

# Asymmetric Chelated Claisen Rearrangements in the Presence of Chiral Ligands—Scope and Limitations

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*Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday*

**Abstract:** Claisen rearrangements of glycine crotyl ester enolates in the presence of chelating metal salts and chiral ligands provide  $\gamma,\delta$ -unsaturated amino acids in a highly stereoselective fashion. Best results are obtained with electron withdrawing protecting groups, isopropylates of aluminum and magne-

sium, and the cinchona alkaloids as chiral ligands. While the use of quinine gives rise to the (2*R*)-configured amino

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acids, quinidine provides the opposite enantiomer. The different enantiomers can also be obtained by using only one of the chiral ligands by simply changing the reaction conditions. A mechanistic rationale for the stereochemical outcome of the reaction is given, which is supported by several experiments.

## Introduction

Sigmatropic rearrangements have received much attention for organic synthesis during the last decades, especially because they belong to the most powerful tools for stereoselective C–C-bond formations.<sup>[1]</sup> Even though Claisen reported the first rearrangement of this type in 1912<sup>[2]</sup> it took quite a while until the Claisen rearrangement became the most synthetically useful [3,3]-sigmatropic rearrangement. The popularity of this stereoselective process resulted in further improvements and the development of variations, such as the Carrol,<sup>[3]</sup> Eschenmoser,<sup>[4]</sup> Johnson,<sup>[5]</sup> Ireland,<sup>[6]</sup> Reformatsky,<sup>[7]</sup> ketene-Claisen rearrangement,<sup>[8]</sup> as well as carbanion accelerated versions.<sup>[9]</sup> During the last years we developed a version especially suitable for the synthesis of amino acids, proceeding via chelated amino acid ester enolates.<sup>[10]</sup> The chelate Claisen rearrangement is an alternative to the oxazole rearrangement developed by Steglich et al. previously.<sup>[11]</sup>

Based on the concerted reaction mechanism and the high preference for a chairlike transition state, Claisen rearrangements are extremely suitable for chirality transfer.<sup>[1]</sup> Therefore it is not surprising that diastereoselective versions have been developed for nearly all types of Claisen rearrange-

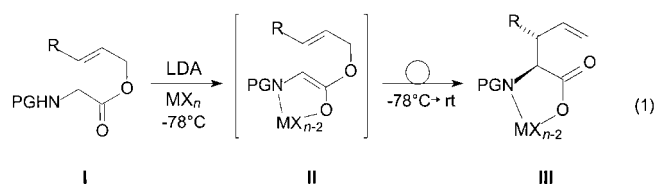
ments.<sup>[12, 13]</sup> In the chelate Claisen rearrangement chiral allylic alcohols can be used to control the stereochemical outcome of the reaction.<sup>[14]</sup> On the other hand it is also possible to integrate a glycine unit into a peptide and to introduce a side chain by a chelate Claisen rearrangement onto the peptide, while the configuration of the new formed stereogenic center is controlled by the peptide chain.<sup>[15]</sup> Even more interesting, in comparison to these auxiliary or substrate controlled reactions, are rearrangements in the presence of chiral modified Lewis acids. The first example of a Lewis acid catalyzed asymmetric Claisen rearrangement was described by Yamamoto et al. in 1990,<sup>[16]</sup> while shortly after that Corey et al. reported on the first ester enolate Claisen rearrangement<sup>[17]</sup> using chiral boron enolates.<sup>[18]</sup> The same chiral boron reagent was used recently by Taguchi et al. for the Claisen rearrangement of fluorinated allyl vinyl ether.<sup>[19]</sup> We found that chelated amino acid ester enolates can also be subjected to a rearrangement in the presence of chiral ligands, such as the cinchona alkaloids, giving rise to  $\gamma,\delta$ -unsaturated amino acids with excellent diastereoselectivity and high enantiomeric excess.<sup>[20]</sup> All these protocols need at least one equivalent of the chiral inductor, probably because the rearrangement product is more Lewis basic than the starting material and therefore forms a stronger complex with the chiral Lewis acid. From a synthetic point of view it would be very welcome to find a catalytic process, requiring only catalytic amounts of chiral ligands. But therefore, it is necessary to find ligands showing a significant ligand acceleration in order to get good chirality transfer, what is not a trivial issue. The first success with this respect was reported by Overman et al. on a palladium(II)-catalyzed rearrangement of

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achiral allyl imidates, in the presence of chiral ligands.<sup>[21]</sup> This is an interesting approach for the stereoselective construction of new C–N bonds. On a comparable catalytic C–C-bond formation was not reported so far.

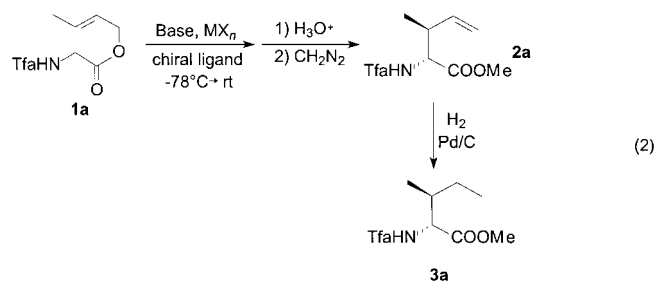
Herein we report on our investigations of chelate Claisen rearrangements of amino acid esters in the presence of chiral ligands. Allylic esters of *N*-protected amino acids **I** (PG: protecting group) undergo a clean Claisen rearrangement when treated with strong bases such as LDA or LHMDS in the presence of metal salts (MX<sub>n</sub>).<sup>[10]</sup> Probably a chelate complex **II** is formed in the first stage which undergoes Claisen rearrangement during warm up to room temperature [Eq. (1)]. In general, the rearrangement starts in the range of



–30 to –20 °C. As a result of a chairlike transition state, the *syn*-configured product **III** is formed preferentially. If a chelate complex such as **II** really exists, one might expect to find an influence of a chiral ligand, coordinating to the metal, on the stereochemical outcome of the rearrangement.

## Results and Discussion

We found, that the chelate Claisen rearrangement is compatible with most common *N*-protecting groups, except base-labile groups such as Fmoc. The rearrangement is widely flexible with respect of the metal salts used, and it tolerates a wide range of substitution pattern in the allyl moiety and the amino acid as well.<sup>[10]</sup> As reference compound for the optimization of the reaction parameters we chose trifluoroacetyl (Tfa)-protected glycine crotyl ester **1a** as starting material. Stereoisomers of 3,4-dehydro isoleucine are obtained by a Claisen rearrangement, and are subsequently compared with natural samples of isoleucine **3a** after esterification and hydrogenation [Eq. (2)].<sup>[22]</sup> The Tfa-pro-



tecting group was used to have an easy determination of the relative and absolute configuration of the rearrangement product by GC using a chiral column (Chirasil-Val).<sup>[23]</sup>

We found that LHMDS in general is superior to LDA regarding the yield. If the chelated Tfa-protected ester is

stirred at 0 °C or room temperature for some time, LDA can cause cleavage of the Tfa-protecting group, a side reaction which is not observed with the less nucleophilic LHMDS.

During an intensive ligand and metal screening we investigated several popular combinations such as Ti<sup>4+</sup>/Taddol,<sup>[24]</sup> Sn<sup>2+</sup>/diamines,<sup>[25]</sup> and Zn<sup>2+</sup>/amino alcohols.<sup>[26]</sup> Unfortunately none of them gave a significant chiral induction (<5% *ee*), although the yield was good in most cases. This is not surprising, because ZnCl<sub>2</sub> is the metal salt of choice for most Claisen rearrangements, with respect to yield and diastereoselectivity as well. But obviously the amino alcohols investigated did not form complexes suitable for chirality transfer. During our metal tuning we made an interesting observation: Al(OiPr)<sub>3</sub>, a metal salt, which always failed in all reactions of chelated enolates investigated so far, gave the best results concerning yield and selectivity. Amino alcohols (Figure 1) were the chiral ligands of choice and the results obtained are collected in Table 1.

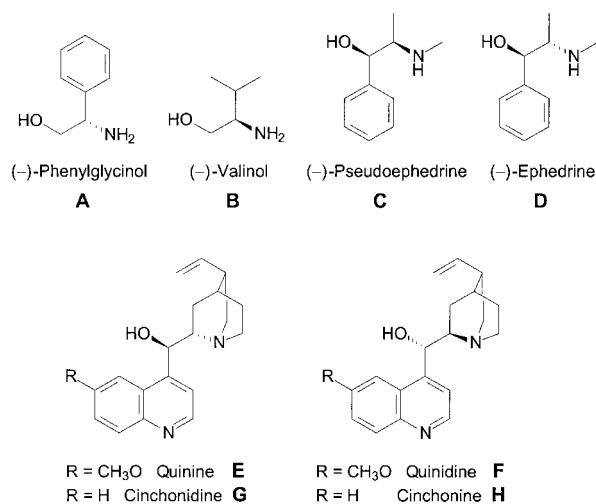


Figure 1. Chiral ligands used in asymmetric Claisen rearrangements.

Table 1. Influence of chiral ligands on chelate Claisen rearrangements of ester **1a** using Al(OiPr)<sub>3</sub> as a chelating metal salt.<sup>[a]</sup>

Ligand	Equiv	Product	Yield [%]	<i>ds</i> [%]	<i>ee</i> [%]	Configuration
1 –	–	<i>rac</i> - <b>2a</b>	96	85	0	–
2 <b>A</b>	1.2	<i>rac</i> - <b>2a</b>	68	85	1	–
3 <b>B</b>	1.5	<i>ent</i> - <b>2a</b>	73	87	4	(2 <i>S</i> ,3 <i>R</i> )
4 <b>C</b>	1.2	<b>2a</b>	30	94	14	(2 <i>R</i> ,3 <i>S</i> )
5 <b>D</b>	1.2	<b>2a</b>	70	96	27	(2 <i>R</i> ,3 <i>S</i> )
6 <i>ent</i> - <b>D</b>	1.2	<i>ent</i> - <b>2a</b>	72	96	27	(2 <i>S</i> ,3 <i>R</i> )
7 <i>ent</i> - <b>D</b>	0.6	<i>ent</i> - <b>2a</b>	75	95	24	(2 <i>S</i> ,3 <i>R</i> )
8 <i>ent</i> - <b>D</b>	0.2	<i>ent</i> - <b>2a</b>	69	91	10	(2 <i>S</i> ,3 <i>R</i> )
9 <b>E</b>	0.6	<b>2a</b>	57	90	38	(2 <i>R</i> ,3 <i>S</i> )
10 <b>E</b>	1.0	<b>2a</b>	98	94	67	(2 <i>R</i> ,3 <i>S</i> )
11 <b>E</b>	2.0	<b>2a</b>	98	97	81	(2 <i>R</i> ,3 <i>S</i> )
12 <b>E</b>	2.5	<b>2a</b>	98	98	87	(2 <i>R</i> ,3 <i>S</i> )
13 <b>E</b>	4.0	<b>2a</b>	79	97	84	(2 <i>R</i> ,3 <i>S</i> )
14 <b>F</b>	2.5	<i>ent</i> - <b>2a</b>	96	98	86	(2 <i>S</i> ,3 <i>R</i> )
15 <b>G</b>	2.5	<b>2a</b>	36	97	64	(2 <i>R</i> ,3 <i>S</i> )
16 <b>H</b>	2.5	<i>ent</i> - <b>2a</b>	42	97	78	(2 <i>S</i> ,3 <i>R</i> )
17 <b>E</b> -OMe	2.5	<i>rac</i> - <b>2a</b>	97	90	0	–

[a] Reaction conditions: 1) **1a**, 1.1 equiv Al(OiPr)<sub>3</sub>, × equiv ligand, 5 equiv LHMDS, –78 °C → RT; 2) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, RT.

**Variations of chiral ligands:** The *ee* values obtained with simple amino alcohols (**A**, **B**) were still very low (Table 1, entries 1 and 2); evidently the chiral center at the amino group does not play an important role. Introduction of a second chiral center at the hydroxy group resulted in a significant increase of the enantio- and diastereoselectivity as well, obviously the influence of this center on the stereochemical outcome of the reaction is much stronger. Switching from (–) valinol (**B**) to (–) pseudoephedrine (**C**) gave the enantiomeric rearrangement product with an increased diastereoselectivity, although the configuration of the amino group in the ligand was the same. Obviously the stereodirecting effect of the two stereogenic centers in pseudoephedrine is contrary (mismatched case). Indeed, after inversion of one of the centers by using the ephedrines (**D** and *ent*-**D**) (entries 5 and 6) the *ee* values were nearly twice as high. Also the yields were much better. Depending on the ephedrine used, both enantiomers of the amino acid can be obtained easily. Even the enantiomeric excess was still moderate, we undertook a first investigation regarding ligand acceleration. Reducing the amount of ligand from 1.2 to 0.6 equivalents had no significant effect (entry 7) but a further reduction to 0.2 equivalents resulted in a dramatic drop, especially of the enantiomeric excess (entry 8). Although there might be a weak ligand acceleration, this effect is not strong enough for a successful catalytic application.

A further improvement was observed by increasing the sterical bulk of the substituents at the amino alcohol moiety. The same relative configuration as in the ephedrines is found in the cinchona alkaloids (**E–H**). For example quinine, which is related to (–)-ephedrine, gave the same major isomer, although in much better yield and enantioselectivity (entries 9–13). Unfortunately again no ligand acceleration was observed in this case; the acceleration was even worse in comparison to ephedrine. Quinine significantly reduces the reactivity of the enolate. While a rearrangement without a ligand takes place already at –30 to –20°C, with quinine  $\approx 0^\circ\text{C}$  are necessary. Because of this ligand deceleration effect, an excess of quinine is necessary to suppress a reaction pathway via a ligand free chelate complex. By far the best results are obtained with 2.5 equivalents of quinine (entry 12). A further increase of the quinine concentration had no significant effect on the *ee*; in addition the yield dropped (entry 13). While quinine gives rise to the (*R*)-configured amino acid, the (*S*)-isomer can be obtained by using the pseudoenantiomeric ligand quinidine (**F**). The yields and selectivities with these two ligands are absolutely identical. Obviously the vinyl group at the bicyclic subunit has no influence on the rearrangement. Dihydroquinine, obtained by catalytic hydrogenation of quinine, gave also the same results.

Two other cinchona alkaloids which are commercially available are cinchonidine (**G**) and cinchonine (**H**) which differ from the previous ligands only in the lack of the methoxy group on the chinolin nucleus. This methoxy group has a positive effect regarding the solubility of the ligands. While quinine and quinidine are soluble in THF in a 0.3 M range even at –70°C, a suspension is obtained with ligands **G** and **H** under the same conditions. This might explain the lower yields and enantioselectivities obtained with these

ligands (entries 15 and 16). A lower concentration of solubilized ligand results in lower *ee* values as shown previously.

The amino alcohols probably bind as bidentate ligands towards the chelated metal ion. Methylation of quinine at the hydroxy group resulted in a completely racemic mixture of the rearrangement product (entry 17), but the diastereoselectivity was better than in reactions without an additional ligand.

**Variations of the N-protecting groups:** In terms of an easy and reliable determination of the stereochemical outcome of the reaction we chose the trifluoroacetyl group as protecting group on the nitrogen. But one might expect a strong influence of this protecting group on the reaction. Therefore, we investigated the influence of the steric and electronic effect of several protecting groups [Eq. (3), Table 2]. By far the best results were obtained with the initially applied Tfa

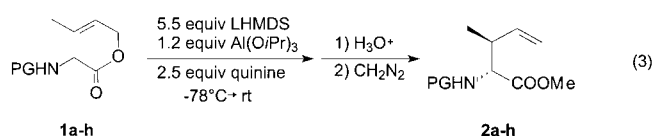


Table 2. Influence of the protecting group (PG) on chelate Claisen rearrangements of ester **1a–h**.<sup>[a]</sup>

	PG	Product	Yield [%]	<i>ds</i> [%]	<i>ee</i> [%]
1	Tfa	<b>2a</b>	98	98	87
2	<b>Bz</b>	<b>2b</b>	50	95	60
3	Cbz	<b>2c</b>	88	90	49
4	Tos	<b>2d</b>	98	90	46
5	Boc	<b>2e</b>	78	90	16
6	Ac	<b>2f</b>	23	85	13
7	<i>p</i> -F-Bz	<b>2g</b>	77	99	58
8	Pfp	<b>2h</b>	93	99	87

[a] Reaction conditions: 1) **1**, 1.1 equiv  $\text{Al}(\text{O}i\text{Pr})_3$ , 2.5 equiv quinine, 5 equiv LHMDS,  $-78^\circ\text{C} \rightarrow \text{RT}$ ; 2)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ , RT.

group (entry 1), while the other protecting groups gave significantly worse results, in terms of both yield and selectivity. Good yields are also obtained with Cbz- and Tosyl-protected crotyl esters (entries 3 and 4), while the benzoyl protected derivatives gave good selectivities. Quite surprising was the big difference between the trifluoroacetyl and the acetyl protected esters (entry 1 vs. 6). From a steric point of view there should be no big difference between these two acyl groups and obviously the strong electron withdrawing effect of the fluorine atoms is responsible for the high selectivities observed. Therefore, we decided to have a closer look on this phenomenon and we investigated the rearrangement of fluorinated benzoyl protected esters. Introduction of one fluorine atom (entry 7) into the *para*-position of the benzoyl group resulted in an increased yield and diastereoselectivity, although the enantiomeric excess was nearly constant. But the pentafluorobenzoyl (Pfp) and the trifluoroacetyl protected derivative gave comparable results (entry 8).

**Variations of the chelating metal salts:** After this successful ligand screening we investigated the influence of the chelating metal salt under these optimized conditions [Eq. (2), 1.1 equiv

metal salt, 2.5 equiv quinine]. The results obtained are listed in Table 3. As mentioned earlier, zinc chloride gave a very clean reaction, providing the expected amino acid in high yield but without significant *ee* (entry 1). Other halides gave better results. Surprisingly even calcium chloride (entry 4),

Table 3. Variation of the metal salts in chelate Claisen rearrangements of ester **1a** to **2a**.<sup>[a]</sup>

	Metal Salt	Yield [%]	<i>ds</i> [%]	<i>ee</i> [%]
1	ZnCl <sub>2</sub>	95	90	10
2	EtAlCl <sub>2</sub>	97	85	28
3	BCl <sub>3</sub>	93	86	42
4	CaCl <sub>2</sub>	73	96	65
5	MgCl <sub>2</sub>	98	91	69
6	Mg(OEt) <sub>2</sub>	98	96	83
7	Al(O <sup><i>i</i></sup> Pr) <sub>3</sub>	98	98	87
8	–	95	97	78

[a] Reaction conditions: 1) **1a**, 1.1 equiv MX<sub>m</sub>, 2.5 equiv quinine, 5 equiv LHMDs, –78 °C → RT; 2) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, RT.

powderized drying agent, gave a colorless clear solution, which is a clear indication for chelate complex formation. The selectivities obtained were good and comparable to the findings obtained with magnesium chloride (entry 5). Interestingly the “counterion” also has an influence (entry 5 vs. 6). Obviously alcoholates are the metal salts of choice giving by far the best results (entries 6 and 7). This was quite a surprise, because alcoholates never gave clean reactions of these enolates before.

For example, in aldol reactions, Michael additions or Claisen rearrangements without chiral ligand the addition of these alcoholates had no influence on the outcome of the reaction, in comparison to the reaction of the lithium enolate. Therefore we had some doubt concerning the transmetalation of the enolates with these metal salts and we investigated also the rearrangement of the lithium enolate (entry 8). Without a chiral ligand, these lithium enolates decompose and do not undergo a Claisen rearrangement. But in the presence of quinine the rearrangement product was obtained in excellent yield and high stereoselectivity.

Although the *ee* values are higher in the presence of the magnesium and aluminium alcoholates, the results are in the same range. Obviously the chiral ligand is able to stabilize the lithium enolate, and we assume that it is this lithium enolate which undergoes the Claisen rearrangement. Probably a bimetallic complex is formed with the bidentate ligand quinine (or quinidine, respectively) coordinating to the lithium enolate (Figure 2). The incorporation of a second

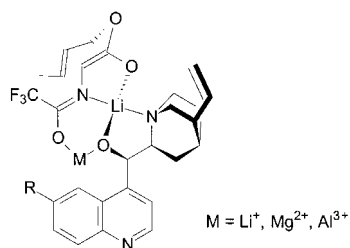
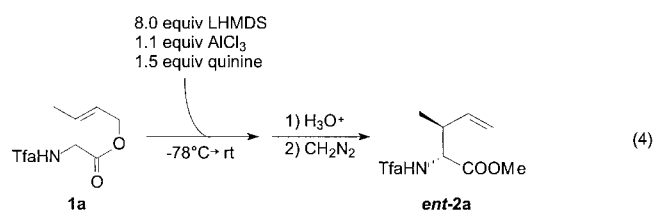


Figure 2. Bimetallic chelate complex.

metal ion M (Li<sup>+</sup>, Al<sup>3+</sup>, Mg<sup>2+</sup>) into the complex should stabilize this complex by forming a very rigid structure, in which one face of the enolate is shielded by the bicyclic substructure of the quinine. This would explain the high *ee* values obtained with this system. Obviously the alcoholates are not involved in enolate formation directly, but they have an influence on the reaction via the bimetallic complex. The similar *ee* values obtained might be explained by similar ion radii of the metal ions (Li<sup>+</sup>: 0.60 Å, Mg<sup>2+</sup>: 0.65 Å, Al<sup>3+</sup>: 0.51 Å).

If this working model is correct, one should find strong effects if the chelating lithium ion is replaced by other metal ions. Indeed, if the reaction was carried out in the absence of lithium, the selectivity dropped dramatically. No rearrangement product at all was obtained when KHMDS was used as a base. With NaHMDS the yield (18 %) and selectivities (85 % *ds*, 14 % *ee*) were low, but could be increased by adding LiCl to the reaction mixture (78 % yield, 96 % *ds*, 59 % *ee*). This clearly demonstrates the importance of the lithium ion for the complex formation.

To proof the position of the lithium ion, we modified the reaction conditions in order to generate the aluminium enolate. For this purpose LHMDs was added to a suspension of AlCl<sub>3</sub> in THF at –20 °C [Eq. (4)]. This mixture was stirred



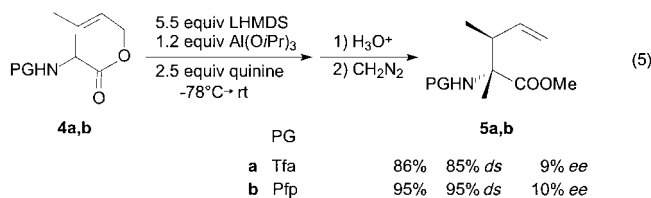
for 10 min at room temperature to form aluminium amide complexes before the quinine was added. After stirring the mixture for further two hours at room temperature, the clear pale yellow solution was added to the crotyl ester at –78 °C. Under these modified conditions highly surprising results were obtained: The rearrangement product was formed in good yield (74 %) with only moderate diastereoselectivity (85 % *ds*). The enantiomeric excess was rather high (71 % *ee*), but what was most astonishing, the opposite enantiomer of the amino acid was obtained when the reaction was carried out under standard conditions. Exactly the same was true with the pentafluorobenzoyl protected derivative, which gave comparable results.

Obviously the chiral aluminium enolate complex prefers another complex geometry than the corresponding lithium complex. Therefore it is now possible to generate both enantiomers of the rearrangement product by using the same substrate, the same chiral ligand, the same base, and the same metal ions by simply changing the reaction conditions.

**Variations of the amino acid:** In general, the chelate Claisen rearrangement can be applied not only to esters of glycine, but also to those of most other amino acids, even those with functionalized side chains.<sup>[27]</sup> In the rearrangement without a chiral ligand, the yields and selectivities are comparable to glycine esters. But if our assumption of a bimetallic enolate

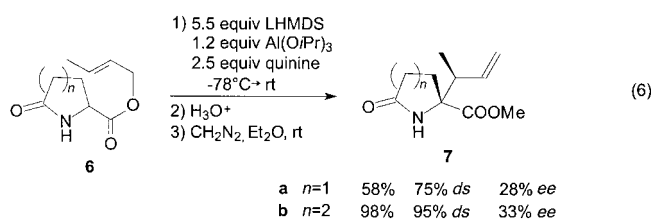
complex was correct, a substituent at the  $\alpha$ -position of the enolate should interact with the N-protecting group in this planar complex, resulting in a destabilization of the complex and a lower enantiomeric excess.

Exactly this effect was observed in the rearrangement of the corresponding alanine esters **4** [Eq. (5)]. Although the yields



were good, the diastereoselectivity was moderate to good and the same as in the reactions without quinine (control experiment). The very low *ee* values (< 10%) are a clear indicate for a collapse of a chiral complex proposed.

On the other hand, if the steric interaction described in here destabilizes the complex, a connection between the *N*-protecting group and the side chain should favor the bimetallic complex by fixation of the spatial orientation of the amino acid ester. For this purpose we synthesized crotyl esters starting from pyroglutaminic acid (**6a**) and 6-oxopipicolinic acid<sup>[28]</sup> (**6b**) and subjected them to our rearrangement conditions [Eq. (6)]. Indeed, the enantioselectivity could be



increased significantly in comparison to the open chain derivatives **4**, even those bearing fluorinated protecting groups. Although the *ee* values are “only” in the range of 30%, one should keep in mind that these derivatives do not contain electron withdrawing groups and that the results should better be compared with those of the acetyl derivatives (Table 2, entry 6) rather than the trifluoroacetylated esters.

## Conclusion

In summary, we have shown that cinchona alkaloids are suitable ligands for asymmetric Claisen rearrangements of achiral chelated enolates. This protocol allows the synthesis of both enantiomers of  $\gamma,\delta$ -unsaturated amino acids not only by switching between the alkaloids quinine and quinidine, but also by changing the reaction conditions.

## Experimental Section

**General remarks:** All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled

from sodium/benzophenone,  $\text{CH}_2\text{Cl}_2$  from  $\text{CaH}_2$  and stored over molecular sieves. The products were purified by flash chromatography on silica gel (32–63  $\mu\text{m}$ ). Mixtures of EtOAc and hexanes were generally used as eluents. TLC: commercially precoated Polygram SIL-G/UV 254 plates (Machery–Nagel). Visualization was accomplished with UV light and  $\text{KMnO}_4$  solution. Melting points were determined on a Büchi melting point apparatus and are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR: Bruker AC-300 or Bruker DRX-500 spectrometer. Selected signals for the minor diastereomers are extracted from the spectra of the diastereomeric mixture. Enantiomeric and diastereomeric excesses were determined on a HP5890 Series II gaschromatograph with a Chirasil-Val capillary column, as well as by analytical HPLC using a Daicel “Chiralcel OD-H”, column (flow:  $0.5\text{ mL min}^{-1}$ ) and a Knauer UV detector. Optical rotations were measured on a Perkin–Elmer polarimeter PE 241. Elemental analysis were carried out at the Department of Chemistry, University of Heidelberg.

**General procedure for the preparation of allylic esters:** Dicyclocarboindimide (2.46 g, 12 mmol) and DMAP (125 mg, 1 mmol) were added to a solution of the allylic alcohol (10 mmol) in methylene chloride (30 mL) at 0 °C. The clear solution was cooled to –20 °C, before the protected amino acid (10 mmol) was added after 5 min. The mixture was allowed to warm to room temperature overnight. After filtration of the precipitate, the organic phase was extracted with 1N  $\text{KHSO}_4$  solution, sat.  $\text{NaHCO}_3$  solution and with brine. Drying of the organic layer over  $\text{Na}_2\text{SO}_4$  and evaporation of the solvent gave crude ester which was purified by flash chromatography (hexanes/ethyl acetate).

**N-Trifluoroacetyl glycine crotyl ester (1a):** Ester **1a** was obtained in a 45 mmol scale according to the general procedure for esterifications in 82% yield. Crystallization from methylene chloride/hexanes gave colorless needles. M.p. 48–49 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.72 (d,  $J$  = 6.8 Hz, 3H,  $\text{CH}_3$ ), 4.11 (d,  $J$  = 5.1 Hz, 2H,  $\text{NCH}_2$ ), 4.61 (d,  $J$  = 6.9 Hz, 2H,  $\text{OCH}_2$ ), 5.58 (dq,  $J$  = 17.4, 6.8 Hz, 1H,  $\text{CHCH}_3$ ), 5.84 (dt,  $J$  = 17.4, 6.9 Hz, 1H,  $\text{CH}_2\text{CH}$ ), 6.96 (brs, 1H, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 17.66 ( $\text{CH}_3$ ), 41.38 ( $\text{NCH}_2$ ), 66.80 ( $\text{OCH}_2$ ), 115.6 (q,  $J$  = 286.7 Hz,  $\text{CF}_3$ ), 123.9 ( $\text{CH}_2\text{CH}$ ), 133.0 ( $\text{CHCH}_3$ ), 157.2 (q,  $J$  = 38.0 Hz, CON), 168.0 (COO); elemental analysis calcd (%) for  $\text{C}_8\text{H}_{10}\text{F}_3\text{NO}_3$  (225.2): C 42.67, H 4.48, N 6.22; found: C 42.82, H 4.61, N 6.30.

**General procedure for Claisen rearrangements in the presence of chiral ligands:** A LHMDS solution was prepared by adding 1.55 *m*-n-buthyllithium in hexane (1.6 mL, 2.5 mmol) at –20 °C under argon to hexamethyldisilazane (470 mg, 2.9 mmol) in dry THF (1.5 mL) and stirring for 20 min. The *N*-protected glycine crotyl ester **1** (0.5 mmol),  $\text{Al}(\text{O}i\text{Pr})_3$  (0.55 mmol) and the ligand (1–1.25 mmol) were dissolved under argon in dry THF (5 mL). The mixture was cooled to –78 °C, and the freshly prepared LHMDS solution was added slowly. The reaction mixture was allowed to warm to room temperature within 12 h. After diluting with diethyl ether (50 mL), the reaction mixture was hydrolyzed by addition of 1M aqueous  $\text{KHSO}_4$  (25 mL). The organic layer was washed again with 1M  $\text{KHSO}_4$ , before the reaction product was extracted with three portions of saturated aqueous  $\text{NaHCO}_3$  solution (25 mL each). The basic solution was subsequently acidified by careful addition of solid  $\text{KHSO}_4$  to pH 1 and extracted with three portions of diethyl ether (25 mL each). The combined organic extracts were dried with  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated under reduced pressure. For the determination of the enantiomeric and diastereomeric ratios of the product, the residue was treated with diazomethane in ether solution. Subsequent chromatography on silica gel gave the corresponding methyl esters.

**(2R,3S)-3-Methyl-2-(trifluoroacetyl amino)-4-pentenoic methyl ester (2a):** According to the general procedure for Claisen rearrangements *syn*-ester **2a** was obtained from crotyl ester **1a** (123 mg, 0.5 mmol),  $\text{Al}(\text{O}i\text{Pr})_3$  (114 mg, 0.55 mmol) and quinine (405 mg, 1.25 mmol) (98% yield, 87% *ee*, 98% *ds*) as a colorless oil;  $[\alpha]_D^{20}$  = –54.4° ( $c$  = 2.0,  $\text{CHCl}_3$ , 87% *ee*, 98% *ds*);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.09 (d,  $J$  = 7.0 Hz, 3H,  $\text{CHCH}_3$ ), 2.73 (ddq,  $J$  = 8.5, 7.0, 6.9 Hz, 1H,  $\text{CHCH}_3$ ), 3.77 (s, 3H,  $\text{OCH}_3$ ), 4.63 (dd,  $J$  = 8.5, 5.0 Hz, 1H,  $\text{NCH}$ ), 5.09 (dd,  $J$  = 17.1, 1.1 Hz, 1H,  $\text{CHCH}_2$ ), 5.14 (dd,  $J$  = 10.5, 1.1 Hz, 1H,  $\text{CHCH}_2$ ), 5.65 (ddd,  $J$  = 17.1, 10.5, 6.9 Hz, 1H,  $\text{CHCH}_2$ ), 6.84 (brs, 1H, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.4 ( $\text{CHCH}_3$ ), 40.6 ( $\text{CHCH}_3$ ), 52.6 ( $\text{OCH}_3$ ), 56.1 ( $\text{OCH}_3$ ), 115.6 (q,  $J$  = 287 Hz,  $\text{CF}_3$ ), 117.3 ( $\text{CHCH}_2$ ), 137.3 ( $\text{CHCH}_2$ ), 156.6 (q,  $J$  = 38 Hz, CON), 170.3 (COO); *anti*-**2a** (selected signals):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.14 (d,  $J$  = 7.0 Hz, 3H,  $\text{CHCH}_3$ ), 2.84 (m, 1H,  $\text{CHCH}_3$ ), 3.80 (s, 3H,  $\text{OCH}_3$ ), 6.75 (brs, 1H, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.8 ( $\text{CHCH}_3$ ), 40.2 ( $\text{CHCH}_3$ ), 52.7

(OCH<sub>3</sub>), 56.5 (NCH), 117.8 (CHCH<sub>2</sub>), 136.7 (CHCH<sub>2</sub>); GC (Chirasil-Val, 80 °C, isothermic):  $t_R$  (2*R*,3*R*) = 6.79 min,  $t_R$  (2*R*,3*S*) = 7.64 min,  $t_R$  (2*S*,3*S*) = 7.99 min,  $t_R$  (2*S*,3*R*) = 8.66 min; elemental analysis calcd (%) for C<sub>9</sub>H<sub>12</sub>NO<sub>3</sub>F<sub>3</sub> (242.2): C 45.19, H 5.06, N 5.86; found: C 45.14, H 5.07, N 5.73.

**(2*S*,3*R*)-3-Methyl-2-(trifluoroacetyl-amino)-4-pentenoic methyl ester (ent-2a)**

1) *syn*-Ester *ent*-2a was obtained according to the general procedure for Claisen rearrangements from crotyl ester **1a** (123 mg, 0.5 mmol), Al(O*i*Pr)<sub>3</sub> (114 mg, 0.55 mmol) and quinidine (405 mg, 1.25 mmol) as a colorless oil (97% yield, 87% *ee*, 98% *ds*). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +53.6° (*c* = 2.0, CHCl<sub>3</sub>, 87%, 98% *ds*).

2) Aluminum chloride (65 mg, 0.49 mmol) was suspended in THF (2 mL) at 0 °C. The suspension was cooled to –20 °C before a solution of LHMDs (8 mL, 3.55 mmol) was added. The cooling bath was removed and the mixture was stirred for 10 min. After cooling to –20 °C, a solution of quinine (216 mg, 0.67 mmol) in THF (3 mL) was added slowly. The mixture was stirred for 2 h at RT. The resulting clear yellow solution was added via syringe to a solution of ester **1a** (100 mg, 0.44 mmol) in THF (2 mL) at –78 °C. The mixture was allowed to warm to room temperature overnight, and the workup was carried out as described in the general procedure for Claisen rearrangements. Ester *ent*-2a was obtained as a colorless oil (74% yield, 71% *ee*, 85% *ds*). [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +40.3° (*c* = 1.7, CHCl<sub>3</sub>, 71% *ee*, 85% *ds*); NMR and GC data see **2a**; elemental analysis calcd (%) for C<sub>9</sub>H<sub>12</sub>NO<sub>3</sub>F<sub>3</sub> (242.2): C 45.19, H 5.06, N 5.86; found: C 45.34, H 4.98, N 5.83.

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