Direct Catalytic Asymmetric Mannich Reactions of Malonates and β-Keto Esters

Mauro Marigo, Anne Kjærsgaard, Karsten Juhl, Nicholas Gathergood, and Karl Anker Jørgensen*[a]

Abstract: The first catalytic asymmetric direct Mannich reaction of malonates and β-keto esters has been developed. Malonates react with an activated *N*-tosyl-α-imino ester catalyzed by chiral *tert*-butyl-bisoxazoline/$Cu(OTf)_2$ to give the Mannich adducts in high yields and with up to 96% *ee*. These reactions create a chiral quaternary carbon center and it is demonstrated that this new direct Mannich reactions provides for example a new synthetic procedure for the formation of optically active β-carboxylic ester α-amino acid derivatives. A series of different β-keto esters with various ester substituents has been screened as substrates for the catalytic asymmetric direct Mannich reaction and it was found that the best results in terms of yield, diastereo- and enantioselectivity were obtained when *tert*-butyl esters of β-keto esters were used as the substrate. The reaction of different β-keto *tert*-butyl esters with the *N*-tosyl-α-imino ester gave the Mannich adducts in high yields, diastereo- and enantioselectivities (up to 95% *ee*) in the presence of chiral *tert*-butyl-bisoxazoline/$Cu(OTf)_2$ as the catalyst. To expand the synthetic utility of this direct Mannich reaction a diastereoselective decarboxylation reaction was developed for the Mannich adducts leading to a new synthetic approach to attractive optically active β-keto α-amino acid derivatives. Based on the stereochemical outcome of the reactions, various approaches of the *N*-tosyl-α-imino ester to the chiral bisoxazoline/Cu^{II}-substrate intermediate are discussed.

Keywords: asymmetric catalysis · imines · Mannich bases · synthetic methods

Introduction

One of the great challenges in organic chemistry is the development of reactions for the construction of complex optically active molecules by bringing simple molecules to react in a stereoselective manner. The catalytic asymmetric aldol reaction is one of these important C–C bond forming reactions and many successful examples have been reported, especially of the catalytic asymmetric Mukaiyama aldol reaction.[1] A reaction that is closely related to the aldol reaction is the Mannich reaction, where enols or enolates react with imines to form β-amino esters or ketones. Despite the importance of this C–C bond forming reaction, only a few examples of effective catalytic enantioselective Mannich-type reactions have been reported.[2]

[a] Prof. Dr. K. A. Jørgensen, M. Marigo,
A. Kjærsgaard, Dr. K. Juhl, Dr. N. Gathergood
Danish National Research Foundation: Center for Catalysis
Department of Chemistry
Aarhus University
8000 Aarhus C (Denmark)
Fax: (+45) 8619 6199
E-mail: kaj@chem.au.dk

The first successful catalytic enantioselective Mannich-type reaction was reported in 1997 by Kobayashi and co-workers using chiral zirconium/BINOL complexes as catalysts.[3] Catalytic enantioselective Mannich-type reactions of silyl enol ethers and α-imino esters were published in two similar and nearly simultaneous reports by Sodeoka et al.[4] and Lectka et al.[5] in 1998, where palladium(II)/BINAP and copper(I)/BINAP complexes, respectively, were applied as the catalysts. However, a disadvantage for these stereoselective Mannich reactions can be the preparation and stability of the enolate, and an important step forward for this class of reactions would be a catalytic enantioselective version using carbonyl compounds rather than the enolates.[6]

Recently, we disclosed the first highly enantioselective catalytic direct Mannich reaction where 2-keto esters were treated with N-protected α-imino esters in the presence of chiral copper(II)/bisoxazoline complexes.[7] The advantage of this reaction is that the formation of silyl enol ethers is not required. Furthermore, it should also be noted that organocatalytic enantioselective direct Mannich reactions catalyzed by organic molecules have been developed.[8]

In this paper, we disclose the use of malonic esters and β-keto esters as pro-nucleophiles in catalytic asymmetric direct Mannich reactions with an activated *N*-tosyl-α-imino ester[9] [Eq. (1)].[10, 11]

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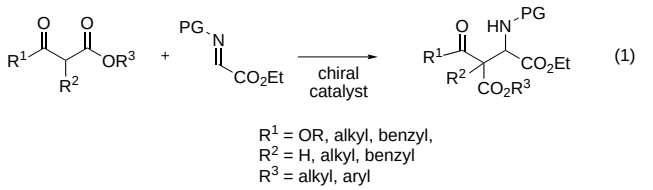
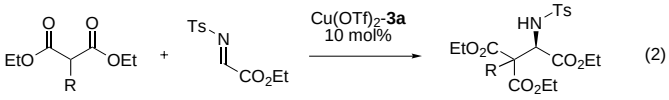


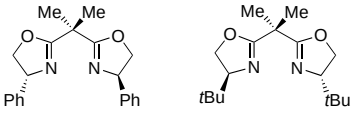
This new chiral Lewis acid-catalyzed reaction gives access to highly functionalized optically active molecules and, furthermore, this reaction is also an easy entry to the formation of chiral quaternary carbon centers.[12]

Results and Discussion

Catalytic enantioselective reactions of malonates: We decided to commence our investigation of direct catalytic asymmetric Mannich reactions of the malonic esters and β-keto esters with the reaction of diethyl malonates **1a**, **b** and the *N*-tosyl-α-imino ester **2** catalyzed by 10 mol% of the chiral copper(II) bisoxazoline[13] (BOX) complex $Cu(OTf)_2$/(*R*)-Ph-BOX (**3a**) [Eq. (2)]. The results are shown in Table 1.

At $-20\,^{\circ}C$ diethyl malonate **1a** reacted smoothly with *N*-tosyl-α-imino ester **2** in CH_2Cl_2 catalyzed by 10 mol% $Cu(OTf)_2$/(*R*)-Ph-BOX (**3a**) affording Mannich adduct **4a** in 95% yield, but with moderate enantioselectivity (Table 1, entry 1). Inspired by Evans'[14] use of electron-poor alcohols as additives in copper(II)-catalyzed Mukaiyama aldol reactions and α-amination reactions, 1.5 equiv of 1,1,1,3,3,3-hexafluoropisopropanol (HFIP) was added to the reaction resulting in a dramatic increase in enantioselectivity to 80% *ee* (entry 2). The role of HFIP in the reaction is not clear, but may be to assist catalyst turnover.





Diethyl malonate having a methyl substituent at the α-position (**1b**) also reacted with **2** giving the Mannich adduct **4b** with a quaternary carbon atom in satisfying 88% yield and 61% *ee* (Table 1, entry 3). Addition of HFIP to the reaction gave a slight increase in enantioselectivity, without affecting the yield significantly (entry 4). Lowering of the reaction temperature increased the enantioselectivities to 72% *ee* and 79% *ee*, at 0 and $-20\,^{\circ}C$, respectively (entries 5, 6). THF was also tested as solvent for the catalytic enantioselective Mannich reaction, but lower yield and enantiomeric excess were obtained in this solvent (entry 5 vs 7). Other substituents of the malonic esters were also allowed as ethyl, *n*-butyl, isobutyl and benzyl substituted diethyl malonates (**1c–f**) all gave the corresponding Mannich adducts with enantioselectivities from 79–87% *ee* and good yields after 4 days reaction time at $-20\,^{\circ}C$ (entries 9–11, 14).

The (*S*)-*t*Bu-BOX ligand **3b** was also used as ligand for $Cu(OTf)_2$ in the catalytic enantioselective Mannich reaction of malonic esters **1a**, **b**, **d–f** with the *N*-tosyl-α-imino ester **2**. Representative results are shown in Table 2.

The reaction of malonic esters **1a**, **b**, **d–f** with *N*-tosyl-α-imino ester **2** also proceeded well with $Cu(OTf)_2$/(*S*)-*t*Bu-BOX (**3b**) as catalyst. Surprisingly HFIP did not increase the enantioselectivity of the reaction. However, cooling the reaction to $-20\,^{\circ}C$ gave a high yielding and highly enantioselective formation of Mannich adducts **4a**, **b**, **d–f** (entries 3, 6, 8, 10, 12) as up to 96% *ee* was obtained; this is a significant improvement compared with the $Cu(OTf)_2$/(*R*)-Ph-BOX catalyzed reaction (Table 1, entry 12 vs Table 2, entry 10).

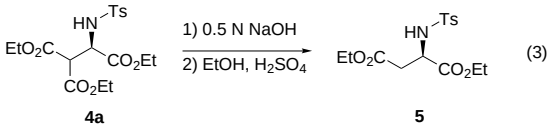


Table 1. Direct Mannich Reaction of **1a–f** with **2** catalyzed by $Cu(OTf)_2$/(*R*)-Ph-BOX (**3a**).

Entry	R	Solvent	$T_{reaction}$ [°C]	*t*	Product (yield[a]/[%])	Additive (mol%)	*ee*[b] [%]
1	H (**1a**)	CH_2Cl_2	−20	40 h	**4a** (95)	none	39
2	H (**1a**)	CH_2Cl_2	−20	40 h	**4a** (63)	HFIP[c] (150)	80
3	Me (**1b**)	CH_2Cl_2	RT[d]	40 h	**4b** (88)	none	61
4	Me (**1b**)	CH_2Cl_2	RT[d]	40 h	**4b** (70)	HFIP[c] (100)	69
5	Me (**1b**)	CH_2Cl_2	0	40 h	**4b** (70)	HFIP[c] (100)	72
6	Me (**1b**)	CH_2Cl_2	−20	4 d	**4b** (71)	HFIP[c] (100)	79
7	Me (**1b**)	THF	0	40 h	**4b** (57)	HFIP[c] (100)	59
8	Et (**1c**)	CH_2Cl_2	RT[d]	16 h	**4c** (47)	HFIP[c] (100)	57
9	Et (**1c**)	CH_2Cl_2	−20	4 d	**4c** (70)	HFIP[c] (100)	87
10	*n*Bu (**1d**)	CH_2Cl_2	−20	4 d	**4d** (80)	HFIP[c] (100)	82
11	*i*Bu (**1e**)	CH_2Cl_2	−20	4 d	**4e** (60)	HFIP[c] (100)	79
12	Bn (**1f**)	CH_2Cl_2	RT[d]	16 h	**4f** (51)	none	35
13	Bn (**1f**)	CH_2Cl_2	RT[d]	16 h	**4f** (77)	HFIP[c] (100)	62
14	Bn (**1f**)	CH_2Cl_2	−20	4 d	**4f** (65)	HFIP[c] (100)	79

[a] Yield of isolated product. [b] Enantiomeric excess was determined by HPLC. [c] HFIP = 1,1,1,3,3,3-hexafluoroisopropanol. [d] RT = room temperature.

The absolute configuration of the Mannich base **4a** was determined after hydrolysis and decarboxylation [Eq. (3)] by comparing the optical rotation of **5** obtained according to Equation (3) with the optical rotation of **5** prepared from L-aspartic acid (see Experimental Section). The absolute configuration was found to be the same for Mannich adducts prepared with $Cu(OTf)_2$-**3a** and $Cu(OTf)_2$-**3b**, although these catalysts have opposite configurations.[15]

Thus, the direct catalytic enantioselective Mannich reac-

Table 2. Direct Mannich reaction of **1a**, **b**,**d**–**f** with **2** catalyzed by $Cu(OTf)_2$/(*S*)-*t*Bu-BOX (**3b**).

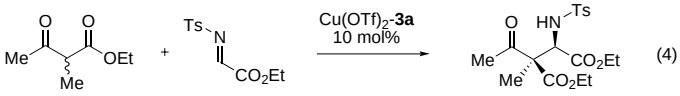
Entry	R	Solvent	$T_{reaction}$ [°C]	*t*	Product (yield[a]/[%])	Additive (mol %)	*ee*[b] [%]
1	H (**1a**)	CH_2Cl_2	RT[d]	40 h	**4a** (76)	none	59
2	H (**1a**)	CH_2Cl_2	RT[d]	40 h	**4a** (80)	HFIP[d] (100)	42
3	H (**1a**)	CH_2Cl_2	−20	4 d	**4a** (80)	none	74
4	H (**1a**)	CH_2Cl_2	−20	4 d	**4a** (80)	HFIP[d] (100)	45
5	Me (**1b**)	CH_2Cl_2	RT[d]	40 h	**4b** (95)	none	82
6	Me (**1b**)	CH_2Cl_2	−20	4 d	**4b** (99)	none	85
7	*n*Bu (**1d**)	CH_2Cl_2	RT[d]	40 h	**4d** (43)	none	70
8	*n*Bu (**1d**)	CH_2Cl_2	−20	4 d	**4d** (63)	none	91
9	*i*Bu (**1e**)	CH_2Cl_2	RT[d]	40 h	**4e** (50)	none	88
10	*i*Bu (**1e**)	CH_2Cl_2	−20	4 d	**4e** (64)	none	96
11	Bn (**1f**)	CH_2Cl_2	RT[d]	40 h	**4f** (77)	none	89
12	Bn (**1f**)	CH_2Cl_2	−20	4 d	**4f** (54)	none	94

[a] Yield of isolated product. [b] Enantiomeric excess was determined by HPLC. [c] HFIP = 1,1,1,3,3,3-hexafluoroisopropanol. [d] RT = room temperature.

The size of the ester moiety of the β-keto esters has been shown to have a significant influence on enantioselectivities of other asymmetric Lewis acid-catalyzed reactions where β-keto esters act as pro-nucleophiles. Togni and co-workers investigated the catalytic enantioselective halogenation of β-keto esters, and found that bulky ester moieties increased the enantioselectivity of the reaction.[16, 17] This effect was also investigated for the present Mannich reaction.

tion of the malonates provides a new approach to the attractive optically active β-carboxylic esters α-amino acid derivatives.

Catalytic enantioselective reactions of β-keto esters: We were happy to find that β-keto esters also underwent the $Cu(OTf)_2$/



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6 **2** **7**

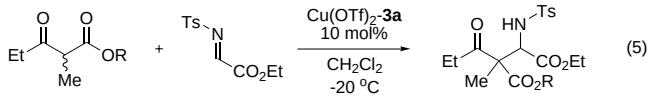
Table 3. Direct Mannich reaction of **6** with **2** catalyzed by $Cu(OTf)_2$/(*R*)-Ph-BOX (**3a**).

Entry	Solvent	$T_{reaction}$ [°C]	Yield[a] [%]	Additive [mol %]	*dr*[b]	*ee*[c] [%]
1	CH_2Cl_2	RT[e]	> 98	none	86:14	24
2	CH_2Cl_2	RT[e]	93	HFIP[d] (100)	88:12	22
3	CH_2Cl_2	0	90	none	89:11	34
4	CH_2Cl_2	−20	90	none	90:10	42
5	THF	0	97	none	76:24	27

[a] Yield of isolated product. [b] Diastereomeric ratio measured by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Enantiomeric excess of the major diastereomer was determined by HPLC. [d] HFIP = 1,1,1,3,3,3-hexafluoroisopropanol. [e] RT = room temperature.

BOX catalyzed asymmetric Mannich reaction with the *N*-tosyl-α-imino ester **2**. For initial testing, the β-keto ester **6** was chosen as pro-nucleophile [Eq. (4)] and the results are shown in Table 3.

At room temperature the Mannich reaction proceeded to completion affording Mannich adduct **7** in quantitative yield and good diastereoselectivity, but with low enantioselectivity (Table 3, entry 1). The addition of HFIP to the reaction did not have any effect like in the Mannich reaction with diethyl malonates (entry 2). Cooling the reaction had a positive effect as the enantioselectivity rose to 34 and 42 % *ee*, at 0 and −20 °, respectively, with only a small reduction in yield (entries 3, 4). Again, CH_2Cl_2 was the better solvent for this reaction as the enantioselectivity and diastereoselectivity were lower in THF (entry 3 vs 5).



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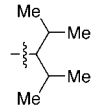
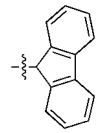
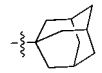
8a-i **2** **9a-i**

Table 4. Direct Mannich reaction of **8a**–**i** with **2** catalyzed by $Cu(OTf)_2$/(*R*)-Ph-BOX (**3a**).

Entry	β-Keto ester R		Product (yield[b]/[%])	*dr*[c]	*ee*[d] [%]
1		(**8a**)	**9a** (76)	84:16	23
2		(**8b**)	**9b** (81)	78:22	23
3		(**8c**)	**9c** (73)	72:28	20
4		(**8d**)	**9d** (70)	70:30	40
5		(**8e**)	**9e** (75)	93:7	51
6		(**8f**)	**9f** (81)	> 95:< 5	53
7		(**8g**)	**9g** (72)	95:5	50
8		(**8h**)	**9h** (43)	> 95:< 5	−66
9		(**8i**)	**9i** (33)	> 95:< 5	−68

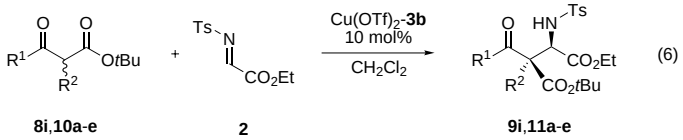
[a] All reactions were performed in CH_2Cl_2 at −20 °C in the presence of 10 mol % $Cu(OTf)_2$/(*R*)-Ph-BOX (**3a**) for 40 h. [b] Yield of isolated product. [c] Diastereomeric ratio measured by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Enantiomeric excess of the major diastereomer was determined by HPLC.

Several β-keto esters (**8a**–**i**) with different ester groups were synthesized by the procedure published by Togni et al.[16] and applied in the $Cu(OTf)_2$/(*R*)-Ph-BOX catalyzed reaction with

the *N*-tosyl-α-imino ester **2** in CH_2Cl_2 at $-20\,^{\circ}C$ [Eq. (5)]. The results are shown in Table 4.

It appears from the results in Table 4 that there is a good correlation between the size of the ester moiety of the β-keto esters **8a–i** and the enantioselectivity of the reaction with the exception of **8c** (R = 2,4-dimethyl-3-pentyl). β-Keto esters derived from primary alcohols (**8a**, **b**) gave the Mannich bases **9a**, **b** in good yields and diastereoselectivities, but with low enantioselectivities (Table 4, entries 1,2). β-Keto esters with secondary alkyl groups on the ester moiety (**8c–f**) were also evaluated in the Mannich reaction under the same conditions. The ester derived from 2,4-dimethyl-3-pentanol (**8c**) (entry 3) gave a similar result as entries 1 and 2, while esters derived from cyclohexanol and benzhydrol (**8e**, **f**) gave an increase in enantioselectivities to 51 and 53% *ee*, respectively. Simultaneously, the diastereoselectivities rose from good to excellent while maintaining the good yields (entries 5, 6). The free rotation of the phenyl groups in benzhydrol was important for the selectivity of the reaction, as the 9-fluorenol derived ester (**8d**) gave the Mannich adduct **9d** with lower enantio- and diastereoselectivity (entry 4). It should also be noted that a phenyl group on the ester moiety did not change the stereoselectivity of the reaction (entry 7). For the catalytic asymmetric Mannich reaction, β-keto esters derived from tertiary alcohols (**8h**, **i**) were the best substrates of the tested series. Although, the yields of the Mannich adducts **9h**, **i** were moderate, excellent diastereoselectivities and improved enantioselectivities were obtained with these substrates (entries 8, 9).

The Mannich adduct from the reaction of *N*-tosyl-α-imino ester **2** and the β-keto ester derived from benzhydrol (**8f**) was recrystallised to 80% *ee* and X-ray crystallography revealed (*R*,*R*)-configuration of the two chiral centers.[18] This information was also used to determine the absolute configuration of **9i**. The two Mannich adducts **9h**, **i** were found to have the same relative configuration, but to our surprise, the absolute configuration of the Mannich adducts was reversed when going from a β-keto ester with an ester group derived from a secondary to a tertiary alcohol. Apparently, a more bulky substituent on the ester moiety caused a change in the geometry of the reactive substrate-Lewis acid complex (see above).



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The Mannich reaction of the α-imino ester **2** and β-keto esters with the optimized ester functionality—the *tert*-butyl ester—was now investigated with the $Cu(OTf)_2$/*t*Bu-BOX (**3b**) complex as the catalyst [Eq. (6)] and Table 5 shows some representative results from this investigation.

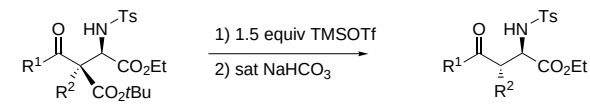
At $-20\,^{\circ}C$ the β-keto ester **10a** reacted with the *N*-tosyl-α-imino ester **2** to give Mannich adduct **11a** with excellent diastereo- and enantioselectivity in 55% yield after 40 h (Table 5, entry 1). β-Keto esters with larger R^1 substituents also reacted in highly stereoselective fashion, but the increased steric bulk also resulted in much lower yields (entries 2, 3). The stereoselectivity of the $Cu(OTf)_2$/(*S*)-*t*Bu-BOX (**3b**) catalyzed reaction was not as temperature dependent as the $Cu(OTf)_2$/(*R*)-Ph-BOX (**3a**) catalyzed reaction (see Table 3). With the exception of the methyl substituted β-keto ester **10a** (entry 4), the β-keto esters reacted with **2** at room temperature with no significant decrease in either diastereo- or enantioselectivity compared to the reaction at $-20\,^{\circ}C$, but with greatly increased yields (entries 5, 6 vs 2, 3). The generality of the reaction was displayed with the reaction of *tert*-butyl β-keto esters with variable substituent patterns (entries 7–9). In general, the Mannich adducts **9i**, **11a–e** were obtained in good yields and with high diastereo- and enantioselectivities. The β-keto esters **8e** and **8f** with ester moieties derived from secondary alcohols were also applied in the $Cu(OTf)_2$/(*S*)-*t*Bu-BOX (**3b**) catalyzed reaction with the *N*-tosyl-α-imino ester **2**. The products from these reactions were obtained with moderate selectivities (*dr* 75:25, 59% *ee* and *dr* 89:11, 57% *ee*, respectively) but with the same relative and absolute configuration as the *tert*-butyl β-keto esters (see below).

Table 5. Direct Mannich reaction of **8i**, **10a–e** with **2** in CH_2Cl_2 catalyzed by $Cu(OTf)_2$/(*S*)-*t*Bu-BOX (**3b**).

Entry	R^1	R^2		$T_{reaction}$ [°C]	t	Product (yield[a]/[%])	*dr*[b]	*ee*[c] [%]
1	Me	Me	(**10a**)	−20	40 h	**11a** (55)	97:3	95
2	Et	Me	(**8i**)	−20	40 h	**9i** (17)	98:2	93
3	*i*Pr	Me	(**10b**)	−20	40 h	**11b** (15)	84:16	92
4	Me	Me	(**10a**)	RT[d]	16 h	**11a** (87)	93:7	88
5	Et	Me	(**8i**)	RT[d]	16 h	**9i** (80)	98:2	92
6	*i*Pr	Me	(**10b**)	RT[d]	16 h	**11b** (55)	84:16	91
7		$(CH_2)_4$	(**10c**)	RT[d]	16 h	**11c** (89)	99:1	86
8	Bn	Me	(**10d**)	RT[d]	16 h	**11d** (83)	96:4	93
9	Me	allyl	(**10e**)	RT[d]	16 h	**11e** (69)	92:8	87

[a] Yield of isolated product. [b] *dr* determined by ^1H NMR spectroscopy or HPLC. [c] Enantiomeric excess of the major diastereomer was determined by HPLC. [d] RT = room temperature.

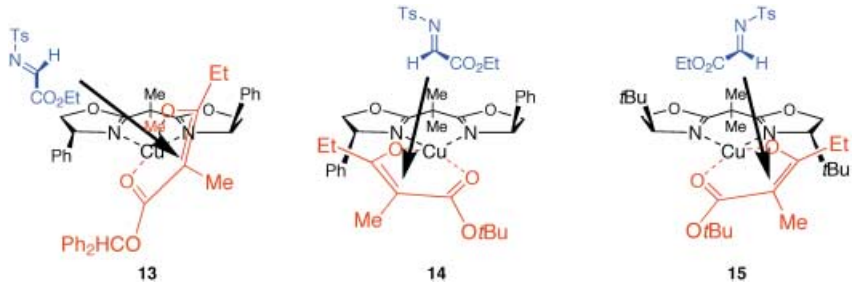
Product modification: The utility of the enantioselective catalytic direct Mannich reaction was enhanced by the development of a diastereoselective decarboxylation reaction of the Mannich adducts derived from β-keto esters.[19] Treatment of Mannich adduct **9i** with 1.5 equiv of TMSOTf in $CHCl_3$ for 60 min followed by the addition of sat. aq. $NaHCO_3$ gave γ-keto α-amino acid ester **12a** in 76% yield and with a diastereomeric ratio of 89:11 [Eq. (7)]. The same reaction was performed on the Mannich base derived from *tert*-butyl cyclohexanone-2-carboxylate (**11c**) with similar diastereoselectivity. The high enantioselectivity was main-



(7)

tained through these transformations (see Experimental Section for assignment of absolute configuration).

Thus, the direct catalytic enantioselective Mannich reaction of the β-keto esters provides an attractive approach to attractive optically active γ-keto α-amino acid derivatives.



Scheme 1. Possible reactive intermediates in the copper bisoxazoline catalyzed enantioselective Mannich reactions of β-keto esters.

Mechanistic considerations: The stereochemical outcome of the copper bisoxazoline catalyzed asymmetric Mannich reactions of the β-keto esters can be explained by the complexes shown in Scheme 1.

The surprising reversal of enantioselectivity we found when going from a β-keto ester with an ester group derived from a secondary to a tertiary alcohol in the Cu(OTf)$_2$/(*R*)-Ph-BOX (**3a**) catalyzed reaction may be accounted for by the approach outlined in **13** and **14**. Coordination of the enolate of **8f** in a twisted tetrahedral-like geometry around the copper center[15a] would allow reaction with the *N*-tosyl-α-imino ester **2** as shown in **13**. A more square-planar-like intermediate of the *tert*-butyl ester **8i** coordinated to the Cu(OTf)$_2$/(*R*)-Ph-BOX would allow the reaction with the imine from above, with the tosyl-group in the less crowded steric environment in the upper left corner of **14** as shown in Scheme 1. The reversal of enantioselectivity when changing the ester moiety is quite remarkable and displays the flexibility of the Cu(OTf)$_2$/(*R*)-Ph-BOX complex as chiral catalyst.[15a] A complex similar to complex **14** could explain the absolute and relative configuration of the Mannich bases formed in the Cu(OTf)$_2$/(*S*)-*t*Bu-BOX (**3b**) catalyzed reaction (see **15**, Scheme 1). The mechanism for the stereochemical outcome of these catalytic direct enantioselective Mannich reactions of malonates and β-keto esters with the *N*-tosyl-α-imino ester seems to be more complex compared to other chiral bisoxazoline/Cu^{II}-catalyzed reactions.

Summary

The first direct catalytic enantioselective Mannich reactions of malonates and β-keto esters with imines have been developed. The different malonates tested reacted with an *N*-tosyl-α-imino ester catalyzed by Cu(OTf)$_2$/(*S*)-*t*Bu-BOX to give the Mannich adducts in high yields and with up to 96% *ee*. The Mannich adducts obtained provides an easy synthetic entry to optically active β-carboxylic ester α-amino acid derivatives by decarboxylation. For the β-keto esters a screening of the ester substituents gave the *tert*-butyl esters as the best class of substrates by reaction with an *N*-tosyl-α-imino ester and the Mannich adducts could be obtained in high yields, diastereo- and enantioselectivities in the presence of Cu(OTf)$_2$/(*S*)-*t*Bu-BOX as the catalyst. A diastereoselective decarboxylation reaction was developed for the Mannich adducts obtained leading to an easy synthetic approach to attractive optically active γ-keto α-amino acid derivatives. Based on the absolute configuration of the Mannich adducts, the mechanism for the direct catalytic enantioselective Mannich reactions was proposed involving a keto to enol transformation of the chiral Lewis acid before the stereoselective formation of the C–C bond.

Experimental Section

General methods: The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to $CHCl_3$ ($\delta = 7.26$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. Coupling constants in ^{1}H NMR are in Hz. Solvents were dried according to standard procedures. Flash chromatography (FC) was carried out using silica gel 60 (230–400 mesh). The enantiomeric excess (*ee*) of the products were determined by HPLC using Daicel Chiracel OJ or Daicel Chiralpak AD or AS columns with *i*PrOH/hexane as eluent. All optical rotations were measured in CH_2Cl_2.

Materials: 2,2′-Isopropylidene[(4*S*)-4-*tert*-butyl-2-oxazoline], 2,2′-isopropylidene-bis[(4*R*)-4-phenyl-2-oxazoline], methylene-bis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline], Cu(OTf)$_2$, ethyl 2-methylacetoacetate (**6**), *n*BuLi, *tert*-butylpropionate, *N*,*O*-dimethylhydroxylamine hydrochloride, *p*-toluenesulfonyl isocyanate, trimethylsilyl trifluoromethanesulphonate and $TMSCHN_2$ are commercially available and used as received. β-Keto esters **8a–j** were prepared by reaction of methylketene dimer with the appropriate alcohol following a literature procedure.[16] β-Keto esters **10a**, **b**, **d**, **e** were prepared by acylation of *tert*-butylpropionate, and *tert*-butyl-4-pentenoate by *N*-methoxy-*N*-methylamides following a literature procedure.[20] β-Keto ester **10c** was prepared from pimelic di-*tert*-butylester following a literature procedure.[21] The alcohols used are all commercially available. The *N*-tosyl-α-imino ester (**2**) was prepared from ethyl glyoxylate and *p*-toluenesulfonyl isocyanate by a literature procedure.[22]

General procedure for catalytic asymmetric direct Mannich reaction of malonic esters: Cu(OTf)$_2$ (18.1 mg, 0.050 mmol) and 2,2′-isopropylidene-bis[(4*S*)-4-*tert*-butyl-2-oxazoline] (15.5 mg, 0.05 mmol) were added to an oven dried Schlenk tube equipped with a magnetic stirring bar. The mixture was stirred under vacuum at 50 °C for 2 h and filled with Ar. Dry CH_2Cl_2 (2 mL) was added and the solution was stirred for ½ h. *N*-Tosyl-α-imino ester (**2**) (153 mg, 0.6 mmol) was added followed by the malonate (0.5 mmol) and stirred over night under Ar at RT. The reaction mixture was filtered through a plug of silica with 30% Et_2O in CH_2Cl_2. The solvent was removed in vacuo and the residue was purified by FC (silica 15% Et_2O/$CH_2Cl_2 \rightarrow CH_2Cl_2$).

2-Ethoxycarbonyl-3-tosyl-succinic diethyl ester (4a): The *ee* was determined by HPLC using a Daicel Chiralpak OJ column (hexane/*i*PrOH 85:15); flow rate 1.0 mL min^{-1}; $\tau_{major} = 23.4$ min; $\tau_{minor} = 18.6$ min). $[\alpha]_D^{RT} = -31.0°$ ($c = 10.0$ mg mL^{-1}, 74% *ee*); ^{1}H NMR: $\delta = 7.69$ (d, $J = 8.2$, 2H, Ar**H**), 7.23 (d, $J = 8.2$, 2H, Ar**H**), 5.66 (d, $J = 8.2$, 1H, N**H**), 4.45 (dd, $J = 8.2$, $J = 4.2$, 1H, NHC**H**), 3.91–4.18 (m, 7H, C**H**($CO_2C\mathbf{H}_2CH_3$)$_2$, O$C\mathbf{H}_2CH_3$), 2.35 (s, 3H, Ar$C\mathbf{H}_3$), 1.10 (t, $J = 7.1$, 6H, ($CO_2CH_2C\mathbf{H}_3$)$_2$), 1.03 (t, $J = 7.2$, 3H, O$CH_2C\mathbf{H}_3$); ^{13}C NMR: $\delta = 169.0$, 167.2, 166.7, 144.0, 137.1, 129.8 (2C), 127.5 (2C), 62.7, 64.4, 62.3, 55.2 55.0, 21.8, 14.2 (2C), 13.9; HRMS: calcd for $C_{18}H_{25}NNaO_8S$: 438.1199; found: 438.1208 $[M+Na]^+$.

2-Ethoxycarbonyl-2-methyl-3-tosyl-succinic diethyl ester (4b): The *ee* was determined by HPLC using a Daicel Chiralpak OJ column (hexane/*i*PrOH 95:5); flow rate 1.0 mL min^{-1}; $\tau_{major} = 30.1$ min; $\tau_{minor} = 38.2$ min). $[\alpha]_D^{RT} = -26.2^\circ$ ($c = 10.0$ mg mL^{-1}, 85% *ee*); ^{1}H NMR: $\delta = 7.67$ (d, $J = 8.4$, 2H, Ar**H**), 7.22 (d, $J = 8.4$, 2H, Ar**H**), 5.42 (d, $J = 9.8$, 1H, N**H**), 4.30 (d, $J = 9.8$, 1H, C**H**), 4.04–4.17 (m, 4H, $(CO_2CH_2CH_3)_2$), 3.82 (q, $J = 7.1$, 2H, OCH_2CH_3), 2.34 (s, 3H, $ArCH_3$), 1.56 (s, 3H, CH_3), 1.21 (t, $J = 7.2$, 3H, $CO_2CH_2CH_3$), 1.19 (t, $J = 7.2$, 3H, $CO_2CH_2CH_3$), 0.94 (t, $J = 7.1$, 3H, OCH_2CH_3); ^{13}C NMR: $\delta = 170.0$, 169.8, 168.6, 143.6, 136.9, 129.6 (2C), 127.3 (2C), 62.0, 61.9, 61.8, 59.9, 58.1, 21.4, 20.2, 13.8 (2C), 13.5; HRMS: calcd for $C_{19}H_{27}NNaO_8S$: 452.1355; found: 452.1347 $[M+Na]^+$.

2-Ethoxycarbonyl-2-ethyl-3-tosyl-succinic diethyl ester (4c): The *ee* was determined by HPLC using a Daicel Chiralpak AS column (hexane/*i*PrOH 99:1); flow rate 1.0 mL min^{-1}; $\tau_{major} = 53.4$ min; $\tau_{minor} = 66.5$ min). $[\alpha]_D^{RT} = -10.1^\circ$ ($c = 10.0$ mg mL^{-1}, 56% *ee*); ^{1}H NMR: $\delta = 7.72$ (d, $J = 8.2$, 2H, Ar**H**), 7.28 (d, $J = 8.2$, 2H, Ar**H**), 5.64 (d, $J = 10.2$, 1H, N**H**), 4.41 (d, $J = 10.2$, 1H, C**H**), 4.13–4.26 (m, 4H, $(CO_2CH_2CH_3)_2$), 3.77–3.82 (m, 2H, OCH_2CH_3), 2.40 (s, 3H, $ArCH_3$), 2.05 (q, $J = 7.6$, 2H, CH_3CH_2), 1.24–1.31 (m, 6H, $(CO_2CH_2CH_3)_2$), 0.94–1.05 (m, 6H, CH_2CH_3, OCH_2CH_3); ^{13}C NMR: $\delta = 169.5$, 169.0, 168.8, 143.4, 137.1, 129.3 (2C), 127.2 (2C), 61.9, 61.7, 61.6, 61.3, 59.5, 27.4, 21.4, 13.8, 13.7, 13.4, 9.3; HRMS: calcd for $C_{20}H_{29}NNaO_8S$: 466.1512; found: 466.1519 $[M+Na]^+$.

2-Butyl-2-ethoxycarbonyl-3-tosyl-succinic diethyl ester (4d): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 99:1); flow rate 1.0 mL min^{-1}; $\tau_{major} = 84.2$ min; $\tau_{minor} = 75.2$ min). $[\alpha]_D^{RT} = -23.2^\circ$ ($c = 10.0$ mg mL^{-1}, 91% *ee*). ^{1}H NMR: $\delta = 7.67$ (d, $J = 8.0$, 2H, Ar**H**), 7.22 (d, $J = 8.0$, 2H, Ar**H**), 5.60 (d, $J = 10.4$, 1H, N**H**), 4.36 (d, $J = 10.4$, 1H, C**H**), 4.07–4.19 (m, 4H, $(CO_2CH_2CH_3)_2$), 3.71–3.85 (m, 2H, OCH_2CH_3), 2.34 (s, 3H, $ArCH_3$), 1.85 (t, $J = 8.2$, 2H, CH_2), 1.17–1.37 (m, 10H, $2 \times CH_2$, $(CO_2CH_2CH_3)_2$), 0.96 (t, $J = 7.4$, 3H, OCH_2CH_3), 0.81 (t, $J = 7.2$, 3H, CH_3); ^{13}C NMR: $\delta = 169.5$, 169.0, 168.9, 143.4, 137.1, 129.3 (2C), 127.2 (2C), 61.8, 61.7, 61.6, 60.8, 59.6, 33.7, 26.6, 22.8, 21.3, 13.8, 13.7, 13.6, 13.4; HRMS: calcd for $C_{22}H_{33}NNaO_8S$: 494.1825; found: 494.1821 $[M+Na]^+$.

2-Ethoxycarbonyl-2-isobutyl-3-tosyl-succinic diethyl ester (4e): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 95:5); flow rate 1.0 mL min^{-1}; $\tau_{major} = 29.6$ min; $\tau_{minor} = 26.0$ min). $[\alpha]_D^{RT} = -20.3^\circ$ ($c = 10.0$ mg mL^{-1}, 96% *ee*); ^{1}H NMR: $\delta = 7.66$ (d, $J = 8{,}0$, 2H, Ar**H**), 7.21 (d, $J = 8.0$, 2H, Ar**H**), 5.66 (d, $J = 10.0$, 1H, N**H**), 4.36 (d, $J = 10.0$, 1H, C**H**), 4.08–4.18 (m, 4H, $(CO_2CH_2CH_3)_2$), 3.65–3.82 (m, 2H, OCH_2CH_3), 2.34 (s, 3H, $ArCH_3$), 1.70–1.89 (m, 3H, CH_2CH), 1.23 (t, $J = 7.2$, 3H, OCH_2CH_3), 1.20 (t, $J = 7.2$, 3H, OCH_2CH_3), 0.96 (t, $J = 7.2$, 3H, OCH_2CH_3), 0.83 (d, $J = 6.4$, 3H, CH_3), 0.80 (d, $J = 6.4$, 3H, CH_3); ^{13}C NMR: $\delta = 169.4$, 169.1, 168.7, 143.4, 137.1, 129.3 (2C), 127.1 (2C), 61.9, 61.6 (2C), 60.1, 59.9, 42.1, 24.5, 23.8, 23.6, 21.3, 13.7, 13.6, 13.4; HRMS: calcd for $C_{22}H_{33}NNaO_8S$: 494.1825; found: 494.1817 $[M+Na]^+$.

2-Benzyl-2-ethoxycarbonyl-3-tosyl-succinic diethyl ester (4f): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 95:5); flow rate 1.0 mL min^{-1}; $\tau_{major} = 51.9$ min; $\tau_{minor} = 40.1$ min). $[\alpha]_D^{RT} = -52.7^\circ$ ($c = 10.0$ mg mL^{-1}, 94% *ee*); ^{1}H NMR: $\delta = 7.67$ (d, $J = 8.4$, 2H, Ar**H**), 7.13–7.23 (m, 7H, Ar**H**), 5.70 (d, $J = 10.4$, 1H, N**H**), 4.50 (d, $J = 10.4$, 1H, C**H**), 4.06 (q, $J = 7.2$, 2H, OCH_2CH_3), 3.96 (q, $J = 7.2$, 2H, OCH_2CH_3), 3.68–3.84 (m, 2H, OCH_2CH_3), 3.28 (dd, $J = 23.2$, $J = 14.0$, 2H, $ArCH_2$), 2.34 (s, 3H, $ArCH_3$), 1.12 (t, $J = 7.2$, 3H, OCH_2CH_3), 1.02 (t, $J = 7{,}2$, 3H, OCH_2CH_3), 0.97 (t, 7.2, 3H, OCH_2CH_3); ^{13}C NMR: $\delta = 168.3$, 168.2, 168.1, 143.1, 136.6, 134.9, 130.3 (2C), 129.0 (2C), 127.4 (2C), 126.8 (2C), 126.6, 61.8, 61.5 (2C), 61.4, 59.4, 38.9, 21.0, 13.3, 13.1 (2C); HRMS: calcd for $C_{25}H_{31}NNaO_8S$: 528.1668; found: 528.1668 $[M+Na]^+$.

Decarboxylation of 2-ethoxycarbonyl-3-tosyl-succinic diethyl ester (4a): Mannich adduct **4a** (100 mg) was stirred in 0.5 N NaOH (10 mL) at room temperature for 2 h. The mixture was neutralised with 1N $KHSO_4$ and stirred at 50 °C over night. Water was removed in vacuo and the residue was redissolved in EtOH. H_2SO_4 (0.5 mL) was added, and the solution was heated under reflux over night. After cooling to room temperature, NaOH was added to pH 8–9. The mixture was extracted with Et_2O (3 ×), and the combined organic extracts was washed with sat. NaCl, dried with Na_2SO_4 and concentrated in vacuo. Absolute configuration was determined by optical rotation, compared to the corresponding tosylated amino ester prepared from L-aspartic acid. Esterfication of L-aspartic acid was carried out as mentioned above. The just prepared ester was dissolved in pyridine (2 mL) and excess tosylchloride was added. Tosylation of the amino group was accomplished by stirring this solution at room temperature over night. The product which precipitated as white crystals, was filtered off and washed with water and diluted hydrochloric acid. The L-*N*-tosyl-aspartic acid diethyl ester was recrystallized in EtOAc/pentane.

(1-Isopropyl-2-methyl)-propyl 2-methyl-3-oxopentanoate (8c): ^{1}H NMR: $\delta = 4.62$ (t, $J = 6.2$, 1H, $OCH(CH_3)_2$), 3.59 (q, $J = 7.2$, 1H, $CHCH_3$), 2.61 (m, 2H, CH_2CH_3), 1.90 (sext, $J = 6.6$, 2H, $CH(CH_3)_2$), 1.36 (d, $J = 7.2$, 3H, $CHCH_3$), 0.92–0.83 (m, 12H, $CH(CH_3)$); ^{13}C NMR: $\delta = 206.6$, 170.6, 83.7, 52.6, 35.4, 29.4, 19.7, 19.7, 17.2, 17.0, 13.0, 7.6; HRMS: calcd for $C_{13}H_{24}NaO_3$: 251.1623; found: 251.1310 $[M+Na]^+$.

(9*H*-Fluoren-9-yl) 2-methyl-3-oxopentanoate (8d): ^{1}H NMR: $\delta = 7.67$ (d, $J = 7.7$, 2H, Ar**H**), 7.53 (m, 2H, Ar**H**), 7.42 (t, $J = 7.7$, 2H, Ar**H**), 7.31 (t, $J = 7.7$, 2H, Ar**H**), 6.84, (s, 1H, OC**H**), 3.66 (q, $J = 7.4$, 1H, $CHCH_3$), 2.57 (m, 2H, CH_2CH_3), 1.44 (d, $J = 7.4$, 3H, CH_3CH), 1.04 (t, $J = 7.1$, 3H, CH_2CH_3); ^{13}C NMR: $\delta = 206.1$, 171.5, 141.5, 141.0, 140.9, 129.6, 129.5, 127.9, 127.9, 125.8, 125.7, 120.1, 75.7, 52.6, 34.7, 13.0, 7.6; HRMS: calcd for $C_{19}H_{18}O_3$: 317.1154, found: 317.1155 $[M+Na]^+$.

Cyclohexyl 2-methyl-3-oxopentanoate (8e): ^{1}H NMR: $\delta = 4.79$ (m, 1H, $OCH(CH_2)_2$), 3.48 (q, 1H, $J = 7.0$, $CHCH_3$), 2.55 (m, 2H, CH_2CH_3), 1.85–1.63 (m, 4H, CH_2), 1.54–1.27 (m, 6H, CH_2), 1.33 (d, $J = 7.0$, 3H, $CHCH_3$), 1.06 (t, $J = 7.2$, CH_2CH_3); ^{13}C NMR: $\delta = 206.6$, 170.1, 73.5, 52.8, 34.6,31.3, 21.2, 25.5, 23.5, 12.7, 7.7; HRMS: calcd for $C_{10}H_{20}NaO_3$: 235.1310; found: 235.1230 $[M+Na]^+$.

Phenyl 2-methyl-3-oxopentanoate (8g): ^{1}H NMR: $\delta = 7.40$ (t, $J = 7.3$, 2H, Ar**H**), 7.25 (t, $J = 7.3$, 1H, Ar**H**), 7.10 (d, $J = 7.3$, 2H, Ar**H**), 3.79 (q, $J = 6.9$, 1H, $CHCH_3$), 2.71 (m, 2H, CH_3CH_2CO), 1.49 (d, $J = 6.9$, 3H, $CHCH_3$), 1.13 (t, 7.3, 3H, CH_2CH_3); ^{13}C NMR: $\delta = 206.0$, 169.2, 150.4, 129.4, 126.1, 121.2, 52.5, 34.6, 12.9, 7.7; HRMS: calcd for $C_{12}H_{14}NaO_3$: 229.0841; found: 229.0844 $[M+Na]^+$.

Adamantyl 2-methyl-3-oxopentanoate (8h): ^{1}H NMR: $\delta = 3.41$ (q, $J = 7.1$, 1H, $CHCH_3$), 2.56 (m, 2H, CH_2CH_3), 2.16 (s, 3H, C**H**), 2.09 (s, 6H, CH_2), 1.66, (s, 6H, CH_2), 1.28 (d, $J = 7.1$, 3H, $CHCH_3$), 1.07 (t, $J = 7.2$, 3H, CH_2CH_3); ^{13}C NMR: $\delta = 206.9$, 196.6, 81.6, 53.7, 41.1, 36.0, 34.5, 30.6, 12.7, 7.8; HRMS: calcd for $C_{19}H_{18}NaO_3$: 317.1154; found: 317.1155 $[M+Na]^+$.

***tert*-Butyl 1-phenyl-2-methyl-3-oxopentanoate (8i)**: ^{1}H NMR: $\delta = 7.28$ (m, 3H, Ar**H**), 7.21 (d, $J = 6.9$, 2H, Ar**H**), 3.88 (d, $J = 15.7$, 1H, $ArCH_2CO$), 3.82 (d, $J = 15.7$, 1H, $ArCH_2CO$), 3.56 (q, $J = 7.2$, 1H, $CHCH_3$), 1.46 (s, 9H, $C(CH_3)_3$), 1.28 (d, $J = 7.1$, 3H, $CHCH_3$); ^{13}C NMR: $\delta = 203.6$, 169.5, 133.5, 129.5, 128.6, 127.1, 81.8, 52.7, 48.5, 27.8, 12.7; HRMS: calcd for $C_{15}H_{20}NaO_3$: 271.1310; found: 271.1308 $[M+Na]^+$.

General procedure for catalytic asymmetric direct Mannich reaction of β-keto esters: In a oven dried Schlenk tube equipped with a magnetic stirring bar, $Cu(OTf)_2$ (9 mg, 0.025 mmol) and 2,2′-isopropylidene [(4*S*)-4-*tert*-butyl-2-oxazoline] (9.2 mg 0.026 mmol) were added. The mixture was stirred under vacuum for 2 h and filled with N_2. Dry CH_2Cl_2 (2 mL) was added and the solution was stirred for 1 h. A 0.3 M solution (1 mL) of α-imino ester (**2**) in dry CH_2Cl_2 and 0.25 mmol of the β-keto esters were added. After 16 h the product was isolated by FC.

Ethyl 3-methyl-4-oxo-3-ethoxycarbonyl-2-(tosylamino)pentanoate (7): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 92:8): flow rate 1.0 mL min^{-1}: $\tau_{major} = 33.7$ min; $\tau_{minor} = 30.9$ min; $\tau_{2nd\ diast.} = 28.8$ and 28.8 min). ^{1}H NMR: $\delta = 7.74$ (d, $J = 8.0$, 2H, Ar**H**), 7.29 (d, $J = 8.0$, 2H, Ar**H**), 5.34 (d, $J = 9.9$, 1H, N**H**), 4.35 (d, $J = 9.7$, 1H, C**H**), 4.22 (m, 2H, OCH_2CH_3), 3.85 (m, 2H, OCH_2CH_3), 2.41 (s, 3H, $ArCH_3$), 2.28 (s, 3H, $COCH_3$), 1.28 (t, $J = 7.2$, 3H, OCH_2CH_3); 0.96 (t, $J = 7.2$, 3H, OCH_2CH_3); ^{13}C NMR: $\delta = 205.7$, 170.8, 168.9, 143.5, 129.4, 127.3, 62.9, 61.9, 61.8, 59.6, 27.1, 21.4, 20.1, 13.8, 13.4; HRMS: calcd for $C_{18}H_{25}NNaO_7S$: 422.1249; found: 422.1259 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-ethoxycarbonyl-2-(tosylamino)hexanoate (9a): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 90:10): flow rate 1.0 mL min^{-1}: $\tau_{major} = 30.4$ min; $\tau_{minor} = 24.5$ min; $\tau_{2nd\ diast.} = 20.8$ and 24.5 min) and Daicel Chiralpak OJ column (hexane/*i*PrOH 90:10): flow rate 1.0 mL min^{-1}: $\tau_{major} = 17.7$ min; $\tau_{minor} = 19.9$ min; $\tau_{2nd\ diast.} = 31.9$ and 67.4 min). ^{1}H NMR: $\delta = 7.73$ (d, $J = 8.1$, 2H, Ar**H**), 7.29 (d, $J = 8.1$, 2H, Ar**H**), 5.41 (d, $J = 10.1$, 1H, N**H**), 4.36 (d, $J = 10.1$, 1H, C**H**), 4.20 (m, 2H, OCH_2), 3.84 (m, 2H, OCH_2), 2.77 (m, 1H, $COCH_2CH_3$), 2.45 (m, 1H, $COCH_2CH_3$), 2.41 (s, 3H, $ArCH_3$), 1.63 (s, 3H, CCH_3), 1.28 (t, $J = 7.0$, 3H, OCH_2CH_3), 1.03 (t, $J = 7.3$, 3H, $COCH_2CH_3$), 0.95 (t, $J = 7.0$, 3H, OCH_2CH_3); ^{13}C NMR: $\delta = 208.5$, 171.0, 169.0, 143.5,

137.0, 129.4, 129.3, 127.3, 127.2, 62.7, 62.6, 61.8, 59.7, 32.5, 21.4, 13.8, 13.4, 7.8, 7.6; HRMS: calcd for $C_{19}H_{27}NNaO_7S$: 436.1406; found: 436.1414 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-(1-naphthyl)-methoxycarbonyl-2-(tosylamino)-hexanoate (9b): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 80:20): flow rate 1.0 mL min^{-1}: $\tau_{major} = 7.3$ min; $\tau_{minor} = 7.8$ min; $\tau_{2nd\ diast.} = 6.0$ and 6.0 min). ^{1}H NMR: $\delta = 8.00$ (m, 1H, Ar**H**), 7.88 (m, 2H, Ar**H**), 7.64 (m, 2H, Ar**H**), 7.54 (m, 3H, Ar**H**), 7.45 (m, 1H, Ar**H**), 7.25 (m, 2H, Ar**H**), 5.69 (d, $J = 22.3$, 1H, OC**H**$_2$Ar), 5.50 (d, $J = 22.3$, 1H, OC**H**$_2$Ar), 5.32 (d, $J = 10.1$, 1H, N**H**), 4.36, (d, $J = 10.1$, 1H, C**H**), 3.72 (m, 2H, OC**H**$_2$), 2.67 (m, 1H, COC**H**$_2$CH$_3$), 2.36 (m, 1H, COC**H**$_2$CH$_3$), 2.41 (s, 3H, ArC**H**$_3$), 1.62 (s, 3H, CC**H**$_3$), 0.89 (t, $J = 7.3$, 3H, COC**H**$_2$CH$_3$), 0.84 (t, $J = 7.0$, 3H, OC**H**$_2$CH$_3$); ^{13}C NMR: $\delta = 208.3$, 170.9, 169.0, 143.5, 136.8, 133.6, 131.6, 130.4, 139.6, 129.4, 128.7, 128.0, 127.3, 126.6, 125.9, 125.2, 123.3, 66.1, 62.9, 61.9, 59.8, 32.5, 21.4, 20.0, 13.4, 7.7; HRMS: calcd for $C_{28}H_{31}NNaO_7S$: 548.1719; found: 548.1719 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-(1′-isopropyl-2′-methyl-propanoxycarbonyl)-2-(tosylamino)hexanoate (9c): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 80:20): flow rate 1.0 mL min^{-1}: $\tau_{major} = 7.3$ min; $\tau_{minor} = 7.8$ min; $\tau_{2nd\ diast.} = 6.0$ and 6.0 min). ^{1}H NMR: $\delta =$ 7.73 (d, $J = 8.1$, 2H, Ar**H**), 7.29 (d, $J = 8.1$, 2H, Ar**H**), 5.50 (d, $J = 9.9$, 1H, N**H**), 4.67 (t, $J = 5.8$, 1H, OC**H**(CH$_2$)$_2$), 4.44, (d, $J = 9.9$, 1H, C**H**), 3.82 (m, 2H, OC**H**$_2$), 2.71 (m, 1H, COC**H**$_2$CH$_3$), 2.41 (s, 3H, ArC**H**$_3$), 1.93 (m, 1H, C**H**(CH$_3$)$_2$), 1.67 (s, 1H, C**H**$_3$), 1.04 (t, $J = 7.1$, 3H, COCH$_2$C**H**$_3$), 0.92 – 0.83 (m, 15H, CH(C**H**$_3$), OCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 208.4$, 170.9, 168.9, 143.5, 137.0, 129.4, 129.4, 127.3, 127.3, 84.9, 62.1, 61.8, 59.7, 32.4, 29.6, 29.5, 21.4, 19.7, 19.6, 17.5, 17.4, 13.5, 7.9, 7.7; HRMS: calcd for $C_{24}H_{37}NO_7S$: 506.2188; found: 506.2185 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-(9′*H*-fluoren-9′-oxycarbonyl)-2-(tosylamino)hexanoate (9d): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 95:5): flow rate 1.0 mL min^{-1}: $\tau_{major} = 58.4$ min; $\tau_{minor} = 44.2$ min; $\tau_{2nd\ diast.} = 30.3$ and 39.7 min). ^{1}H NMR: $\delta = 7.75 – 7.27$ (m, 10H, Ar**H**), 6.80, (s, 1H, OC**H**), 5.42 (d, $J = 9.5$, 1H, N**H**), 4.40 (d, $J = 9.5$, 1H, C**H**), 3.87 (q, $J = 7.1$, 2H, OC**H**$_2$CH$_3$), 2.77 (m, 1H, COC**H**$_2$CH$_3$), 2.48 (m, 1H, COC**H**$_2$CH$_3$), 2.42 (s, 3H, ArC**H**$_3$), 1.67 (s, 1H, C**H**$_3$), 1.00 – 0.95 (m, 6H, OCH$_2$C**H**$_3$, COCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 208.4$, 171.9, 169.0, 143.5, 141.1, 141.1, 141.0, 140.9, 136.8, 129.6, 129.4, 127.8, 127.7, 127.3, 125.9, 125.7, 120.0, 76.3, 62.7, 61.9, 59.8, 32.5, 21.4, 20.2, 13.4, 1.8; HRMS: calcd for $C_{30}H_{31}NO_7S$: 572.1719; found: 572.1718 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-cyclohexoxycarbonyl-2-(tosylamino)hexanoate (9e): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 80:20): flow rate 1.0 mL min^{-1}: $\tau_{major} = 9.7$ min; $\tau_{minor} = 12.4$ min; $\tau_{2nd\ diast.} = 7.6$ and 8.6 min). ^{1}H NMR: $\delta = 7.73$ (d, $J = 8.0$, 2H, Ar**H**), 7.28 (d, $J = 8.0$, 2H, Ar**H**), 5.46 (d, $J = 9.9$, 1H, N**H**), 4.67 (sep, $J = 4.2$, 1H, OC**H**(CH$_2$)$_2$), 4.44 (d, $J = 9.9$, 1H, C**H**), 3.83 (m, 2H, OC**H**$_2$CH$_3$), 2.81 (dq, $J = 18.0$, $J = 7.2$, 1H, COC**H**$_2$CH$_3$), 2.57 (m, 1H, COC**H**$_2$CH$_3$), 2.41 (s, 3H, ArC**H**$_3$), 1.85 – 1.63 (m, 4H, C**H**$_2$), 1.61 (s, 3H, CC**H**$_3$), 1.54 – 1.27 (m, 6H, C**H**$_2$), 1.03, (t, $J = 7.2$, 3H, OCH$_2$C**H**$_3$), 1.03 (t, $J = 7.2$, 3H, COCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 208.5$, 170.4, 168.9, 143.4, 136.9, 129.4, 127.2, 74.3, 62.6, 61.7, 59.7, 33.4, 32.6, 31.1, 25.1, 23.4, 21.4, 21.0, 20.2, 13.4, 7.8; HRMS: calcd for $C_{23}H_{33}NNaO_7S$: 490.1875; found: 490.1877 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-(diphenyl)-methoxycarbonyl-2-(tosylamino)hexanoate (9f): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 90:10): flow rate 1.0 mL min^{-1}: $\tau_{major} = 42.6$ min; $\tau_{minor} = 28.4$ min; $\tau_{2nd\ diast.} = 19.1$ and 22.7 min). ^{1}H NMR: $\delta = 7.70$ (d, $J = 8.4$, 2H, Ar**H**), 7.38 – 7.25 (m, 12H, Ar**H**), 5.41 (d, $J = 9.9$, 1H, N**H**), 4.39 (d, $J =$ 9.9, 1H, C**H**), 3.68 (m, 2H, OC**H**$_2$CH$_3$), 2.71 (m, 1H, COC**H**$_2$CH$_3$), 2.41 (m, 1H, COC**H**$_2$CH$_3$) and (s, 3H, ArC**H**$_3$), 1.67 (s, 3H, CC**H**$_3$), 1.00 (t, $J = 7.1$, 3H, OCH$_2$C**H**$_3$), 0.80 (t, $J = 7.1$, 3H, COCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 208.1$, 170.0, 168.7, 143.5, 139.3, 139.1, 136.7, 129.4, 128.6, 128.4, 128.1, 127.3, 127.1, 126.9, 78.3, 62.6, 61.9, 59.8, 32.6, 21.4, 20.1, 13.3, 7.7; HRMS: calcd for $C_{30}H_{33}NNaO_7S$: 574.1875, found: 574.1876 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-phenoxycarbonyl-2-(tosylamino)hexanoate (9g): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 90:10): flow rate 1.0 mL min^{-1}: $\tau_{major} = 38.6$ min; $\tau_{minor} =$ 34.7 min. ^{1}H NMR: $\delta = 7.56$ (d, $J = 8.0$, 2H, Ar**H**), 7.40 (t, $J = 7.9$, 2H, Ar**H**), 7.32 – 7.25 (m, 3H, Ar**H**), 7.14 (d, $J = 8.0$, 2H, Ar**H**), 5.38 (d, $J = 10.2$, 1H, N**H**), 4.51 (d, $J = 10.2$, 1H, C**H**), 3.90 (m, 2H, OC**H**$_2$CH$_3$), 2.91 (m, 1H, COC**H**$_2$CH$_3$), 2.56 (m, 1H, COC**H**$_2$CH$_3$), 2.42 (s, 3H, ArC**H**$_3$), 1.83 (s, 3H, CC**H**$_3$), 1.08 (t, $J = 7.0$, 3H, OCH$_2$C**H**$_3$), 0.95 (t, $J = 7.0$, 3H, COCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 208.3$, 169.8, 169.1, 150.1, 143.7, 137.0, 129.6, 129.5, 127.4, 126.3, 121.2, 62.9, 62.1, 59.9, 32.6, 21.5, 20.2, 13.5, 7.9; HRMS: calcd for $C_{23}H_{27}NO_7S$: 484.1406; found: 484.1410 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-adamantoxycarbonyl-2-(tosylamino)hexanoate (9h): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 95:5): flow rate 1.0 mL min^{-1}: $\tau_{major} = 18.0$ min; $\tau_{minor} = 13.0$ min; $\tau_{2nd\ diast.} = 9.2$ and 11.8 min). $[\alpha]_D = -18.8°$ ($c =$ 52 mg mL^{-1}, 90 % *ee*); ^{1}H NMR: $\delta = 7.73$ (d, $J = 8.0$, 2H, Ar**H**), 7.28 (d, $J = 8.0$, 2H, Ar**H**), 5.37 (d, $J = 10.0$, 1H, N**H**), 4.30 (d, $J = 10.0$, 1H, C**H**), 3.83 (q, $J = 6.8$, 2H, OC**H**$_2$CH$_3$), 2.77 (m, 1H, COC**H**$_2$CH$_3$), 2.45 (m, 1H, COC**H**$_2$CH$_3$), 2.41 (s, 3H, ArC**H**$_3$), 2.18 (s, 3H, C**H**), 2.13 (s,6H, C**H**$_2$), 1.66 (s, 6H, C**H**$_2$), 1.57 (s, 3H, CC**H**$_3$), 0.96, (t, $J = 7.4$, 3H, OCH$_2$C**H**$_3$), 0.91 (t, $J = 7.2$, 3H, COCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 208.7$, 169.7, 169.2, 143.5, 137.0, 129.4, 127.4, 83.1, 63.4, 61.7, 59.8, 41.0, 36.0, 30.8, 21.4, 13.6, 8.0; HRMS: calcd for $C_{27}H_{37}NO_7S$: 542.2188, found: 542.2186 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-*tert*-butoxycarbonyl-2-(tosylamino)hexanoate (9i): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 95:5): flow rate 1.0 mL min^{-1}: $\tau_{major} = 36.6$ min; $\tau_{minor} = 22.6$ min; $\tau_{2nd\ diast.} = 14.4$ and 38.1 min). $[\alpha]_D = -21.6°$ ($c =$ 43 mg mL^{-1}, 92 % *ee*); ^{1}H NMR: $\delta = 7.73$ (d, $J = 8.4$, 2H, Ar**H**), 7.28 (d, $J = 8.4$, 2H, Ar**H**), 5.36 (d, $J = 10.4$, 1H, N**H**), 4.31 (d, $J = 10.4$, 1H, C**H**), 3.86 (q, $J = 7.3$, 2H, OC**H**$_2$CH$_3$), 2.76 (m, 1H, COC**H**$_2$CH$_3$), 2.47 (m, 1H, COC**H**$_2$CH$_3$), 2.41 (s, 3H, ArC**H**$_3$), 1.58 (s, 3H, CC**H**$_3$), 1.49 (s, 9H, C(C**H**$_3$)$_3$), 1.03 (t, $J = 7.3$, 3H, OCH$_2$C**H**$_3$), 0.96 (t, $J = 7.3$, 3H, COCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 208.6$, 169.5, 169. 0, 143.5, 137.0, 129.4, 127.3, 82.9, 62.3, 61.6, 59.7, 32.5, 27.7, 21.4, 13.5, 7.9; HRMS: calcd for $C_{21}H_{31}NNaO_7S$: 464.1719, found: 464.1715 $[M+Na]^+$.

Ethyl 3-methyl-4-oxo-3-*tert*-butoxycarbonyl-2-(tosylamino)pentanoate (11a): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 90:10): flow rate 1.0 mL min^{-1}: $\tau_{major} = 24.2$ min; $\tau_{minor} = 16.0$ min; $\tau_{2nd\ diast.} = 11.4$ and 26.5 min). $[\alpha]_D = -27.7°$ ($c =$ 38 mg mL^{-1}, 88 % *ee*); ^{1}H NMR: $\delta = 7.73$ (d, $J = 8.1$, 2H, Ar**H**), 7.28 (d, $J = 8.1$, 2H, Ar**H**), 5.34 (d, $J = 9.9$, 1H, N**H**), 4.33 (d, $J = 9.9$, 1H, C**H**), 3.85 (m, 2H, OC**H**$_2$CH$_3$), 2.41 (s, 3H, ArC**H**$_3$), 2.26 (s, 3H, COC**H**$_3$), 1.59 (s, 3H, CC**H**$_3$), 1.49 (s, 9H, C(C**H**$_3$)$_3$), 0.96 (t, $J = 7.2$, 3H, OCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 206.0$, 169.7, 169.2, 143.5, 137.0, 129.5, 127.4, 83.1, 63.6, 61.8, 59.6, 27.8, 27.2, 21.5, 20.4, 13.6; HRMS: calcd for $C_{20}H_{29}NNaO_7S$: 450.1562, found: 450.1565 $[M+Na]^+$.

Ethyl 3,5-dimethyl-4-oxo-3-*tert*-butoxycarbonyl-2-(tosylamino)hexanoate (11b): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 95:5): flow rate 1.0 mL min^{-1}: $\tau_{major} = 19.8$ min; $\tau_{minor} = 14.2$ min; $\tau_{2nd\ diast.} = 11.9$ and 32.4 min). $[\alpha]_D = -10.8°$ ($c =$ 38 mg mL^{-1}, 91 % *ee*); ^{1}H NMR: $\delta = 7.75$ (d, $J = 8.1$, 2H, Ar**H**), 7.29 (d, $J = 8.1$, 2H, Ar**H**), 5.34 (d, $J = 9.9$, 1H, N**H**), 4.31 (d, $J = 9.9$, 1H, C**H**), 3.85 (m, 2H, OC**H**$_2$CH$_3$), 3.09 (q, $J = 6.5$, 1H, COC**H**(CH$_3$)$_2$), 2.41 (s, 3H, ArC**H**$_3$), 1.64 (s, 3H, CC**H**$_3$), 1.48 (s, 9H, C(C**H**$_3$)$_3$), 1.10 (d, $J = 6.9$, 3H, CH(C**H**$_3$)$_2$), 1.05 (d, $J = 6.9$, 3H, CH(C**H**$_3$)$_2$), 0.93 (t, $J = 7.1$, 3H, OCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 213.1$, 170.0, 169.2, 143.4, 137.0, 129.4, 127.4, 83.1, 64.3, 61.7, 59.6, 37.2, 27.8, 21.5, 20.9, 20.2, 19.5, 13.6; HRMS: calcd for $C_{22}H_{33}NO_7S$: 478.1875; found: 478.1872 $[M+Na]^+$.

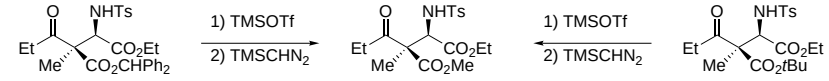
Ethyl 3-(2′-oxocyclohexyl)-3-*tert*-butoxycarbonyl-2-(tosylamino)propanoate (11c): The *ee* was determined by HPLC using a Daicel Chiralpak AS column (hexane/*i*PrOH 97:3): flow rate 1.0 mL min^{-1}: $\tau_{major} = 25.2$ min; $\tau_{minor} = 33.1$ min. $[\alpha]_D = -1.9°$ ($c = 83$ mg mL^{-1}, 86 % *ee*); ^{1}H NMR: $\delta = 7.73$ (d, $J = 8.1$, 2H, Ar**H**), 7.29 (d, $J = 8.1$, 2H, Ar**H**), 5.20 (d, $J = 9.9$, 1H, N**H**), 4.17 (d, $J = 9.7$, 1H, C**H**), 3.86 (m, 2H, OC**H**$_2$CH$_3$), 2.94 (m, 1H, C**H**$_2$), 2.41 (s, 3H, ArC**H**$_3$), 2.30 (m, 3H, C**H**$_2$), 2.04 (m, 1H, C**H**$_2$), 1.83 (m, 1H, C**H**$_2$), 1.64 (m, 2H, C**H**$_2$), 1.51 (s, 9H, C(C**H**$_3$)$_3$), 0.94 (t, $J = 7.2$, 3H, OCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 208.3$ 169.5, 168.9, 143.5, 136.9, 129.4, 127.4, 83.1, 66.3, 61.7, 59.0, 40.7, 36.0, 27.8, 26.7, 21.5, 21.1, 13.6; HRMS: calcd for $C_{22}H_{31}NNaO_7S$: 476.1719, found: 476.1716 $[M+Na]^+$.

Ethyl 5-phenyl-3-methyl-4-oxo-3-*tert*-butoxycarbonyl-2-(tosylamino)pentanoate (11d): The *ee* was determined by HPLC using a Daicel Chiralpak OD column (hexane/*i*PrOH 98:2): flow rate 1.0 mL min^{-1}: $\tau_{major} = 18.0$ min; $\tau_{minor} = 21.7$ min; $\tau_{2nd\ diast.} = 17.0$ and 20.2 min). $[\alpha]_D = +2.7°$ ($c =$ 70 mg mL^{-1}, 93 % *ee*); ^{1}H NMR: $\delta = 7.75$ (d, $J = 8.1$, 2H, Ar**H**), 7.30 (m, 5H, Ar**H**), 7.29 (d, $J = 8.1$, 2H, Ar**H**), 5.40 (d, $J = 9.9$, 1H, N**H**), 4.42 (d, $J =$ 9.9, 1H, C**H**), 4.09 (d, $J = 10.3$, 1H, ArC**H**$_2$CO), 3.86 (m, 3H, ArC**H**$_2$CO and OC**H**$_2$CH$_3$), 2.42 (s, 3H, ArC**H**$_3$), 1.71 (s, 3H, CC**H**$_3$), 1.56 (s, 9H, C(C**H**$_3$)$_3$), 0.93 (t, $J = 7.1$, 3H, OCH$_2$C**H**$_3$); ^{13}C NMR: $\delta = 205.7$, 169.7, 169.0,

143.4, 137.0, 133.7, 129.6, 129.4, 128.3, 127.2, 126.8, 83.3, 63.6, 61.7, 59.8, 45.6, 27.7, 21.4, 20.4, 13.5; HRMS: calcd for $C_{26}H_{33}NNaO_7S$: 526.1875; found: 526.1870 $[M+Na]^+$.

Ethyl 3-(3′-propenyl)-4-oxo-3-*tert*-butoxycarbonyl-2-(tosylamino)pentanoate (11e): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 95:5): flow rate 1.0 mL min^{-1}: $\tau_{major} = 27.1$ min; $\tau_{minor} = 22.8$ min; $\tau_{2nd\ diast.} = 17.0$ and 33.5 min). $[\alpha]_D = -27.7°$ ($c = 38.5$ mg mL^{-1}, 87% *ee*). ^{1}H NMR: $\delta = 7.73$ (d, $J = 8.2$, 2H, Ar**H**), 7.28 (d, $J = 8.2$, 2H, Ar**H**), 5.91 (m, 1H, $CH_2C\mathbf{H}CH_2$), 5.73 (d, $J = 10.3$, 1H, N**H**), 5.17 (m, 2H, $C\mathbf{H}_2CH$), 4.48 (d, $J = 10.3$, 1H, C**H**), 3.80 (m, 2H, $OC\mathbf{H}_2CH_3$), 2.78 (dd, $J = 14.7$, $J = 6.3$, 1H, CC**H**CH), 2.62 (dd, $J = 14.7$, $J = 6.3$, 1H, CC**H**CH), 2.60 (s, 3H, $C\mathbf{H}_3CO$), 2.41 (s, 3H, $ArC\mathbf{H}_3$), 1.49 (s, 9H, $C(C\mathbf{H}_3)_3$), 0.96 (t, $J = 7.0$, 3H, $OCH_2C\mathbf{H}_3$); ^{13}C NMR: $\delta = 205.8$, 169.2, 168.4, 143.3, 137.4, 132.0, 129.3, 127.2, 119.9, 83.5, 66.0, 59.4, 38.3, 29.2, 27.7, 21.4, 13.5; HRMS: calcd for $C_{22}H_{31}NNaO_7S$: 476.1719; found: 476.1714 $[M+Na]^+$.

Procedure for the transesterification of ethyl 3-methyl-4-oxo-3-(diphenylmethoxycarbonyl)-2-(tosylamino)hexanoate and ethyl 3-methyl-4-oxo-3-*tert*-butoxycarbonyl-2-(tosylamino)hexanoate: 0.20 mmol of **9f** or **9i** was dissolved in $CDCl_3$ (1 mL). Trimethylsilyl trifluoromethanesulfonate (0.30 mmol) was added and the solution was stirred for 20 and 60 min, respectively. After this time $TMSCHN_2$ (0.30 mmol) was added. The reaction was quenched with sat. $NaHCO_3$, extracted with Et_2O (3×10 mL) and the organic phase was dried with Na_2SO_4 and concentrated in vacuo.



9f **16** **9i**

Absolute configuration known from X-ray structure

The product was isolated by FC. Comparison of HPLC traces showed identical absolute configuration of compound **16** derived from **9f** and **9i**.

Ethyl 3-methyl-4-oxo-3-methoxycarbonyl-2-(tosylamino)hexanoate (15): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 90:10): flow rate 1.0 mL min^{-1}: $\tau_{major} = 25.1$ min; $\tau_{minor} = 23.3$ min; $\tau_{2nd\ diast.} = 19.6$ and 21.2 min). $[\alpha]_D = -39.6°$ ($c = 2$ mg mL^{-1}, 92% *ee*). ^{1}H NMR: $\delta = 7.73$ (d, $J = 8.1$, 2H, Ar**H**), 7.28 (d, $J = 8.1$, 2H, Ar**H**), 5.35 (d, $J = 9.8$, 1H, N**H**), 4.33 (d, $J = 9.8$, 1H, C**H**), 3.84 (m, 2H, $OC\mathbf{H}_2CH_3$), 3.77 (s, 3H, $OC\mathbf{H}_3$), 2.77 (m, 1H, $COC\mathbf{H}_2CH_3$), 2.52 (m, 1H, $COC\mathbf{H}_2CH_3$), 2.41 (s, 3H, $ArC\mathbf{H}_3$), 1.64 (s, 3H, $CC\mathbf{H}_3$), 1.49 (s, 9H, $C(C\mathbf{H}_3)_3$), 1.06 (t, $J = 7.3$, 3H, $OCH_2C\mathbf{H}_3$), 0.96 (t, $J = 7.3$, 3H, $COCH_2C\mathbf{H}_3$); ^{13}C NMR: $\delta = 208.5$, 171.6, 169.1, 143.6, 137.0, 129.5, 127.3, 62.7, 61.9, 59.9, 52.7, 32.5, 21.5, 20.1, 13.5, 7.9; HRMS: calcd for $C_{18}H_{25}NNaO_7S$: 422.1249; found: 422.1234 $[M+Na]^+$.

General procedure for decarboxylation of ethyl-3-methyl-4-oxo-3-*tert*-butoxycarbonyl-2-(tosylamino)alkanoate: TMSOTf (0.26 mmol) was added to the purified Mannich adduct (0.20 mmol) stirred in $CHCl_3$ (1 mL). After 1 h sat. $NaHCO_3$ (10 mL) was added to the solution. After 16 h the mixture was extracted with Et_2O (3×10 mL). The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The product was isolated by FC.

Ethyl 3-methyl-4-oxo-2-(tosylamino)hexanoate (12a): The *ee* was determined by HPLC using a Daicel Chiralpak AD column (hexane/*i*PrOH 90:10): flow rate 1.0 mL min^{-1}: $\tau_{major} = 19.3$ min; $\tau_{minor} = 22.4$ min; $\tau_{2nd\ diast.} = 13.8$ and 16.1 min). $[\alpha]_D = -44.7°$ ($c = 10$ mg mL^{-1}, 92% *ee*); ^{1}H NMR: $\delta = 7.71$ (d, $J = 8.0$, 2H, Ar**H**), 7.27 (d, $J = 8.0$, 2H, Ar**H**), 5.61 (d, $J = 9.5$, 1H, N**H**), 3.99 (dd, $J = 9.5$, 4.2, 1H, CHC**H**NH), 3.85 (m, 2H, $OC\mathbf{H}_2CH_3$), 3.20 (dq, $J = 7.3$, 4.2, 1H, $CH_3C\mathbf{H}CH$), 2.44 (m, 2H, CH_2CH_3), 2.40 (s, 3H, $ArC\mathbf{H}_3$), 1.27 (d, $J = 7.3$, 3H, $C\mathbf{H}_3CH$), 0.98 (t, $J = 7.2$, 3H, $OCH_2C\mathbf{H}_3$); ^{13}C NMR: $\delta = 212.6$, 170.2, 143.3, 137.3, 129.4, 127.2, 61.6, 57.7, 48.1, 21.4, 13.6, 13.6, 7.4; HRMS: calcd for $C_{16}H_{23}NNaO_5S$: 364.1195; found: 364.1195 $[M+Na]^+$.

(2-Oxocyclohexyl)-(toluene-4-sulfonylamino)-acetic ethyl ester (12b): The major diastereomer was isolated in 74% yield from the starting compound by FC using pentane/diethyl ether. Spectral data were in agreement with literature data.[5b] $[\alpha]_D = -36°$ (corrected to enantiopurity). Literature value for opposite enantiomer: $[\alpha]_D = +38.5°$.[5b]

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