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Enantioselective One-Pot Conjugate Addition of Grignard Reagents Followed by a Mannich Reaction

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Asymmetric addition of Grignard reagents to cyclohexenone, catalyzed by ferrocene diphosphanes, afforded chiral magnesium enolates. These enolates reacted in a one-pot arrangement with *N*-benzylidenetoluenesulfonamide to give β-amino carbonyl compounds with three contiguous stereocenters. Two major diastereoisomers (*dr* = 60:40) of product with enantioselectivities up to 95% *ee* were separated by flash chromatography.

Introduction

Rapid and efficient synthesis of complex molecules from simple starting materials is one of the major challenges of modern synthetic chemistry. Preparation of structurally complex compounds usually requires numerous synthetic steps followed by many, often laborious, purification operations. Therefore, combination of several synthetic steps into a tandem or one-pot procedure can be an elegant solution to this issue. Development of asymmetric multicomponent reactions is motivated by similar reasons.[1] A number of tandem or domino reactions have already been described that use stoichiometric amounts of reagents.[2] Their potential has also been recognized in the total synthesis of complex natural products.[3] On the other hand, catalytic enantioselective tandem transformations are less explored, although the combination of two or more asymmetric catalytic reactions in a one-pot arrangement is a very appealing concept. This approach has been realized in several ways, which usually encompass the formation of a reactive intermediate followed by its subsequent reaction with another reagent.[4] Great progress in this field has occurred in organocatalyzed tandem and domino reactions as well.[5] For metal-catalyzed processes, several approaches have been developed, such as carbonyl additions of carbanions formed by hydrogenation of alkenes or allenes.[6] Conjugate addition of organometallic reagents to Michael acceptors seems particularly well suited for this purpose.[7] Especially copper-catalyzed additions of dialkylzinc,[8] Grignard reagents,[9] organoaluminium reagents,[10] or conjugate reduction[11] produce reactive metal enolates. Such functionalized enolates are often inaccessible by other means. The metal enolate could then be conveniently trapped by an appropriate electrophile. The usefulness of this idea has been demonstrated by the trapping of enolates with aldehydes,[12] allylic cations,[13] nitroso compounds,[14] bromine,[15] or acid anhydrides.[16] Metal enolates were also enantioselectively protonated.[17] Effectiveness of enolate trapping is usually greatly enhanced by intramolecular arrangement.[18]

Gonzalez-Gomez and Foubelo have recently described the trapping of zinc enolates with chiral sulfinimines.[19] The reactive enolate was formed by enantioselective conjugate addition of dialkylzinc reagents to cyclohexenone catalyzed by a Cu–phosphoramidite complex. However, the stereochemical outcome of the enolate addition to imine was controlled by the chirality of the sulfinimine. Huang and coworkers recently used the addition of dialkylzinc reagents to chalcones followed by the reaction with an imine.[20] Successful use of more reactive Grignard reagents would complement dialkylzinc reagents and significantly broaden the scope of this transformation. An important factor is also the commercial availability of a wide range of Grignard reagents. Furthermore, we set out to investigate the reaction controlled by a single chiral catalyst without use of another source of stereogenic information. In this paper, we report the addition of Grignard reagents to cyclohexenone followed by the trapping of the resulting enolate with *N*-benzylidenetoluensulfonamide.

Results and Discussion

Feringa described the highly enantioselective addition of Grignard reagents to cyclic enones catalyzed by Cu complexes with ferrocene diphosphanes.[21] The highest enantioselectivities (up to 96% *ee*) were obtained with the *Taniaphos* ligand. This prompted us to start an investigation using the same reaction conditions: $CuBr{\cdot}SMe_2$ (5 mol-%), *Taniaphos* ligand (6 mol-%), and simple alkylmagnesium bromides in Et_2O. Addition of methylmagnesium bromide

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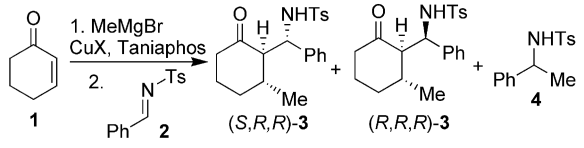
in Et_2O to cyclohex-2-enone (**1**) followed by addition of imine **2** resulted in the formation of product **3** (Table 1). Flash chromatography of the rather complex reaction mixture afforded two major diastereoisomers (Scheme 1).

Table 1. Screening of experimental conditions for the reaction of **1** with MeMgBr catalyzed by Cu/*Taniaphos*, followed by the addition of imine **2**.

Entry	CuX	Solvent	Yield [%][b]	*ee* [%][c]
1	$CuBr{\cdot}SMe_2$	Et_2O[a]/THF	32:8	31:29
2	$CuBr{\cdot}SMe_2$	Et_2O[a]/mTHF	15:10	53:56[d]
3	$CuBr{\cdot}SMe_2$	Et_2O/THF	30:21	90:90
4	$CuBr{\cdot}SMe_2$	mTHF/mTHF	17:10	12:14[d]
5	$CuBr{\cdot}SMe_2$	Et_2O/mTHF	33:27	90:89[d]
6	$CuBr{\cdot}SMe_2$	Et_2O	12:12	80:82
7	$CuBr{\cdot}SMe_2$	*t*BuOMe/mTHF	24:14	92:93[d]
8	CuCl	Et_2O/mTHF	29:19	82:84[d]
9	CuCl	*t*BuOMe/mTHF	33:26	94:94[d]
10	CuCl	*t*BuOMe/mTHF	37:15	94:95[e]
11	CuTC[f]	*t*BuOMe/mTHF	14:14	93:93
12	$Cu(OTf)_2$	*t*BuOMe/mTHF	13:10	59:70

[a] Initial concentration of cyclohexenone 0.15 M in Et_2O. [b] Isolated yields of pure diastereoisomers (*R*,*R*,*S*)-**3**/(*R*,*R*,*R*)-**3**. [c] Enantiomeric purities of diastereoisomers (*R*,*R*,*S*)-**3**/(*R*,*R*,*R*)-**3**. Determined by HPLC by using a Chiralcel OD-H column. [d] Yields and *ee* values are average values from two parallel runs. [e] Experiment on a larger scale: **1** (6.75 mmol), CuCl (0.169 mmol, 2.5 mol-%), *Taniaphos* (0.203 mmol, 3 mol-%), **2** (4.5 mmol). [f] Cu^I thiophene-2-carboxylate.



Scheme 1.

We were able to separate, purify, and identify these isomers. Unfortunately, imine **2** is rather insoluble in Et_2O; therefore, an alternative solvent had to be found. Addition of imine **2** in THF led to diastereoisomeric products with only 31 and 29% *ee* (Table 1, Entry 1). We found that the best solvent for this purpose was 2-methyltetrahydrofuran (mTHF), which led to increased enantioselectivity of the reaction. We also noticed that the enantioselectivity and diastereoselectivity of the reaction depended on the concentration of the reactants. A more diluted reaction mixture resulted in a dramatic increase in enantioselectivity, but diastereoselectivity slightly decreased (Table 1, cf. Entries 1 and 3). Further optimization of the reaction conditions led to good yields of the product and high *ee* values. Two major diastereoisomers were isolated in 60% overall combined yield (74% yield if product **3** was isolated as a mixture of diastereoisomers) and with high enantiomeric purity (94% *ee* for both diastereoisomers). Similar results were obtained with a *t*BuOMe/mTHF combination of solvents and CuCl as a copper source, and these conditions proved to be more reliable. During screening for the best reaction conditions, we noted that the outcome of the reaction is very dependent on the experimental conditions. When the reaction was performed with cyclohex-2-enone (**1**) and imine **2** mixed together from the beginning, the products of the tandem reaction (*S*,*R*,*R*)-**3** and (*R*,*R*,*R*)-**3** were obtained in a small combined yield (24%), and the major product **4** (44% yield) resulted from direct addition of MeMgBr to imine **2** (Table 1, entry 6). Byproduct **4** was isolated as a racemate.

Interestingly, the reaction proceeded well also on a larger, 6.75 mmol scale. Catalyst loading was lowered to 2.5 mol-% in this experiment, but no detrimental effect was observed (Table 1, Entry 10). Diastereoisomers isolated by flash chromatography were also recrystallized from heptane. The enantiomeric purity of (*S*,*R*,*R*)-**3** remained the same (94% *ee*), but the optical purity of (*R*,*R*,*R*)-**3** rose to 98% *ee*.

We evaluated a range of ferrocene phosphane ligands from Solvias ligand kit (Figure 1). The best results were obtained with *Taniaphos* ligand **L1**. Ligands **L3**, **L4**, and **L9** afforded product **3** in good yields, but the enantioselectivities were low (Table 2, Entries 3, 4 and 9). All other ligands afforded product **3** with practically no *ee*. The results of the tandem addition of methylmagnesium bromide and imine **2** to ketone **1** with various ferrocene phosphane ligands are summarized in Table 2.

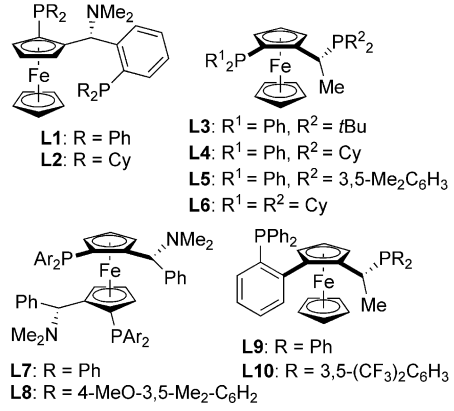


Figure 1. Structures of the ferrocene phosphane ligands used in this study.

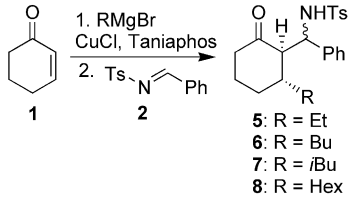
Table 2. Screening of ferrocene ligands.

Entry	Ligand	Yield [%][a]	*ee* [%][b]
1	**L1**	32:28	90:94
2	**L2**	29:7	1(–):1(+)
3	**L3**	28:24	10(–):21(+)
4	**L4**	20:9	11(–):12(–)[c]
5	**L5**	23:5	4(–):9(–)[c]
6	**L6**	28:3	2(–):1(–)
7	**L7**	30:5	1(+):7(–)
8	**L8**	24:6	0/10(–)
9	**L9**	40:13	28(–):30(–)
10	**L10**	34:7	0:3(–)

[a] Isolated yields of pure diastereoisomers (*R*,*R*,*S*)-**3**/(*R*,*R*,*R*)-**3**. [b] Enantiomeric purities of diastereoisomers (*R*,*R*,*S*)-**3**/(*R*,*R*,*R*)-**3**. Determined by HPLC by using a Chiralcel OD-H column. [c] Yields and *ee* values are average values from two parallel runs.

Besides MeMgBr, the tandem Michael addition with Mannich reaction was successfully performed also with ethylmagnesium bromide (Scheme 2). The resulting diastereoisomeric products **5** were isolated in 30 and 17% yields and

with good enantioselectivity (90 and 94% *ee*, respectively). Reaction with EtMgCl afforded product **5** in a lower yield and also with lower enantiomeric purity (Table 3, Entry 2). Similarly, the reaction with BuMgCl also gave diastereomers **6** in low yields and with mediocre *ee* (Table 3, Entry 3). Also, branched *i*BuMgBr reacted poorly (Table 3, Entry 4). Addition of hexylmagnesium bromide proceeded well and also with high enantioselectivity (Table 3, Entry 5). An attempt on the reaction with allylmagnesium bromide failed. From the complex reaction mixture only the compound resulting from the reduction of the C=N double bond of imine **2** was observed.



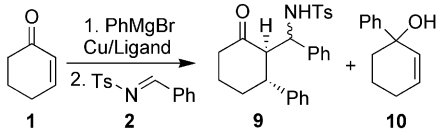
Scheme 2.

Table 3. Reaction of ketone **1** and imine **2** with various Grignard reagents (RMgX).

Entry	RMgX	Yield [%][a]	*ee* [%][b]
1	EtMgBr	30:17	90:94
2	EtMgCl	18:7	71:67
3	BuMgCl	9:5	52:–
4	*i*BuMgBr	13:4	26:–
5	HexMgBr	32:17	91:94
6	AllylMgBr	–	–
7	PhMgBr	–	–

[a] Isolated yields of diastereoisomers (*R*,*R*,*S*)/(*R*,*R*,*R*). [b] Enantiomeric purities of diastereoisomers (*R*,*R*,*S*)/(*R*,*R*,*R*). Determined by HPLC by using a Chiralcel OD-H column. Yields and *ee* values are average values from two parallel runs.

A catalytic amount of Cu/*Taniaphos* catalyst with PhMgBr did not afford the expected tandem reaction product **9** (Scheme 3). The main isolated compound, apart from starting imine **2** (23%), was compound **10** (7%), which resulted from 1,2-addition to the carbonyl group. The likely reason for this is slow transmetallation of the phenyl group from Mg to Cu, which enabled an uncatalyzed background reaction with the carbonyl group to prevail. This notion is supported by the fact that during the preparation of a racemate with a stoichiometric amount of $CuBr{\cdot}SMe_2$ and Bu_3P, the product of the tandem reaction **9** was isolated in good yield. Slow addition of PhMgBr during the experiment with *Taniaphos* ligand did not improve the situation, and compound **10** was still dominant.



Scheme 3.

Preliminary experiments with other benzaldehyde-derived imines (*N*-benzylidenemethanesulfonamide, *N*-benzylidenenaphthalene-2-sulfonamide, *tert*-butyl benzylidenecarbamate, and *N*-benzylidenebenzamide) were also performed. With MeMgBr, these reactions ran similarly to imine **2**.

The absolute configuration of the more polar diastereoisomer **3** was determined by X-ray crystallographic analysis to be (*R*,*R*,*R*). Figure 2 shows the structure of (*R*,*R*,*R*)-**3**. We also tested the configurational stability of product **3**. Its optical purity did not deteriorate even after 4 months in the refrigerator nor after 1 month at room temperature in CH_2Cl_2 solution.

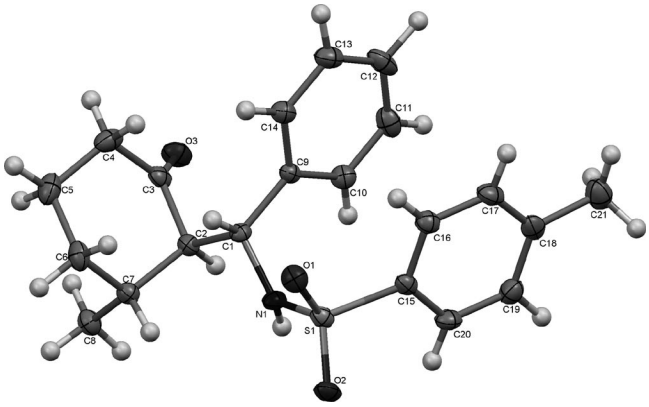


Figure 2. Thermal ellipsoid (50% probability) plot of (*R*,*R*,*R*)-**3**.[22]

The stereoselectivity of the Grignard addition is controlled by the chiral catalyst, thus (*R*,*R*)-**L1** affords the (*R*) configuration on C-3 of the product. Enolate addition to imine **2** proceeds preferentially from the *Si* face (*anti* to the alkyl group introduced by conjugate addition to the enone). This leads to the (*R*) configuration on C-2. The diastereoselectivity of this step is high; the *cis* diastereoisomer was not isolated. The facial selectivity of the imine approach is poorly controlled by the Cu/*Taniaphos* catalyst. ^1H NMR spectroscopy of the crude reaction mixture revealed a diastereomer ratio of (*S*,*R*,*R*)-**3**/(*R*,*R*,*R*)-**3** up to 60:40, but the resulting diastereoisomers can be separated by flash chromatography.

Conclusions

We have developed the first enantioselective tandem conjugate Grignard addition and Mannich reaction. Chiral enolates produced by enantioselective addition of organomagnesium halides to cyclohex-2-enone are trapped by *N*-benzylidenetoluenesulfonamide to generate separable diastereoisomers of β-amino carbonyl compounds in good yields and with high enantiomeric purity (up to 95% *ee*). Work on a wider substrate scope and improved enantio- and especially diastereocontrol is underway in our laboratory.

Experimental Section

Typical Procedure for the Tandem Reaction: Ligand **L1** (18.6 mg, 22.5 μmol) and CuCl (1.9 mg, 18.8 μmol) were dissolved in *t*Bu-

OMe (3.75 mL), and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was then cooled to –60 °C. Cyclohex-2-enone (36 mg, 0.375 mmol) was added to this solution, and the resulting mixture was stirred at –60 °C for an additional 10 min. MeMgBr (3 M in Et_2O, 188 μL, 0.563 mmol) was added over 5 min, and the resulting mixture was stirred at –60 °C for an additional 2 h. Finally, imine **2** (65 mg, 0.25 mmol), dissolved in mTHF (2.5 mL), was added, and the reaction mixture was slowly allowed to reach room temperature overnight. The reaction was then quenched with aq. NH_4Cl and extracted with Et_2O. The combined organic extracts were concentrated. The crude product was purified by column chromatography.

(*S*,*R*,*R*)-4-Methyl-*N*-[(2-methyl-6-oxocyclohexyl)(phenyl)methyl]-benzenesulfonamide [(*S*,*R*,*R*)-3]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3) afforded pure (*S*,*R*,*R*)-**3** (34 mg, 36%). M.p. 117–119 °C (heptane). $[a]_D$ = +23.7 (*c* = 0.75 in $CHCl_3$, 94% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.3 Hz, 2 H, Ar), 7.04–6.97 (m, 7 H, Ar), 6.28 (d, *J* = 10.5 Hz, 1 H, NH), 4.78 (dd, *J* = 3.1, 10.5 Hz, 1 H, CH), 2.46 (dd, *J* = 3.0, 7.5 Hz, 1 H, CH), 2.29 (s, 3 H, CH_3), 2.21–1.90 (m, 5 H), 1.77–1.40 (m, 2 H, CH_2), 1.25 (d, *J* = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.9 (CO), 142.6 (qC-SO_2), 139.7 (qC-Ph), 138.1 (qC-CH_3), 129.0 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 126.5 (CH), 64.1 (CH), 55.7 (CH), 42.7 (CH_2), 37.2 (CH), 33.6 (CH_2), 26.4 (CH_2), 21.3 (CH_3),20.3 (CH_3) ppm. $C_{21}H_{25}NO_3S$ (371.49): calcd. C 67.89, H 6.78, N 3.77; found C 67.53, H 7.03, N 3.72. HPLC (OD-H; hexane/*i*PrOH = 90:10; 0.55 mL min^{-1}): t_R(minor) = 20.3, t_R(major) = 24.7 min. IR (neat): $\tilde{\nu}$ = 3172 (m, N–H), 1697 (s, C=O), 1325 (s), 1163 (s, SO_2) cm^{-1}.

(*R*,*R*,*R*)-4-Methyl-*N*-[(2-methyl-6-oxocyclohexyl)(phenyl)methyl]-benzenesulfonamide [(*R*,*R*,*R*)-3]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3) afforded pure (*R*,*R*,*R*)-**3** (28 mg, 30%). M.p. 127–129 °C (hexane/$CHCl_3$). $[a]_D$ = +35.2 (*c* = 0.75 in $CHCl_3$, 94% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.3 Hz, 2 H, Ar), 7.10–7.01 (m, 7 H, Ar), 6.49 (d, *J* = 10.3 Hz, 1 H, NH), 4.78 (dd, *J* = 5.3, 10.3 Hz, 1 H, CH), 2.50 (ddd, *J* = 1.1, 5.3, 10.6 Hz, 1 H, CH), 2.31 (s, 3 H, CH_3), 2.25–2.10 (m, 1 H, CH), 1.94–1.70 (m, 2 H, CH_2), 1.65–1.20 (m, 4 H, CH_2), 1.25 (d, *J* = 6.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.9 (CO), 142.6 (qC-SO_2), 138.1 (qC-Ph), 137.4 (qC-CH_3), 129.1 (CH), 128.8 (CH), 128.2 (CH), 127.4 (CH), 126.8 (CH), 61.6 (CH), 57.2 (CH), 42.0 (CH_2), 34.7 (CH), 33.0 (CH_2), 23.8 (CH_2), 21.4 (CH_3), 20.3 (CH_3) ppm. $C_{21}H_{25}NO_3S$ (371.49): calcd. C 67.89, H 6.78, N 3.77; found C 68.09, H 7.10, N 3.70. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.55 mL min^{-1}): t_R(major) 28.2, t_R(minor) 23.0 min. IR (neat): $\tilde{\nu}$ = 3265 (m, N–H), 1710 (s, C=O), 1321 (s), 1153 (s, SO_2) cm^{-1}.

(*S*,*R*,*R*)-*N*-[(2-Ethyl-6-oxocyclohexyl)(phenyl)methyl]-4-methyl-benzenesulfonamide [(*S*,*R*,*R*)-5]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3) afforded pure (*S*,*R*,*R*)-**5** (30 mg, 32%). M.p. 118–120 °C (hexane). $[a]_D$ = +29.5 (*c* = 0.75 in $CHCl_3$, 90% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.41 (m, 2 H, Ar), 7.10–6.95 (m, 7 H, Ar), 6.18 (d, *J* = 10.2 Hz, 1 H, CH), 4.77 (dd, *J* = 10.2, 4.4 Hz, 1 H, CH), 2.58 (dd, *J* = 8.6, 4.3 Hz, 1 H, CH), 2.34–2.13 (m, 2 H, CH_2), 2.28 (s, 3 H, CH_3), 2.08–1.85 (m, 3 H, CH + CH_2), 1.78–1.62 (m, 2 H, CH_2), 1.61–1.43 (m, 2 H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.4 (CO), 142.6 (qC-SO_2), 139.6 (qC-Ph), 138.1 (qC-CH_3), 129.0 (CH), 128.0 (CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 61.4 (CH), 55.7 (CH), 42.3 (CH_2), 42.0 (CH), 28.5 (CH_2), 25.7 (CH_2), 25.3 (CH_2), 21.3 (CH_3),10.0 (CH_3) ppm. $C_{22}H_{27}NO_3S$ (385.52): calcd. C 68.54, H 7.06, N 3.63; found C 68.52, H 7.30, N 3.53. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.6 mL min^{-1}): t_R(minor) = 19.6, t_R(major) = 27.2 min. IR (neat): $\tilde{\nu}$ = 3205 (m, N–H), 1700 (s, C=O), 1328 (s), 1159 (s, SO_2) cm^{-1}.

(*R*,*R*,*R*)-*N*-[(2-Ethyl-6-oxocyclohexyl)(phenyl)methyl]-4-methyl-benzenesulfonamide [(*R*,*R*,*R*)-5]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3) afforded pure (*R*,*R*,*R*)-**5** (17 mg, 18%). M.p. 111–113 °C (hexane). $[a]_D$ = +30.4 (*c* = 0.75 in $CHCl_3$, 94% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.2 Hz, 2 H, Ar), 7.22–6.90 (m, 7 H, Ar), 6.33 (d, *J* = 10.1 Hz, 1 H, CH), 4.67 (dd, *J* = 10.0, 6.0 Hz, 1 H, CH), 2.62 (dd, *J* = 8.7, 6.2 Hz, 1 H, CH), 2.42–2.23 (m, 1 H), 2.31 (s, 3 H, CH_3), 2.22–2.07 (m, 1 H), 1.98–1.78 (m, 2 H, CH_2), 1.70–1.20 (m, 5 H), 0.88 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.2 (CO), 142.7 (qC-SO_2), 138.0 (qC-Ph), 137.4 (qC-CH_3), 129.1 (CH), 128.5 (CH),128.2 (CH) 127.4 (CH), 126.8 (CH), 59.6 (CH), 57.0 (CH), 41.8 (CH_2), 40.1 (CH), 27.9 (CH_2), 25.6 (CH_2), 23.4 (CH_2), 21.4 (CH_3),10.3 (CH_3) ppm. $C_{22}H_{27}NO_3S$ (385.52): calcd. C 68.54, H 7.06, N 3.63; found C 68.02, H 7.02, N 3.48. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.6 mL min^{-1}): t_R(major) = 15.9, t_R(minor) = 20.3 min. IR (neat): $\tilde{\nu}$ = 3267 (m, N–H), 1708 (s, C=O), 1320 (s), 1152 (s, SO_2) cm^{-1}.

(*S*,*R*,*R*)-*N*-[(2-Butyl-6-oxocyclohexyl)(phenyl)methyl]-4-methyl-benzenesulfonamide [(*S*,*R*,*R*)-6]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2; 83:14:3 and CH_2Cl_2 with 5% MeOH) afforded pure (*S*,*R*,*R*)-**6** (11 mg, 11%). M.p. 126–128 °C (EtOAc/hexane). $[a]_D$ = +21.4 (*c* = 0.35 in $CHCl_3$, 73% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.3 Hz, 2 H, Ar), 7.09–6.96 (m, 7 H, Ar), 6.12 (d, *J* = 10.0 Hz, 1 H, NH), 4.77 (dd, *J* = 4.9, 10.0 Hz, 1 H, CH), 2.55 (dd, *J* = 4.7, 8.3 Hz, 1 H, CH), 2.29 (s, 3 H, CH_3), 2.32–2.13 (m, 2 H, CH_2), 2.08–1.84 (m, 3 H), 1.79–1.55 (m, 2 H, CH_2), 1.54–1.35 (m, 2 H, CH_2), 1.35–1.13 (m, 4 H, CH_2), 0.91 (t, *J* = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.4 (CO), 142.6 (qC-SO_2), 139.6 (qC-Ph), 138.1 (qC-CH_3), 129.0 (CH), 128.0 (CH), 126.9 (CH), 126.86 (CH), 126.7 (CH), 61.9 (CH), 55.9 (CH), 42.1 (CH_2), 40.6 (CH) 32.5 (CH_2), 28.8 (CH_2), 28.1 (CH_2),25.6 (CH_2), 22.8 (CH_2),21.3 (CH_3), 14.1 (CH_3) ppm. $C_{24}H_{31}NO_3S$ (413.57): calcd. C 69.70, H 7.56, N 3.39; found C 69.97, H 8.03, N 3.30. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.6 mL min^{-1}): t_R(minor) = 14.2, t_R(major) = 23.2 min. IR (neat): $\tilde{\nu}$ = 3193 (m, N–H), 1699 (s, C=O), 1333 (s), 1160 (s, SO_2) cm^{-1}.

(*R*,*R*,*R*)-*N*-[(2-Butyl-6-oxocyclohexyl)(phenyl)methyl]-4-methyl-benzenesulfonamide [(*R*,*R*,*R*)-6]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2; 83:14:3 and CH_2Cl_2 with 5% MeOH) afforded pure (*R*,*R*,*R*)-**6** (6 mg, 6%). M.p. 133–136 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.43 (m, 2 H, Ar), 7.15–7.00 (m, 7 H, Ar), 6.25 (d, *J* = 10.1 Hz, 1 H), 4.67 (dd, *J* = 6.1, 10.1 Hz, 1 H), 2.59 (ddd, *J* = 1.0, 6.1, 9.4 Hz, 1 H), 2.32 (s, 3 H, CH_3), 2.30–2.23 (m, 1 H), 2.23–2.08 (m, 1 H), 1.96–1.80 (m, 2 H, CH_2), 1.70–1.40 (m, 3 H), 1.39–1.19 (m, 5 H), 1.19–1.05 (m, 1 H), 0.89 (t, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.2 (CO), 142.8 (qC-SO_2), 138.1 (qC-Ph), 137.5 (qC-CH_3), 129.2 (CH), 128.5 (CH), 128.2 (CH), 127.5 (CH), 126.9 (CH), 60.0 (CH), 57.1 (CH), 41.8 (CH_2), 38.9 (CH) 32.8 (CH_2), 28.4 (CH_2), 28.3 (CH_2),23.4 (CH_2), 22.8 (CH_2), 21.4 (CH_3), 14.0 (CH_3) ppm. $C_{24}H_{31}NO_3S$ (413.57): calcd. C 69.70, H 7.56, N 3.39; found C 69.22, H 7.59, N 3.26. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.6 mL min^{-1}): t_R(minor) = 12.4, t_R(major) = 16.5 min. IR (neat): $\tilde{\nu}$ = 3249 (m, N–H), 1704 (s, C=O), 1333 (s), 1184 (s, SO_2) cm^{-1}.

(*S*,*R*,*R*)-*N*-[(2-Isobutyl-6-oxocyclohexyl)(phenyl)methyl]-4-methyl-benzenesulfonamide [(*S*,*R*,*S*)-7]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3 and CH_2Cl_2 with 5% MeOH) afforded pure (*S*,*R*,*R*)-**7** (14 mg, 14%). M.p. 163–165 °C (heptane).

$[\alpha]_D$ = +10.0 (*c* = 0.45 in $CHCl_3$, 34% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.39 (m, 2 H, $ArSO_2$), 7.09–6.94 (m, 7 H, Ar), 5.98 (d, *J* = 9.7 Hz, 1 H, NH), 4.80 (dd, *J* = 6.0, 9.7 Hz, 1 H, CH), 2.46 (ddd, *J* = 1.0, 6.2, 7.2 Hz, 1 H, CH), 2.28 (s, 3 H, CH_3), 2.39–2.16 (m, 2 H, CH_2), 2.13–1.87 (m, 3 H), 1.83–1.67 (m, 1 H, CH_2), 1.65–1.45 (m, 2 H), 1.41–1.24 (m, 1 H), 1.21–1.11 (m, 1 H), 0.80 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.77 (d, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.3 (CO), 142.6 (qC-SO_2), 139.3 (qC-Ph), 138.0 (qC-CH_3), 129.0 (CH), 128.0 (CH), 127.0 (CH), 126.9 (CH), 62.6 (CH), 56.3 (CH), 42.5 (CH_2), 41.5 (CH_2) 37.9 (CH), 28.2 (CH_2), 24.99 (CH_2), 24.98 (CH), 23.4 (CH_3), 21.44 (CH_3), 21.34 (CH_3) ppm. $C_{24}H_{31}NO_3S$ (413.57): calcd. C 69.70, H 7.56, N 3.39; found C 69.47, H 7.48, N 3.36. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.6 mL min^{-1}): t_R(minor) = 14.6, t_R(major) = 24.2 min. IR (neat): $\tilde{\nu}$ = 3208 (m, N–H), 1698 (s, C=O), 1333 (s), 1165 (s, SO_2) cm^{-1}.

(*R*,*R*,*R*)-*N*-[(2-Isobutyl-6-oxocyclohexyl)(phenyl)methyl]-4-methylbenzenesulfonamide [(*R*,*R*,*S*)-7]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3 and CH_2Cl_2 with 5% MeOH) afforded pure (*R*,*R*,*R*)-**7** (5 mg, 5%). M.p. 149–151 °C (heptane). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.42 (m, 2 H, $ArSO_2$), 7.14–6.98 (m, 7 H, Ar), 6.18 (d, *J* = 10.0 Hz, 1 H, NH), 4.69 (dd, *J* = 6.4, 10.0 Hz, 1 H, CH), 2.52 (ddd, *J* = 1.0, 6.5, 8.3 Hz, 1 H, CH), 2.32 (s, 3 H, CH_3), 2.32–2.22 (m, 1 H), 2.21–2.08 (m, 1 H), 2.02–1.69 (m, 3 H), 1.68–1.41 (m, 2 H, CH_2), 1.41–1.08 (m, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.64 (d, *J* = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.2 (CO), 142.7 (qC-SO_2), 138.1 (qC-Ph), 137.4 (qC-CH_3), 129.2 (CH), 128.5 (CH), 128.2 (CH), 127.6 (CH), 126.9 (CH), 60.8 (CH), 57.3 (CH), 42.7 (CH_2), 41.7 (CH_2) 36.7 (CH), 28.0 (CH_2), 24.9 (CH), 24.0 (CH_3), 23.3 (CH_2), 21.4 (CH_3), 21.1 (CH_3) ppm. $C_{24}H_{31}NO_3S$ (413.57): calcd. C 69.70, H 7.56, N 3.39; found C 69.65, H 7.67, N 3.22. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.6 mL min^{-1}): t_R(minor) = 11.1, t_R(major) = 14.2 min. IR (neat): $\tilde{\nu}$ = 3319 (m, N–H), 1698 (s, C=O), 1333 (s), 1160 (s, SO_2) cm^{-1}.

(*S*,*R*,*R*)-*N*-[(2-Hexyl-6-oxocyclohexyl)(phenyl)methyl]-4-methylbenzenesulfonamide [(*S*,*R*,*R*)-8]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3 and CH_2Cl_2 with 5% MeOH) afforded pure (*S*,*R*,*R*)-**8** (36 mg, 32%). M.p. 94–97 °C (hexane). $[\alpha]_D$ = +28.2 (*c*=0.63 in $CHCl_3$, 93% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.50 (m, 2 H, $ArSO_2$), 7.12–6.90 (m, 7 H, Ar), 6.08 (d, *J* = 10.0 Hz, 1 H, NH), 4.77 (dd, *J* = 4.8, 10.0 Hz, 1 H, CH), 2.54 (dd, *J* = 4.7, 8.4 Hz, 1 H, CH), 2.36–2.12 (m, 1 H), 2.29 (s, 3 H, CH_3), 2.06–1.83 (m, 3 H), 1.81–1.54 (m, 2 H, CH_2), 1.53–1.01 (m, 10 H, CH_2), 0.98–0.79 (m, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.4 (CO), 142.6 (qC-SO_2), 139.6 (qC-Ph), 138.1 (qC-CH_3), 129.0 (CH), 128.0 (CH), 126.9 (CH), 126.86 (CH), 126.7 (CH), 61.9 (CH), 55.8 (CH), 42.1 (CH_2), 40.7 (CH) 32.8 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 22.6 (CH_2),21.4 (CH_3), 14.1 (CH_3) ppm. $C_{26}H_{35}NO_3S$ (441.63): calcd. C 70.71, H 7.99, N 3.17; found C 70.65, H 7.99, N 3.09. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.6 mL min^{-1}): t_R(minor) = 13.2, t_R(major) = 19.8 min. IR (neat): $\tilde{\nu}$ = 3260 (m, N–H), 1699 (s, C=O), 1329 (s), 1159 (s, SO_2) cm^{-1}.

(*R*,*R*,*R*)-*N*-[(2-Hexyl-6-oxocyclohexyl)(phenyl)methyl]-4-methylbenzenesulfonamide [(*R*,*R*,*R*)-8]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3; and SiO_2, CH_2Cl_2 with 5% MeOH) afforded pure (*R*,*R*,*R*)-**8** (20 mg, 18%). M.p. 88–91 °C (heptane). $[\alpha]_D$ = +13.6 (*c* = 0.8 in $CHCl_3$, 94% *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.42 (m, 2 H, $ArSO_2$), 7.16–6.94 (m, 7 H, Ar), 6.26 (d, *J* = 10.1 Hz, 1 H), 4.67 (dd, *J* = 6.1, 10.1 Hz, 1 H), 2.60 (ddd, *J* = 1.0, 6.0, 9.3 Hz, 1 H), 2.32 (s, 3 H, CH_3), 2.35–2.07 (m, 2 H), 1.97–1.77 (m, 2 H), 1.70–1.41 (m, 3 H), 1.42–1.02 (m, 10 H, CH_2), 0.89 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.2 (qCO), 142.7 (Cq-SO_2), 138.1 (qC-Ph), 137.5 (qC-CH_3), 129.2 (CH), 128.5 (CH), 128.2 (CH), 127.5 (CH), 126.9 (CH), 60.0 (CH), 57.1 (CH), 41.8 (CH_2), 39.0 (CH) 33.1 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 26.0 (CH_2), 23.5 (CH_2), 22.6 (CH_2), 21.4 (CH_3), 14.1 (CH_3) ppm. $C_{26}H_{35}NO_3S$ (441.63): calcd. C 70.71, H 7.99, N 3.17; found C 70.52, H 7.97, N 2.98. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.6 mL min^{-1}): t_R(major) = 12.7, t_R(minor) = 17.5 min. IR (neat): $\tilde{\nu}$ = 3287 (m, N–H), 1705 (s, C=O), 1332 (s), 1184 (s, SO_2) cm^{-1}.

(*S*,*R*,*R*)-4-Methyl-*N*-[(2-oxo-6-phenylcyclohexyl)(phenyl)methyl]-benzenesulfonamide [(*S*,*R*,*R*)-9]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3). M.p. 125–127 °C (heptane). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.38 (m, 2 H, $ArSO_2$), 7.37–7.24 (m, 5 H, Ar), 7.02–6.85 (m, 5 H, Ar), 6.81–6.71 (m, 2 H, Ar), 6.48 (d, *J* = 11.0 Hz, 1 H, NH), 4.24 (dd, *J* = 1.2, 10.9 Hz, 1 H, CH), 3.32 (dt, *J* = 3.7, 11.6 Hz, 1 H, CH), 2.98 (d, *J* = 11.9 Hz, 1 H, CH), 2.43–2.32 (m, 2 H, CH_2), 2.25 (s, 3 H, CH_3), 2.16–2.02 (m, 2 H, CH_2), 1.99–1.68 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.0 (CO), 142.50 (qC), 142.49 (qC), 140.0 (qC-Ph), 138.0 (qC-CH_3), 129.0 (CH), 128.9 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 126.9 (CH), 126.6 (CH), 126.4 (CH), 62.6 (CH) 56.2 (CH), 49.2 (CH), 43.3 (CH_2), 34.7 (CH_2), 26.5 (CH_2), 21.3 (CH_3) ppm. $C_{26}H_{27}NO_3S$ (433.56): calcd. C 72.03, H 6.28, N 3.23; found C 71.48, H 6.26, N 3.03. HPLC (OD-H; hexane/*i*PrOH, 90:10; 0.6 mL min^{-1}): t_R(1) = 14.5, t_R(2) = 23.8 min. IR (neat): $\tilde{\nu}$ = 3348 [m (N–H)], 1703 (s, C=O), 1344 (s), 1158 (s, SO_2) cm^{-1}.

(*R*,*R*,*R*)-4-Methyl-*N*-[(2-oxo-6-phenylcyclohexyl)(phenyl)methyl]-benzenesulfonamide [(*R*,*R*,*R*)-9]: Column chromatography (SiO_2; hexane/EtOAc/CH_2Cl_2, 83:14:3). M.p. 104–106 °C (heptane). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.21 (m, 5 H, Ar), 7.19–6.88 (m, 7 H, Ar), 6.86–6.72 (m, 2 H, Ar), 6.53 (d, *J* = 10.5 Hz, 1 H, NH), 4.22 (dd, *J* = 4.7, 10.5 Hz, 1 H, CH), 3.29 (dd, *J* = 4.4, 12.3 Hz, 1 H, CH), 2.59–2.32 (m, 3 H), 2.30 (s, 3 H, CH_3), 2.02–1.80 (m, 2 H, CH_2), 1.80–1.47 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.4 (CO), 142.6 (qC), 141.8 (qC), 137.8 (qC-Ph), 137.1 (qC-CH_3), 129.2 (CH), 129.1 (CH), 129.0 (CH), 127.9 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 58.6 (CH) 56.9 (CH), 47.1 (CH), 42.2 (CH_2), 35.5 (CH_2), 24.5 (CH_2), 21.4 (CH_3) ppm. $C_{26}H_{27}NO_3S$ (433.56): calcd. C 72.03, H 6.28, N 3.23; found C 71.60, H 6.40, N 2.99. IR (neat): $\tilde{\nu}$ = 3294 (m, N–H), 1712 (s, C=O), 1327 (s), 1163 (s, SO_2) cm^{-1}.

Supporting Information (see footnote on the first page of this article): Compound characterization data, copies of ^1H and ^{13}C NMR spectra, and chromatograms.

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[22] CCDC-781688 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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