [c] Determined by chiral HPLC. [d] Yield of the isolated product mixture = 93%. [e] 0.1 mol% [Ni(allyl)(cod)]BArF, 0.11 mol% ligand, 16 h, toluene, −20 °C.

achieved with ligands **L23** and **L24** as with the acetonide-protected ligand **L21**. Only the more flexible methyl-protected phosphoramidite **L25** gave a slightly lower *ee* value of 62%; the activity and selectivity remained unaffected.

Next, the influence of the aryl substituents on the TADDOL backbone was investigated in more detail. For this purpose, TADDOL derivatives **12a–12h** bearing various aryl substituents



Scheme 4. Synthesis of TADDOL derivatives and ligands thereof with different aryl substituents on the TADDOL backbone.

were synthesized. The synthesis of **12a–12h** was realized by a Grignard reaction of acetonide-protected (*R,R*)-diethyl tartrate **11** and commercially available arylmagnesium halides or aryl bromides and magnesium. After purification by column chromatography, the TADDOL derivatives were obtained in 22–78% yield and used for the synthesis of the corresponding new ligands **L26–L34** obtained in 41–74% yield (Scheme 4).

The catalytic results demonstrate the remarkable impact of the substitution pattern of the aryl substituents on activity, selectivity, and enantioselectivity (Table 2, entries 5–13). Here, ligands **L26** and **L27**, bearing *tert*-butyl or trifluoromethyl groups in the 3,5-position led to a drop in activity, isomer selectivity, and enantioselectivity. In particular, the cyclization products of type **C** and **D** were obtained preferentially in the presence of **L26**, and the desired *exo*-methylenecyclopentane (**6a**) was only formed with 36% *ee*.

Moreover, the introduction of substituents at the *para* position (i.e., **L28**–**L30**) did not result in an improvement with respect to the parent ligand **L21**. A strong electron-donating methoxy group slowed down the reaction considerably and led to an *ee* value of only 7%. In direct comparison, an electron-withdrawing chloro substituent did not significantly affect the catalyst activity, yet a poor *ee* value of 34% was achieved. Ligand **L30**, with a 4-tBu-Ph substituent, gave similar results to **L21**, albeit with a slightly decreased isomer selectivity.

Finally, **L31**, bearing 2-Me-Ph substituents in the TADDOL backbone, led to a significant improvement. Here, 93% conversion, 96% isomer selectivity, and 73% *ee* were achieved. Consequently, an increased steric demand without significantly changing the electronic properties of the aryl substituent seems to be beneficial for the reaction. This assumption was confirmed by the results with **L32** and **L33**, featuring sterically demanding 2-naphthyl or 9-phenanthryl substituents. Although **L32** gave an enantioselectivity comparable to **L21** (71 vs. 67% *ee*, respectively), the use of **L33** achieved an even higher enantioselectivity of 76% *ee*, albeit at the expense of catalyst activity and selectivity. The best result was obtained

when **L34**, bearing a 2-Et-Ph substituent, was used. The Ni catalyst based on this ligand gave a conversion of 98%, a selectivity of 96% toward the desired *exo*-methylenecyclopentane (**6a**), and an enantiomeric excess of 80% (−; Table 2, entry 13). After optimization of the reaction conditions (see Table S1 in the Supporting Information for full details), this result could be further improved to 88% *ee*, even at 0.1 mol% catalyst loading by lowering the reaction temperature to −20 °C and using toluene instead of CH_2Cl_2 as the reaction medium (Table 2, entry 14). These results represent the highest *ee* values in the asymmetric cycloisomerization of diethyl diallylmalonate reported up to now and illustrate the great potential and the high variability of TADDOL-based phosphoramidites.

A conversion–time profile was compiled to sample the reaction at defined time intervals to investigate the activity of the catalyst system in more detail (Figure 3). A conversion of 45% was found after just two minutes. After five minutes, 68% of the initial substrate had been converted, thus corresponding to a $TOF_{2\,min}$ of approximately 13500 h^{-1} and exceeding the previously investigated BINOL phosphoramidites and the *all*-(*R*)-**1** Wilke ligand by at least one order of magnitude. Nearly quantitative conversion (97%) was reached within one hour. The selectivity was 90% at the beginning and further increased along the reaction,[30] whereas the enantioselectivity was constant throughout the reaction. Within 60 minutes, 97% conversion, 96% selectivity, and 83% *ee* were obtained.

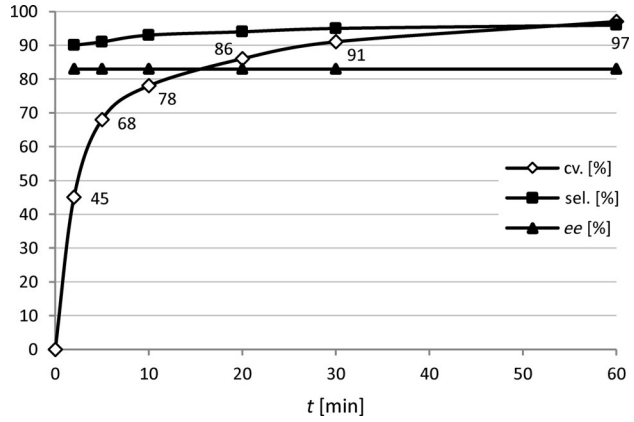
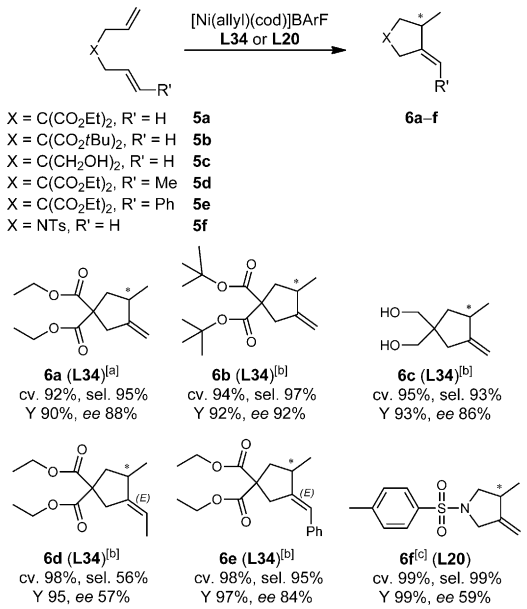


Figure 3. Conversion–time profile of the cycloisomerization of diethyl diallylmalonate by using [Ni(allyl)(cod)]BArF and **L34** (CH_2Cl_2, RT, 0.1 mol% catalyst).

Next the substrate scope of the best catalysts was evaluated in the asymmetric cycloisomerization of various 1,6-diene substrates (Scheme 5). The catalyst system was conveniently prepared in situ from [Ni(allyl)(cod)]BArF and **L34** or **L20** (see Table S2 in the Supporting Information for details of the full screening).

The cycloisomerization of the sterically demanding di-*tert*-butyl diallylmalonate (**5b**) proceeded with 94% conversion, 97% selectivity toward the desired *exo*-methylenecyclopentane (**6b**), and 92% *ee* by using **L34**. In the cycloisomerization of 4,4-hydroxymethyl-1,6-heptadiene (**5c**), *exo*-methylenecyclopentane (**6c**) was obtained with 93% selectivity and 86% *ee* at 95% conversion by using **L34**.



Scheme 5. Ni-catalyzed cycloisomerization of symmetrical and unsymmetrical 1,6-dienes **5a**–**5e** and diallyltosylamide (**5f**). Reaction conditions: [a] cat. 0.11 mol%, toluene, 16 h, −20 °C; [b] cat. 0.5 mol%, CH_2Cl_2, RT, 3 h; [c] cat. 1.0 mol%, CH_2Cl_2, RT, 14 h. cv. = conversion, sel. = selectivity, Y = yield (refers to the isolated product mixture).

The cycloisomerization of unsymmetrically substituted 1,6-dienes imposes additional challenges on the control of selectivity because the addition of the catalytically active nickel hydride can occur either at the terminal or internal double bond. The addition to the terminal double bond leads to cyclic products with a trisubstituted double bond, which can have an *E* or *Z* configuration. In contrast, the addition to the higher substituted internal double bond yields products with an exocyclic methylene group.[18,31]

The (*E*)-diethyl allylcrotylmalonate (**5d**) underwent cycloisomerization in a less selective manner relative to symmetrical 1,6-diene substrates. The major product *exo*-ethylidencyclopentane (**5d**) with an internal *E*-configured trisubstituted double bond was formed with 56% isomer selectivity and 57% *ee* by using **L34**. When (*E*)-phenyl-substituted malonate substrate **5e** was used, high selectivities were observed again, thus leading to the chiral (*E*)-*exo*-benzylidencyclopentane (**6e**). In this case, **L34** led to 95% isomer selectivity with 84% *ee*. Consequently, the regio- and enantio-differentiating abilities of the catalyst benefit from the increased steric demand of the phenyl group in **5e** relative to the methyl substituent in **5d**.

Finally, the cycloisomerization of *N,N*-diallyltosylamide (X = NTs; **5f**) was investigated, thus representing a feasible route to five-membered chiral *N*-heterocycles. Up to now, only low-to-moderate enantioselectivities have been achieved for this class of substrate, from which the best result was obtained by using the Wilke azaphospholene *all*-(*R*)-**1** and [Ni(allyl)(cod)][Al(pftb)$_4$] (i.e., 99% selectivity and 54% *ee*; pftb = perfluoro-*tert*-butoxide).[17b]

For the cycloisomerization of **5 f,** various TADDOL phosphoramidites were applied, which led to good results in the case of the malonate substrates (see Table S3 in the Supporting Information for details of the full screening). The best result was obtained by using **L20** and [Ni(allyl)(cod)]BArF to give full conversion, 99% selectivity toward the desired *exo*-methylene *N*-heterocyclic product **6 f**, and 59% *ee*.

Conclusion

A library of 34 monodentate TADDOL-based phosphoramidites have been synthesized (including 25 new ligands) and evaluated in the cycloisomerization of the benchmark substrate diethyl diallylmalonate. By using a sequential optimization approach, first the amine part of the ligand was systematically varied and the novel pinene-piperidine species was identified as the best suited *N*-moiety. The subsequent introduction of different protecting groups on the TADDOL backbone had little effect on catalysis, whereas a major improvement could be achieved through variation of the aryl substituents. In particular, the ligand bearing *ortho*-ethylphenyl groups resulted in the best outcome of the series by giving an enantiomeric excess of up to 88% and a selectivity of 95% toward the desired chiral *exo*-methylenecyclopentane under the optimized reaction conditions. This catalyst showed very high activity with an initial TOF value of approximately 13500 h^{-1}. Finally, the substrate scope was evaluated and enantiomeric excesses of up to 92% were achieved. Even for challenging unsymmetrical 1,6-dienes, an *ee* value of up to 84% was obtained.

In conclusion, a new ligand lead structure for the Ni-catalyzed enantioselective cycloisomerization of 1,6-dienes has been established. The described TADDOL phosphoramidites offer unprecedented activity, higher selectivity, and enantioselectivity in the Ni-catalyzed asymmetric cycloisomerization relative to previously described ligand classes. Thus, these readily available ligands render the cycloisomerization a synthetically useful methodology for the preparation of chiral five-membered carbon or heterocyclic rings with exocyclic methylene groups.

Experimental Section

General procedure for a typical cycloisomerization reaction

A solution of the ligand (10.5 μmol) in CH_2Cl_2 (3 mL) was added to a solution of [Ni(allyl)(cod)][BArF] (10.0 μmol) in CH_2Cl_2 (1 mL) at room temperature and under inert-gas conditions. The desired amount of substrate was added after 15 min by syringe to the yellow catalyst solution. The reaction mixture was stirred for the desired reaction time and then quenched by the addition of aqueous ammonia (3 mL), thus leading to a colorless solution. The organic phase was diluted with CH_2Cl_2 (5 mL), washed with water (2×3 mL), dried over sodium sulfate, and analyzed by NMR spectroscopic, GC, and/or HPLC analysis. Further details and modifications of the conditions are given in Tables 1 and 2 and Scheme 5. For determination of the *ee* value by chiral HPLC, the chlorinated solvent was removed and replaced by *n*-heptane/2-propanol.

For determination of the *ee* value by ^{13}C NMR spectroscopy, the chlorinated solvent was replaced by diethyl ether and the cycloisomerization products were reduced to the corresponding diols by $LiAlH_4$ (6 equiv). After extraction with diethyl ether and drying over sodium sulfate, a sample of the diol was dissolved in $CDCl_3$ and treated with anhydrous pyridine and (−)-menthoxyacetyl chloride. The resulting solution was washed with water, dried over sodium sulfate, filtered through flourisil, and analyzed by means of quantitative dept45 ^{13}C NMR (150 MHz) spectroscopy with D1 = 10 s and a spectral width of 30 ppm.

Full details of the experimental procedures for the synthesis of the TADDOL derivatives, TADDOL-phosphoramidites, and 1,6-dienes are available in the Supporting Information.

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Keywords: asymmetric catalysis · cycloisomerization · nickel · phosphoramidites · TADDOL

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