Synthesis and Screening of New Chiral Ligands for the Copper-Catalysed Enantioselective Allylic Substitution

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This paper is dedicated to Professor *Dieter Seebach*, on the occasion of his 65th birthday, for his prominent contributions to synthetic chemistry

The synthesis of the new chiral ligands **6ae**, **8ae**, **9ae**, and **11ae** starting from the chiral β-[(Boc)amino]-sulfonamide **3ae** is reported. The β-amino group of **3ae** was deprotected and condensed with 3,5-dichlorosalicylaldehyde (**4**) to yield the known *Schiff* base **5ae**, which was then reduced to the amino compound **6ae** (*Scheme 3*). Alternatively, condensation of the free amino compound with 2-(diphenylphosphanyl)benzaldehyde (**7**) afforded the imino ligand **8ae** which upon reduction yielded the amino ligand **9ae** (*Scheme 4*). The free amino compound derived from **3ae** was also coupled with 2-(diphenylphosphanyl)benzoic acid (**10**) to give ligand **11ae** (*Scheme 5*). These ligands were tested in the copper-catalysed allylic substitution reaction of cinnamyl (= 3-phenylprop-2-enyl) phosphate **12** with diethylzinc as a nucleophile. Ligands **5ae**, **6ae**, **8ae**, and **11ae** gave excellent ratios (100 :0) of the S_N2'/S_N2 products (*Scheme 6* and *Table 1*). Ligand **11ce**, identified from the screening of a small library of ligands of general formula **11**, promoted the allylic substitution reaction with moderate enantioselectivity (40% for the S_N2' product **13** (*Scheme 8* and *Table 3*)).

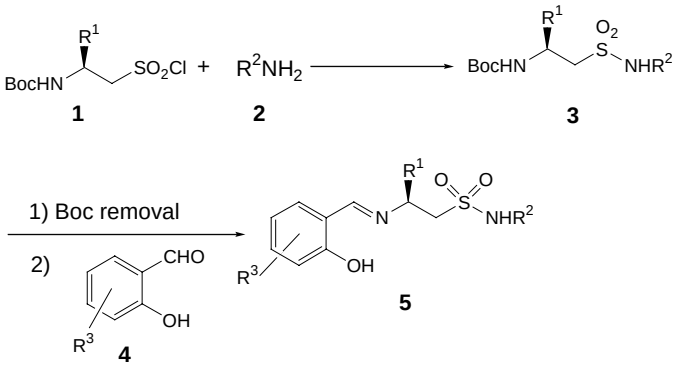
Introduction. – The efficiency (activity and selectivity) of a ligand for asymmetric catalysis depends on a subtle balance of the electronic, geometric, and steric influences between the ligand, the metal center, and the substrate. In such a complicated scenario, the development of effective new ligands and metal complexes based purely on intuition and trial-and-error is a very challenging task. The use of combinatorial methodologies for the rapid synthesis and screening of a large number of structures represents an important breakthrough in this area[1]). Two different basic approaches have been considered: optimization of the reaction conditions (solvent, temperature, stoichiometry, different ligands or metal ions) and the synthesis of new ligands *via* a modular building-block strategy, where the stereoelectronic properties of a metal-binding site (*e.g.* a phosphine, a sulfonamide, or a *Schiff* base) are tuned by variation of the substituents and side chains. In the case of screening members of a library containing ligands for enantioselective catalysis, the identification of a hit requires a demanding selection procedure, since the screening ultimately involves catalysis of a

[1]) For reviews on the combinatorial development of new catalysts, see [1]. See also [2a – k]. For the screening of a pooled stereoselective polymerization catalyst library, see [2l].

reaction and analysis of its stereochemical outcome. For this reason, a combinatorial system that allows the synthesis of discrete isolated compounds is usually chosen. Parallel synthesis (as opposed to the 'split and pool' methodology) allows one to know the identity of each ligand and keeps the ligands separate so that screening of individual complexes can be performed.

We have recently developed a new family of chiral *Schiff*-base ligands of general structure **5** (*Scheme 1*), which contains a set of different metal-binding sites (a phenol, an imine, and a secondary sulfonamide moiety), with the expectation that such a multidentate array would favor the formation of organometallic complexes with well-organized spatial arrangements, and with the goal of obtaining ligands for asymmetric catalysis capable of broad applicability. The main feature of these ligands is their modular assembly through the subsequent coupling of the three components (*Scheme 1*), namely sulfonyl chlorides **1**, amines **2**, and aldehydes **4**, which make these ligands well-suited for a combinatorial development. A library of ligands **5** (125 compounds) was synthesized in solution (with resin scavenging of excess reagents and by-products) and tested in the copper-catalysed, conjugate addition of Et_2Zn to enones [3a,c] and nitroolefins [3b].

Scheme 1. *Synthesis of a Library of Chiral* Schiff-*Base Ligands* **5** [3]



Results and Discussion. – To broaden the scope of this approach, we undertook a variation of the ligand structure by transformation or substitution of the phenolic *Schiff*-base moiety. The newly synthesized ligands **6**, **8**, **9**, and **11** (*Fig.*) containing the chiral β-aminosulfonamide substructure were screened in the copper-catalysed allylic substitution reaction of cinnamyl phosphate with diethylzinc as a nucleophile.

A small library of ligands of general formula **11** were prepared and screened for enantioselective allylic substitution.

Synthesis of the Ligands. The synthesis of a few representatives of the different ligand classes **6**, **8**, **9**, and **11** was undertaken starting from sulfonyl chloride **1a** ($R^1 = PhCH_2$) [4]. Sulfonyl chloride **1a** was coupled to an excess of amine **2e** (1.2 equiv.) in the presence of dimethylketene methyl trimethylsilyl acetal (DMTA) (2.0 equiv.) and a catalytic amount (0.2 equiv.) of *N*,*N*-dimethylpyridin-4-amine (DMAP) in CH_2Cl_2 (*Scheme 2*) [4a]. Once the coupling was complete, the reaction mixture was washed

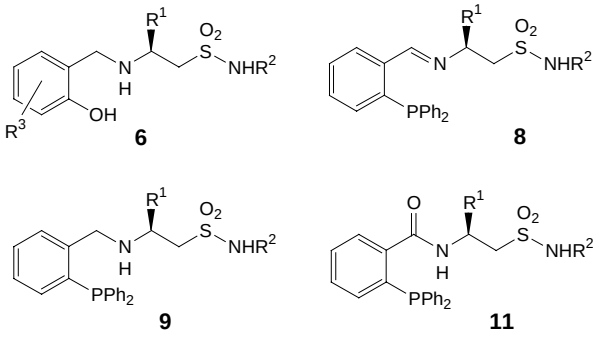
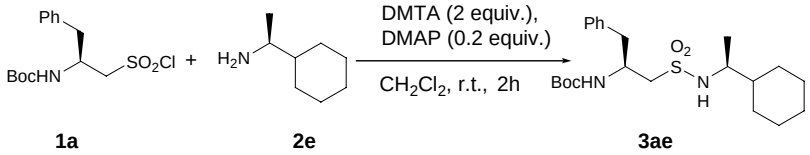


Figure. *Chiral ligands* **6**, **8**, **9** *and* **11**

Scheme 2. *Synthesis of Sulfonamide* **3ae**



1a **2e** **3ae**

with a saturated citric acid solution, and sulfonamide **3ae** was obtained in 88% yield without the need for any further purification.

Removal of the Boc protecting group of **3ae** (25% CF_3COOH in CH_2Cl_2) afforded the trifluoroacetate ammonium salt, which was then liberated ($NaHCO_3$). The resulting amino compound was then transformed into the different ligands **5ae**, **6ae**, **8ae**, **9ae**, and **11ae**. Thus, condensation with 3,5-dichlorosalicylaldehyde (**4**) in MeOH yielded the *Schiff*-base ligand **5ae** in practically quantitative yield without the need for any further purification. *Schiff*-base ligand **5ae** was then reduced to the amino compound **6ae** by reaction with $NaBH_3CN$ in MeOH in the presence of HCl [5].

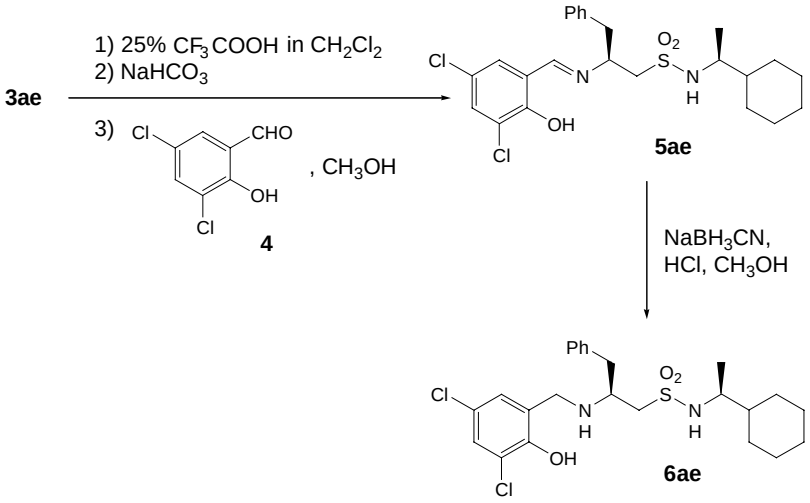
Formation of the *Schiff*-base ligand **8ae** required a different synthetic protocol: condensation of the amino compound obtained by deprotection of β-[(Boc)amino]-sulfonamide **3ae** with 2-(diphenylphosphanyl)benzaldehyde was performed in dry toluene at room temperature with $MgSO_4$ as dehydrating agent [6]. Removal of the salt by filtration and evaporation of toluene afforded **8ae**, which was not further purified. Reduction of the imino moiety of ligand **8ae** under the same conditions as described above yielded the amino ligand **9ae** in 63% yield.

For the synthesis of **11ae**, the chiral β-aminosulfonamide derived from **3ae** was coupled with 2-(diphenylphosphanyl)benzoic acid (**10**) in the presence of BOP ((1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate) and Et_3N [7] (70% yield). Use of EDC (*N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide]) and DMAP in THF [8] proved less satisfactory (yield $\leq$ 29%).

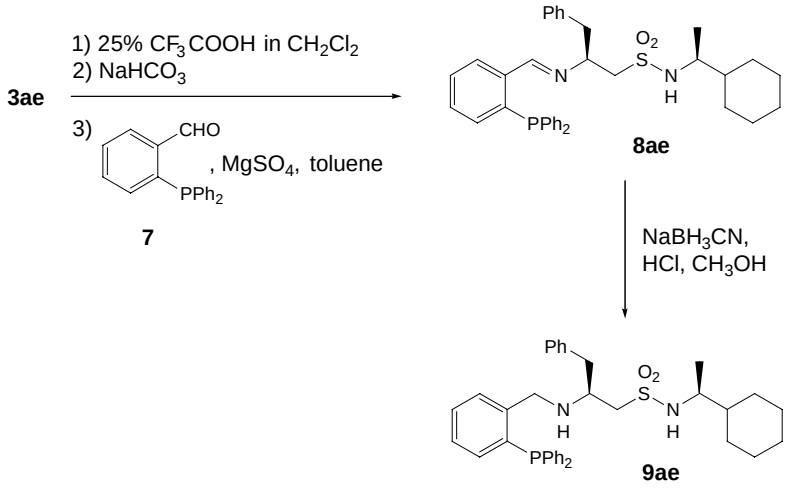
With these ligands in our hands, we considered their application in the copper-catalysed asymmetric allylic substitution.

Allylic-Substitution Reaction. The substitution of allylic alcohol derivatives by hard C-nucleophiles, such as organometallics, has recently attracted much attention, and

Scheme 3. *Synthesis of* Schiff-*Base Ligand* **5ae** *and Reduction to the Amino Ligand* **6ae**

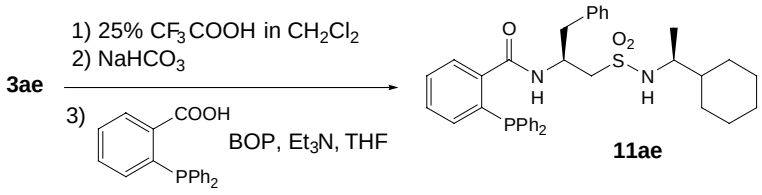


Scheme 4. *Synthesis of Imino Ligand* **8ae** *and Reduction to the Amino Ligand* **9ae**



several methods have been developed for the control of the regio- and stereochemistry in this type of reaction. The leaving group can be displaced either in an α (S_N2) or γ (S_N2') fashion by the organometallic reagent depending on the substrate, leaving group, organometallic, and metal source. Some enantioselective protocols that use catalytic amounts of a chiral copper complex, and organozinc [9] or *Grignard* [10] reagents have recently appeared: high ee were obtained in special cases with hindered organozinc reagents [9a] or 3-substituted cinnamyl (= 3-phenylprop-2-enyl) derivatives leading to

Scheme 5. *Synthesis of Amide Ligand* **11ae**



quaternary C-atoms [9b]. We decided to test the chiral *Schiff-base* ligand **5ae** and the modified ligands **6ae**, **8ae**, **9ae**, and **11ae** in the copper-catalysed allylic substitution of cinnamyl derivatives with diethylzinc. At the beginning, we screened several cinnamyl derivatives to find a suitable substrate; it was soon clear that halogenated derivatives (chloride and bromide) did not give a regioselective substitution reaction (low S_N2'/S_N2 ratio) either in the presence or absence of ligands. In the case of cinnamyl chloride (= 3-chloro-1-phenylprop-1-ene), a smooth reaction took place in toluene at $-20°$, even in the absence of any copper source, yielding an equimolar mixture of S_N2' and S_N2 products **13** and **14**[2]). Following the discovery by *Hoveyda et al.* of cinnamyl phosphate **12** as a suitable substrate for the enantioselective copper-catalysed allylic substitution with alkylzinc reagents [9b], we screened ligands **5ae**, **6ae**, **8ae**, **9ae**, and **11ae** using CuCN as the metal salt (see *Scheme 6* and *Table 1*). All ligands (except **9ae**, *Entry 7*) gave fair-to-good yields in THF (the reaction did not proceed in toluene) with practically complete S_N2' regioselectivity (**13**/**14** 100 : 0). As for the enantioselectivity, all the ligands tested gave racemic mixtures, except for **11ae** which gave **13** with a very modest 9% ee (*Entry 8*).

Scheme 6. *Copper-Catalysed Allylic Substitution of Cinnamyl Phosphate* **12** *with* Et_2Zn

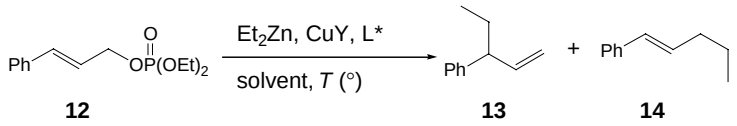


Table 1. *Copper-Catalysed Allylic Substitution of Cinnamyl Phosphate* **12** *with Diethylzinc* (see *Scheme 6*)

Entry	L*	CuY	Solvent	T [°]	Conversion[a])	S_N2'/S_N2 (**13**/**14**)[a])	ee (**13**)[a])
1	–	–	THF	–30	0	–	–
2	–	CuCN	THF	–30	0	–	–
3	–	CuCN	THF	0	39	100 : 0	–
4	**5ae**	CuCN	THF	–30	100	100 : 0	0
5	**6ae**	CuCN	THF	–30	55	100 : 0	0
6	**8ae**	CuCN	THF	–30	53	100 : 0	0
7	**9ae**	CuCN	THF	–30	0	–	–
8	**11ae**	CuCN	THF	–30	91	100 : 0	9

[a]) Determined by chiral GC analysis (*Megadex DACTBSβ*) with decane as internal standard.

[2]) *Feringa et al.* showed that cinnamyl halides can be used as substrates for the enantioselective copper-catalysed allylic substitution only in strongly coordinating solvent (*e.g.*, diglyme) [9c].

A screening of the copper sources was then performed with **11ae** as ligand (*Table 2*), and a more-interesting 30% ee was obtained by lowering the temperature to $-55°$ and running the reaction in the presence of copper(I) triflate dimer (benzene complex) (*Entry 1*). The use of copper(II) triflate gave almost complete S_N2' regioselectivity and the same ee, albeit in much lower yield (*Entry 2*).

Table 2. *Copper-Catalysed Allylic Substitution of Cinnamyl Phosphate* **12** *with Diethylzinc, Chiral Ligand* **11ae**, *and Different Copper Sources*

Entry	L*	CuY	Solvent	T [°]	Conversion[a])	S_N2'/S_N2 (**13**/**14**)[a])	ee (**13**)[a])
1	**11ae**	$[(CuOTf)_2 \cdot C_6H_6]$	THF	–55	95	89:11	30
2	**11ae**	$Cu(OTf)_2$	THF	–55	15	100:0	30
3	**11ae**	CuCN	THF	–55	0	–	–
4	**11ae**	$CuBr \cdot SMe_2$	THF	–55	10	85:15	0
5	**11ae**	CuI	THF	–55	0	–	–

[a]) Determined by chiral GC analysis (*Megadex DACTBSβ*) with decane as internal standard.

Based on these results, we undertook the synthesis of a small library of ligands of general formula **11**, changing the residues at the β-position of the β-aminosulfonamide (R^1) and at the N-atom of the amide moiety (R^2). Thus 14 different ligands were prepared starting from the 4-different β-aminosulfonyl chlorides [4] **1a**–**d** (R^1 = Me, $PhCH_2$, ^{i}Pr, ^{i}Bu) and 7 different amines **2e**–**k** according to the general procedure described above[3])[4]) (*Scheme 7*).)

The screening of the ligands required complexation *in situ* with $[(CuOTf)_2 \cdot C_6H_6]$ in THF at room temperature for 45 min. After addition of phosphate **12**, the reaction mixture was cooled to $-78°$, and Et_2Zn was added. The mixtures were warmed to $-55°$ and stirred for 20 h before quenching with NH_4Cl (*Scheme 8*). The ee and conversions were measured by GC with a chiral column and with decane as an internal standard. The absolute configuration of the stereogenic center of **13** was assigned as (*S*), based on the sign of the optical rotation [11]. The results are summarized in *Table 3*.

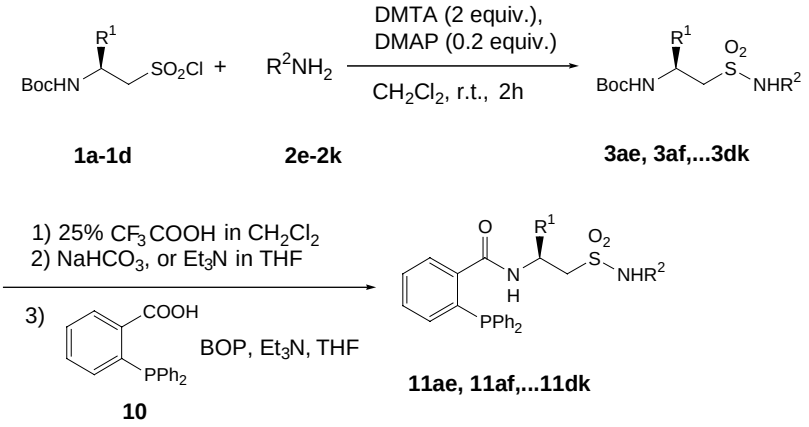
From these results, one can draw the following conclusions: *a*) The stereogenic center bearing R^1 dictates the absolute configuration of compound **13**, and not the stereogenic center present in R^2 (*cf. Entries 4* and *5*, *Table 3*). b) The ee of **13** depends on a subtle balance of the mutual influences of R^1 and R^2; no linear relationship between the steric hindrance of these residues and ee can be clearly identified. c) The best combination of R^1 and R^2 (R^1 = ^{i}Pr and R^2 = (*S*)-ChxCH(Me)), *i.e.* ligand **11ce**, gave **13** with an ee of 40% and a ratio **13**/**14** of 90:10.

Conclusions. – We reported the synthesis of the new chiral ligands **6**, **8**, **9**, and **11** (*Fig.*), encompassing the chiral β-aminosulfonamide substructure. These ligands were

[3]) We did not synthesize the full matrix of all possible different ligands (*i.e.* $7 \cdot 4 = 28$), but only half of them (14). We followed a sort of 'positional scanning' approach, *e.g.*, synthesized ligands **11ce**–**ck** with all seven possible R^2 (**e**–**k**) in the case of the best R^1 (**c**).

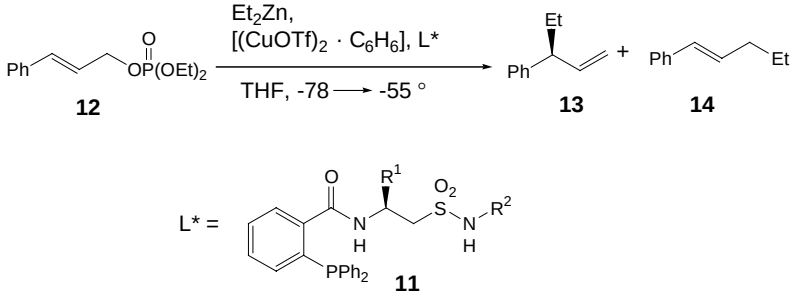
[4]) In some cases, after removal of the Boc protecting group from the amino group, the amino derivative was obtained from the intermediate trifluoroacetate salt by treatment with Et_3N (2 equiv.) in THF. The resulting solution was used directly in the following coupling step with 2-(diphenylphosphanyl)benzoic acid.

Scheme 7. *Synthesis of the Library of Ligands* **11**



1a R^1 = $PhCH_2$ **2e** R^2 = (*S*)-ChxCH(Me)
b R^1 = Me **f** R^2 = (*R*)-ChxCH(Me)
c R^1 = ^{i}Pr **g** R^2 = $PhCH_2$
d R^1 = ^{i}Bu **h** R^2 = ^{i}Pr
i R^2 = Ph_2CH
j R^2 = (*S*)-CH_2(OH)CH(Ph)
k R^2 = (*S*)PhCH(Me)

Scheme 8. *Screening of the Library of Ligands* **11** *in the Copper-Catalysed Allylic Substitution of Cinnamyl Phosphate* **12** *with* Et_2Zn



tested in the copper-catalysed allylic substitution reaction of cinnamyl phosphate with diethylzinc as a nucleophile. Ligands **5**, **6**, **8**, and **11** gave excellent ratios (100 : 0) of the S_N2'/S_N2 products **13** and **14**. The screening of a small library of ligands of general formula **11** (14 compounds) allowed the identification of **11ce** as the best ligand for enantioselective allylic substitution (ee 40% for the S_N2' product **13**). Work is now in progress to test the applicability of these ligand structures to other catalytic asymmetric reactions of interest.

Table 3. *Copper-Catalysed Allylic Substitution of Cinnamyl Phosphate* **12** *with Diethylzinc, [(CuOTf)$_2$·C$_6$H$_6$], and a Library of Ligands* **11** (see *Scheme 8*)

Entry	L*	R^1	R^2	Conversion[a])	S_N2'/S_N2 (**13**/**14**)[a])	ee (**13**)[a])[b])
1	**11ae**	$PhCH_2$	(*S*)-ChxCH(Me)	95	89 : 11	30
2	**11be**	Me	(*S*)-ChxCH(Me)	50	89 : 11	30
3	**11de**	^{i}Bu	(*S*)-ChxCH(Me)	76	89 : 11	38
4	**11ce**	^{i}Pr	(*S*)-ChxCH(Me)	93	90 : 10	40
5	**11cf**	^{i}Pr	(*R*)-ChxCH(Me)	55	87 : 13	21
6	**11ci**	^{i}Pr	Ph_2CH	41	83 : 17	13
7	**11cg**	^{i}Pr	$PhCH_2$	75	57 : 43	0
8	**11ch**	^{i}Pr	^{i}Pr	7	75 : 25	0
9	**11cj**	^{i}Pr	(*S*)-CH_2(OH)CH(Ph)	80	80 : 20	13
10	**11ck**	^{i}Pr	(*S*)-PhCH(Me)	3	–	–
11	**11ak**	$PhCH_2$	(*S*)-PhCH(Me)	50	90 : 10	27
12	**11dk**	^{i}Bu	(*S*)-PhCH(Me)	17	90 : 10	0
13	**11ah**	$PhCH_2$	^{i}Pr	65	90 : 10	22
14	**11bg**	Me	$PhCH_2$	100	70 : 30	13

[a]) Determined by chiral GC analysis (*Megadex DACTBSβ*) with decane as internal standard. [b]) The absolute configuration of the stereogenic center of **13** was assigned as (*S*), based on the sign of the optical rotation [11].

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Experimental Part

General. Manipulations involving air-sensitive compounds were carried out under Ar by *Schlenk* and syringe techniques. Anh. solvents were obtained from Na (toluene), sodium benzophenone ketyl (oxidodiphenylmethyl sodium salt; THF and Et_2O), or by refluxing over CaH_2 for at least 4 h prior to use. Reagents were used as received without any further purification and were generally purchased from *Aldrich* and *Fluka AG*. Compounds **3ae** [3c], **5ae** [3c], and **12** [9a] were obtained as previously described. Anal. TLC: *Merck* silica-gel *60 F_{254}* glass plates; visualization with UV light and by staining with a cerium reagent followed by heating. Flash chromatography [12] (FC): silica gel *60* (230–400 mesh) from *Macherey Nagel*. GC: *Dani GC-3800* instrument equipped with a FID and a chiral capillary column (*Megadex DACTBSβ*, decane as internal standard); t_R in min. Optical rotations: *Perkin-Elmer 241* polarimeter. IR Spectra: *Perkin-Elmer 681*; in cm^{-1}. NMR Spectra: *Bruker* instruments (*AC-200* and *400 Avance*); δ in ppm rel. to $SiMe_4$; *J* in Hz.

1. *(2*S*)-*N*-[(1*S*)-1-Cyclohexylethyl]-2-[(3,5-dichloro-2-hydroxybenzyl)amino]-3-phenylpropane-1-sulfonamide* (**6ae**). To a soln. of **5ae** (240 mg, 0.48 mmol) in MeOH (27 ml), $NaBH_3CN$ was added (155 mg, 2.46 mmol). The soln. was stirred for 5 min and 37% (*w*/*w*) conc. HCl soln. (263 µl) was added dropwise. The yellow soln. discolored, and stirring was maintained for 2 h at r.t. A 3M KOH soln. was added until the pH of the soln. became basic, the mixture was diluted with H_2O (50 ml) and extracted several times with CH_2Cl_2. The combined org. extract was washed with brine, dried (Na_2SO_4), and evaporated; and the residue was purified by FC (hexane/AcOEt 80 : 20): 171 mg (71%) of pure **6ae**. ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 1.75–0.83 (*m*, 14 H, Chx, Me); 3.12–2.83 (*m*, CH_2SO_2, ChxC*H*(Me), Ph*CH*$_2$); 3.49–3.45 (*m*, ChxC*H*(Me)); 3.99 (*s*, C*H*$_2$NH); 4.68 (br. *s*, $NHSO_2$); 7.36–6.87 (*m*, arom. 7 H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 19.4; 26.0; 26.2; 28.6; 28.8; 39.4; 43.5; 49.5; 54.9; 55.2; 55.8; 121.7; 123.6; 124.9; 126.7; 127.2; 128.6; 129.0; 129.3; 136.5; 152.3. IR ($CHCl_3$): 1099 (CN), 1333 (SO_2), 1435, 2857, 2932, 3387 (NH). $[\alpha]_D^{25} = +15.2$ (*c* = 0.25, $CHCl_3$). HR-EI-MS: 498.1276 ($C_{24}H_{32}Cl_2N_2O_3S^+$; calc. 498.15).

2. *(2*S*)-*N*-[(1*S*)-1-Cyclohexylethyl]-2-[[2-(diphenylphosphanyl)benzylidene]amino]-3-phenylpropane-1-sulfonamide* (**8ae**). β-[(Boc)amino]sulfonamide **3ae** (50 mg, 0.12 mmol) was dissolved in 25% CF_3COOH in CH_2Cl_2 (5.2 ml). The resulting soln. was stirred for 1 h, and sat. aq. $NaHCO_3$ soln. was added until pH 7. The aq.

phase was extracted with AcOEt (6 × 10 ml) and the combined org. extract dried (Na_2SO_4) and evaporated. The residue was suspended in dry toluene (5 ml), and 2-(diphenylphosphanyl)benzaldehyde (33 mg, 0.12 mmol) and anh. $MgSO_4$ (14 mg, 0.12 mmol) were added. The resulting suspension was stirred at r.t. for 15 h under Ar. The solid salts were filtered and washed with AcOEt, and the combined filtrates were evaporated to yield 70 mg (quant.) of **8ae**. ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 1.81–0.74 (*m*, 14 H, Chx, Me); 2.87–2.57 (*m*, CH_2SO_2); 3.29–3.19 (*m*, ChxC*H*(Me), PhCH_2); 3.95–3.92 (*m*, C*H*N=CH); 4.13 (*d*, *J* = 8.78, $NHSO_2$); 7.38–6.93 (*m*, 19 arom. H); 8.64 (*s*, CH=N). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 18.8; 26.1; 26.3; 28.5; 29.0; 42.3; 43.7; 54.5; 57.8; 67.9; 126.6; 128.3; 128.6; 128.8; 128.9; 129.4; 129.6; 130.5; 133.5; 133.9 (*d*, *J* = 19.6); 135.0 (*d*, *J* = 18.8); 136.9 (*d*, *J* = 19.5); 137 (*d*, *J* = 19.7); 141.8 (*d*, *J* = 27.8); 161.2; 161.4. IR ($CHCl_3$): 960, 1340 (SO_2), 1456 (CH_2, Me), 1640 (C=N), 3412 (NH). $[\alpha]_D^{25} = -155.71$ (*c* = 0.21, $CHCl_3$). HR-EI-MS: 596.2664 ($C_{36}H_{41}N_2O_2PS^+$; calc. 596.2626).

3. *(2*S*)-*N*-[(1*S*)-1-Cyclohexylethyl]-2-{[2-diphenylphosphanyl)benzyl]amino}-3-phenylpropane-1-sulfonamide* (**9ae**). As described for **6ae**, with **8ae** (290 mg, 0.48 mmol), MeOH (27 ml), $NaBH_3CN$ (149 mg, 2.37 mmol), and 37% (*w*/*w*) conc. HCl soln. (200 µl): 114 mg (39%) of pure **9ae**. ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 1.84–0.82 (*m*, 15 H, Chx, Me, NH); 2.92–2.61 (*m*, CH_2SO_2); 3.07–2.99 (*m*, PhCH_2); 3.27–3.25 (*m*, Chx, C*H*Me); 3.51–3.47 (*m*, PhCH_2C*H*); 4.26–3.93 (*dd*, *J* = 114.69, 12.89, CH_2NH); 4.97 (*d*, *J* = 8.38, $NHSO_2$); 7.49–6.91 (*m*, 19 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 18.7; 26.1; 26.3; 28.5; 28.7; 40.0; 43.7; 49.7; 49.9; 54.3; 55.8; 56.6; 71.8; 126.6; 127.6; 128.6; 128.8; 128.9; 129.2; 129.4; 129.5; 133.7 (*d*, *J* = 18.5); 134.0; 135.7 (*d*, *J* = 18.8); 136.4 (*d*, *J* = 19.5); 137.3 (*d*, *J* = 19.7); 143.7 (*d*, *J* = 23.6). IR (nujol): 710 (C–P), 746 (S–N), 1099 (CN), 1310 (SO_2), 3283 (NH). $[\alpha]_D^{25} = +5.9$ (*c* = 0.51, $CHCl_3$). HR-EI-MS: 598.2754 ($C_{36}H_{43}N_2O_2PS^+$; calc. 598.2783).

4. *Ligands* **11**. *General Procedure a*. *β*-(Boc)aminosulfonamide **3** (1 equiv.) was dissolved in 25% CF_3COOH in CH_2Cl_2 (0.1M based on the sulfonamide). The resulting soln. was stirred for 1 h, and sat. aq. $NaHCO_3$ soln. was added until pH 7. The aq. phase was extracted with AcOEt (6 × 10 ml). The combined org. extracts were dried (Na_2SO_4) and evaporated. In a separate flask, (1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 1 equiv.) was added to a soln. of 2-(diphenylphosphanyl)benzoic acid in dry THF (1 equiv., 0.07M) and Et_3N (1 equiv.). After 10 min, a soln. of the deprotected amino compound in THF (0.35M) was added, and the mixture was stirred overnight. The mixture was evaporated and AcOEt (10 ml) was added. The soln. was washed with 5% HCl, sat. $NaHCO_3$ soln., and brine, and was dried (Na_2SO_4). Purification by FC (hexane/AcOEt:) afforded pure **11**.

General Procedure b. *β*-[(Boc)amino]sulfonamide **3** (1 equiv.) was dissolved in 25% CF_3COOH in CH_2Cl_2 (0.1M based on the sulfonamide). The resulting soln. was stirred for 1 h and then evaporated. The residue was dissolved in THF (0.35M based on the sulfonamide), and Et_3N (2 equiv.) was added. The resulting soln. was stirred for 30 min and directly used in the subsequent coupling step. In a separate flask, BOP (1 equiv.) was added to a soln. of 2-(diphenylphosphanyl)benzoic acid in dry THF (1 equiv., 0.07M) and Et_3N (1 equiv.). After 10 min, the soln. of the deprotected amino compound in THF/CF_3COOH was added, and the mixture was stirred overnight. After evaporation, AcOEt (10 ml) was added. The soln. was washed with 5% HCl soln. sat. $NaHCO_3$ soln., and brine, and was dried (Na_2SO_4). Purification by FC (hexane/AcOEt 8:2) afforded pure **11**.

*N-{(1*S*)-1-Benzyl-2-{[(1*S*)-1-cyclohexylethyl]sulfamoyl}ethyl}-2-(diphenylphosphanyl)benzamide* (**11ae**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 1.75–0.89 (*m*, 14 H, Chx, Me); 3.03–2.84 (*m*, CH_2SO_2); 3.14–3.13 (*m*, PhCH_2); 3.31–3.26 (*m*, ChxC*H*(Me)); 4.73–4.68 (*m*, PhCH_2C*H*); 4.79 (*d*, *J* = 8.68, $NHSO_2$); 6.5 (br., NHCO); 7.38–7.02 (*m*, 19 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 19.4; 26.1; 26.3; 28.5; 29.0; 39.6; 43.6; 48.0; 54.8; 55.3; 57.0; 126.9; 127.6; 128.7; 129.1; 129.4; 130.4; 133.7 (*d*, *J* = 19.1); 134.3; 136.7. IR (nujol): 734 (C–P), 750 (S–N), 1322 (SO_2), 1646 (C=N), 3440 (NH). $[\alpha]_D^{25} = +9.0$ (*c* = 0.40, $CHCl_3$). HR-EI-MS: 612.2587 ($C_{36}H_{41}N_2O_3PS^+$; calc. 612.2576).

*N-{(1*S*)-2-{[(1*S*)-1-Cyclohexylethyl]sulfamoyl}-1-methylethyl}-2-(diphenylphosphanyl)benzamide* (**11be**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 1.79–0.96 (*m*, 17 H, Chx, 2 Me); 3.23–3.08 (*m*, CH_2SO_2); 3.38–3.32 (*m*, ChxC*H*(Me)); 4.57–4.51 (*m*, NHC*H*(Me)); 4.69 (*d*, *J* = 8.74, $NHSO_2$); 7.67–6.96 (*m*, 14 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 19.2; 19.7; 26.1; 26.3; 28.5; 29.0; 42.5; 43.7; 54.7; 58.1; 127.8; 128.6; 129.0; 130.3; 133.8 (*d*, *J* = 16.5); 134.1; 134.8 (*d*, *J* = 18.0); 136.3 (*d*, *J* = 19.5); 136.8 (*d*, *J* = 19.5); 142.8 (*d*, *J* = 26.8); 168.7. IR (nujol): 698 (C–P), 743 (S–N), 1130, 1306 (SO_2), 1520, 1640 (C=N), 3221 (NH). $[\alpha]_D^{25} = +14.0$ (*c* = 0.30, $CHCl_3$). HR-EI-MS: 536.2216 ($C_{30}H_{37}N_2O_3PS^+$; calc. 536.2262).

*N-{(1*S*)-1-{{[(1*S*)-1-Cyclohexylethyl]sulfamoyl}methyl}-3-methylbutyl}-2-(diphenylphosphanyl)benzamide* (**11de**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 0.87–2.06 (*m*, 23 H, 3 Me, Chx, Me_2CH, Me_2CHCH_2); 3.16–3.14 (*m*, CH_2SO_2); 3.38 (*m*, ChxC*H*(Me)); 4.44 (br. *m*, ^{i}BuC*H*); 4.80–4.78 (*m*, $NHSO_2$); 6.38 (br. *s*, CONH); 7.40–7.26 (*m*, 14 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 19.4; 21.8; 22.8; 24.7; 26.2; 26.3; 28.6; 29.0; 42.9; 43.7; 44.8; 54.8; 57.4; 128.6; 130.3; 133.7 (*d*, *J* = 19.2); 134.3; 135.0 (*d*, *J* = 18.8); 136.9 (*d*, *J* = 19.5); 137.0

(d, J = 19.7); 141.8 (d, J = 27.8); 169.6. IR (nujol): 720 (C–P), 753 (S–N); 1168, 1315 (SO_2), 1512, 1651 (C=N), 3378 (NH). $[\alpha]_D^{25}$ = +16.5 (c = 0.51, $CHCl_3$). HR-EI-MS: 578.2705 ($C_{33}H_{43}N_2O_3PS^+$; calc. 578.2732).

N-*{(1S)-1-{[[(1S)-1-Cyclohexylethyl]sulfamoyl}methyl]-2-methylpropyl}-2-(diphenylphosphanyl)benzamide* (**11ce**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 0.87 (d, J = 6.8, Me); 0.91 (d, J = 6.7, Me); 1.82–0.95 (m, 14 H, Chx, Me); 2.04–1.96 (m, Me_2CH); 3.21–3.10 (m, CH_2SO_2); 3.46–3.37 (m, ChxC*H*(Me)); 4.52–4.46 (m, ^{i}PrC*H*); 5.01 (d, J = 8.6, $NHSO_2$); 6.26 (d, J = 9.1, NHCO); 7.71–6.98 (m, 14 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 18.2; 18.8; 19.3; 26.1; 26.2; 26.3; 28.5; 29.0; 31.3; 43.7; 51.3; 54.7; 54.9; 127.6; 127.7; 128.5; 128.6; 128.7; 128.8; 129.0; 130.2; 133.6 (d, J = 19.9); 134.4; 135.0 (d, J = 18.8); 136.9 (d, J = 19.5); 137.0 (d, J = 19.7); 141.8 (d, J = 27.8); 169.6. IR (nujol): 723 (C–P), 746 (S–N), 1161, 1310 (SO_2), 1512, 1651 (C=N), 3430 (NH). $[\alpha]_D^{25}$ = +40.6 (c = 0.50, $CHCl_3$). HR-EI-MS: 564.2601 ($C_{32}H_{41}N_2O_3PS^+$; calc. 564.2575).

N-*{(1S)-1-{[[1(R)-1-Cyclohexylethyl]sulfamoyl}methyl]-2-methylpropyl}-2-(diphenylphosphanyl)benzamide* (**11cf**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 0.90–0.88 (m, 2 Me); 1.94–0.95 (m, 15 H, Chx, 1 Me, Me_2CH); 3.18–3.16 (m, CH_2SO_2); 3.42–3.37 (m, ChxC*H*(Me)); 4.52–4.48 (m, ^{i}PrC*H*); 5.37 (m, $NHSO_2$); 6.28 (br., NHCO); 7.72–7.03 (m, 14 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 18.4; 18.6; 19.0; 26.1; 26.2; 28.7; 31.7; 43.8; 51.1; 54.2; 54.6; 127.6; 128.4; 128.5; 128.6; 128.7; 130.2; 133.5 (d, J = 19.5); 133.7; 134.5 (d, J = 18.8); 136.9 (d, J = 19.5); 137.0 (d, J = 19.7); 142.0 (d, J = 27.8); 169.6. IR (nujol): 710 (C–P), 750 (S–N), 1130, 1310 (SO_2), 1521, 1645 (C=N), 3280 (NH). $[\alpha]_D^{25}$ = +55.4 (c = 0.52, $CHCl_3$). HR-EI-MS: 564.2591 ($C_{32}H_{41}N_2O_3PS^+$; calc. 564.2576).

N-*{(1S)-1-[(Benzhydrylsulfamoyl)methyl]-2-methylpropyl}-2-(diphenylphosphanyl)benzamide* (**11ci**). ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 0.62–0.57 (m, 2 Me); 1.45–1.40 (m, Me_2CH); 3.00–2.69 (m, $PhCH_2$); 4.12–4.05 (m, Me_2CHCH); 5.8 (d, J = 8.96, $NHSO_2$); 6.07 (br. s, NHCO); 7.50–6.90 (m, 24 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 17.6; 18.4; 31.8; 50.3; 54.5; 61.4; 127.2; 127.7; 128.0; 128.2; 128.4; 128.9; 130.2; 133.5 (d, J = 19.6); 134.6; 135.0 (d, J = 18.8); 136.9 (d, J = 19.5); 137 (d, J = 19.7); 141.2 (d, J = 27.8); 169.6. IR (nujol): 723 (C–P), 750 (S–N), 1315 (SO_2), 1536, 1645 (C=N), 3452 (NH). $[\alpha]_D^{25}$ = 66.83 (c = 0.41, $CHCl_3$). HR-EI-MS: 620.2273 ($C_{37}H_{37}N_2O_3PS^+$; calc. 620.2263).

N-*{(1S)-1-[(Benzylsulfamoyl)methyl]-2-methylpropyl}-2-(diphenylphosphanyl)benzamide* (**11cg**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 0.74–0.72 (d, J = 6.84, Me); 0.78–0.76 (d, J = 7.53, Me); 1.68–1.80 (m, Me_2CH); 3.13–2.85 (m, CH_2SO_2); 4.43–4.25 (m, ^{i}PrC*H*, $PhCH_2$); 6.30–6.08 (br., $NHSO_2$, NHCO); 7.85–7.07 (m, 19 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 17.7; 18.0; 18.7; 31.1; 31.7; 47.2; 50.8; 51.4; 52.3; 54.0; 127.8; 128.3; 128.6; 128.7; 128.8; 129.2; 130.3; 131.8; 132.3; 133.5; 133.6 (d, J = 12.6); 133.8; 134.4; 137.1; 137.2; 170.0. IR (nujol): 696 (C–P), 723 (S–N), 1150, 1308 (SO_2), 1541, 1641 (C=N), 3190, 3356 (NH). $[\alpha]_D^{25}$ = +48.04 (c = 0.51, $CHCl_3$). HR-EI-MS: 544.1984 ($C_{31}H_{33}N_2O_3PS^+$; calc. 544.1949).

2-(Diphenylphosphanyl)-N-*{(1S)-1-[(isopropylsulfamoyl)methyl]-2-methylpropyl}benzamide* (**11ch**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 0.86–0.89 (m, 2 Me); 1.26–1.24 (m, 2 Me); 1.57 (m, Me_2CH); 3.17–3.16 (m, CH_2SO_2); 3.68–3.63 (m, SO_2CH(Me)); 4.57–4.51 (m, ^{i}PrC*H*); 5.06–5.04 (m, $NHSO_2$); 6.20 (br., NHCO); 7.70–6.98 (m, 14 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 21.9; 22.7; 24.0; 24.4; 24.6; 43.0; 44.8; 46.3; 57.0; 127.9; 128.6; 128.9; 130.3; 133.6 (d, J = 19.9); 134.2; 135.0 (d, J = 18.8); 136.9 (d, J = 19.5); 137.0 (d, J = 19.7); 141.8 (d, J = 27.8); 169.6. IR (nujol): 698 (C–P), 735 (S–N), 900, 1009, 1159, 1300 (SO_2), 1539, 1649 (C=N), 2251, 3215, 3369 (NH). $[\alpha]_D^{25}$ = +14.0 (c = 0.50, $CHCl_3$). EI-MS: 495, 433, 388, 348, 332, 304 (100), 289, 277, 261, 241, 226, 212, 199, 183, 165, 149, 139, 123, 108, 91, 83, 77, 69, 57, 43, 29.

2-(Diphenylphosphanyl)-N-*{(1S)-1-{[[(1S)-2-hydroxy-1-phenylethyl]sulfamoyl}methyl}-2-methylpropyl}-benzamide* (**11cj**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 0.69–0.98 (m, 2 Me); 1.98–1.63 (m, Me_2CH); 3.83–2.65 (m, $PhCH_2$, CH_2OH, CH_2SO_2, $CHCH_2OH$); 4.82–4.58 (m, ^{i}PrC*H*); 6.45–6.12 (m, $NHSO_2$); 7.70–6.83 (m, 19 arom. H). IR (nujol): 730 (C–P), 748 (S–N), 1312 (SO_2), 1518, 1655 (C=N), 3398 (NH). $[\alpha]_D^{25}$ = +124.7 (c = 0.51, $CHCl_3$). EI-MS: 573, 557, 513, 497, 423, 374, 363, 330, 305 (100), 289, 277, 254, 241, 226, 211, 199, 183, 165, 152, 120, 105, 91, 77, 69, 41.

2-(Diphenylphosphanyl)-N-*{(1S)-2-methyl-1-{[[(1S)-1-phenylethyl]sulfamoyl}methyl}propyl}benzamide* (**11ck**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 0.53 (d, J = 6.91, Me); 0.67 (d, J = 6.85, Me); 0.94–0.88 (m, Me_2CH); 1.58 (d, J = 6.99, Me); 2.87–2.59 (m, CH_2SO_2); 3.90–3.80 (m, Me_2CHCH); 4.63–4.53 (m, $PhCH$); 7.64–7.06 (m, 21 H, arom. H, $NHSO_2$, NHCO). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 17.3; 17.9; 24.0; 30.8; 50.9; 52.0; 54.0; 126.8; 127.6; 128.5; 128.6; 128.7; 129.0; 129.1; 129.6; 129.7; 131.7; 131.8; 132.1; 133.6 (d, J = 11.9); 135.0 (d, J = 18.8); 136.9 (d, J = 19.5); 137 (d, J = 19.7); 141.8 (d, J = 27.8); 143.6; 169.2. IR (nujol): 723 (C–P), 754 (S–N), 1315 (SO_2), 1556, 1670 (C=N), 3267; 3384 (NH). $[\alpha]_D^{25}$ = +132.0 (c = 0.50, $CHCl_3$). EI-MS: 531, 497, 481, 454, 391, 376, 348, 322, 305 (100), 292, 277, 258, 244, 227, 199, 183, 166, 152, 120, 105, 91, 77, 69.

N-*{(1S)-1-Benzyl-2-{[(1S)-1-phenylethyl]sulfamoyl}ethyl}-2-(diphenylphosphanyl)benzamide* (**11ak**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 1.53 (d, J = 7.03, Me); 2.48–2.80 (m, CH_2SO_2, +$PhCH_2$); 4.68–4.30

(*m*, $PhCH_2CH$, PhC*H*); 5.76 (br. *d*, $NHSO_2$); 6.2 (br., NHCO); 7.71–6.80 (*m*, 24 arom. H). IR (nujol): 723 (C–P), 750 (S–N), 1161, 1312 (SO_2), 1510, 1648 (C=N), 3415 (NH). $[\alpha]_D^{25} = +60.2$ ($c = 0.50$, $CHCl_3$). EI-MS: 591, 529, 515, 501, 421, 409, 393, 357, 330, 305 (100), 289, 277, 254, 241, 226, 212, 199, 183, 165, 144, 117, 105, 91, 77, 65, 51.

2-(Diphenylphosphanyl)-N-*{(1*S*)-3-methyl-1-{[[(1*S*)-1-phenylethyl]sulfamoyl}methyl}butyl}benzamide* (**11dk**). ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 0.62 (*d*, $J = 6.5$, 1 Me); 0.65 (*d*, $J = 6.6$, 1 Me); 1.07–1.48 (*m*, Me_2CH, Me_2CHCH_2); 1.57 (*d*, $J = 5.1$, 1 Me); 2.82–2.73 (*m*, CH_2SO_2); 4.10–4.01 (*m*, PhC*H*(Me)); 4.69–4.63 (*m*, ^{i}BuC*H*); 7.63–7.06 (*m*, 19 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 21.5; 22.5; 23.8; 23.9; 24.2; 43.1; 44.9; 53.9; 54.4; 126.5; 126.7; 127.5; 128.6; 128.7; 128.8; 128.9; 130.2; 132.1 (*d*, $J = 17.3$); 134.4; 135.0 (*d*, $J = 18.8$); 136.9 (*d*, $J = 19.5$); 137.0 (*d*, $J = 19.7$); 141.8 (*d*, $J = 27.8$). IR (nujol): 700 (C–P), 752 (S–N), 1159, 1308 (SO_2), 1528, 1645 (C=N), 3390 (NH). $[\alpha]_D^{25} = +58.0$ ($c = 0.40$, $CHCl_3$). HR-EI-MS: 573.2266 ($C_{33}H_{38}N_2O_3PS^+$, $[M+1]^+$; calc. 573.2341).

N-*[(1*S*)-1-Benzyl-2-(isopropylsulfamoyl)ethyl]-2-(diphenylphosphanyl)benzamide* (**11ah**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 1.21–1.11 (*m*, 2 Me); 2.98–2.81 (*m*, CH_2SO_2); 3.12 (*d*, $J = 6.27$, PhCH_2); 3.59–3.51 (*m*, Me_2CH); 4.70–4.65 (*m*, $PhCH_2CH$); 4.97–4.95 (*m*, $NHSO_2$); 6.40 (br. *s*, NHCO); 7.41–6.98 (*m*, 19 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 23.8; 24.3; 39.7; 46.3; 47.8; 55.0; 127.0; 127.5; 128.6; 128.7; 128.8; 129.4; 130.3; 133.7 (*d*, $J = 19.9$); 134.2; 135.2 (*d*, $J = 19.0$); 136.5 (*d*, $J = 19.5$); 137.2 (*d*, $J = 19.7$); 141.8 (*d*, $J = 27.8$); 169.6. IR (nujol): 733 (C–P), 748 (S–N), 1161, 1314 (SO_2), 1645 (C=N), 3227, 3356 (NH). $[\alpha]_D^{25} = +18.8$ ($c = 0.50$, $CHCl_3$). HR-EI-MS 544.1954 ($C_{31}H_{33}N_2O_3PS^+$; calc. 544.1949).

N-*[(1*S*)-2-(Benzylsulfamoyl)-1-methylethyl]-2-(diphenylphosphanyl)benzamide* (**11bg**): ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°): 1.11 (*d*, $J = 6.83$, 1 Me); 1.90 (*m*, MeC*H*); 3.14–2.91 (*dm*, CH_2SO_2); 4.40–4.29 (*m*, PhCH_2, MeC*H*); 5.67 (*t*, $J = 6.1$, $NHSO_2$); 6.19 (*d*, $J = 7.92$, NHCO); 7.39–6.95 (*m*, 19 arom. H). ^{13}C-NMR ($CDCl_3$, 100.13 MHz): 19.9; 42.3; 47.2; 57.1; 127.9; 128.2; 128.7; 129.0; 130.3; 133.8 (*d*, $J = 19.9$); 134.0; 135.4 (*d*, $J = 18.8$); 137.1 (*d*, $J = 19.5$); 137.2 (*d*, $J = 19.7$); 142.0 (*d*, $J = 27.8$). IR (nujol): 698 (C–P), 741 (S–N), 1150, 1317 (SO_2), 1537, 1638 (C=N), 3354 (NH). $[\alpha]_D^{25} = +29.2$ ($c = 0.51$, $CHCl_3$). HR-EI-MS: 516.1750 ($C_{29}H_{29}N_2O_3PS^+$; calc. 516.1636).

5. *Representative Procedure for the Allylic Alkylation Reaction.* A *Schlenk* tube was charged with $(CuOTf)_2 \cdot C_6H_6$ (4.3 mg, 0.0085 mmol) and the ligand **11ce** (10 mg, 0.018 mmol) under Ar. After addition of THF (0.5 ml), the mixture was stirred at r.t. for 45 min. A soln. of diethyl 3-phenylprop-2-enyl phosphate (**12**; 47 mg, 0.174 mmol) in THF (0.5 ml) was then added. After 15 min, the mixture was cooled to −78°, and 1M Et_2Zn in toluene (0.522 mmol) was added dropwise. The mixture was allowed to warm to −55°, stirred for 20 h, and quenched by addition of a sat. NH_4Cl soln. A sample of the org. layer was analyzed by GC for the determination of conversion and ee. The org. layer was evaporated and the residue purified by FC (hexane): **13**/**14**, inseparable mixture. GC (*Megadex DACTBSβ*, 25 m, film 0.25 μm; H_2 (70 kPa); injector 200°, detector 200°, oven temp. 50°; 1°/min to 70°, then 4°/min to 200°): t_R (**13**) 13.9 ((3*R*) enantiomer) and 14.1 ((3*S*) enantiomer), t_R (**14**) 27.7, t_R (**12**) 53.5.

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