Enantioselective copper-catalysed addition of organometallic reagents using phosphoramidite ligands

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Chapter 4

Catalytic enantioselective addition of organometallic reagents to *N*–formylimines using copper/phosphoramidite catalysts

The asymmetric synthesis of protected amines via the copper/phosphoramidite-catalyzed addition of organozinc and organoaluminum reagents to N-formylimines, generated in situ from aromatic and aliphatic α-amidosulfones, is reported. High yields of optically active N-formyl protected amines and enantioselectivities of up to 99% were obtained. Under the reaction conditions, partial oxidation of the phosphoramidite ligand to the corresponding phosphoric amide was detected. A preliminary study on the origin of this oxidation and its effect on the catalytic addition reaction is presented.

Part of this chapter was published:

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4.1 Introduction

Enantiomerically pure chiral amines play a prominent role in the area of fine chemicals and pharmaceuticals comprising resolving agents,[1] chiral auxiliaries[2] and catalysts[3] as well as building blocks for the synthesis of biologically active compounds.[4]

The asymmetric nucleophilic addition to imines and their derivatives is one of the most powerful methods available to synthesize α-chiral amines.[5] As shown in Scheme 4.1, this strategy provides access to a wide range of compounds with different functionalization patterns.

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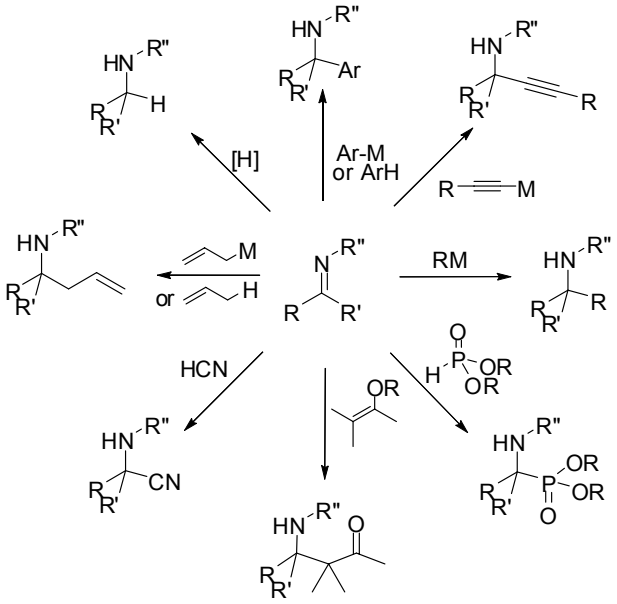
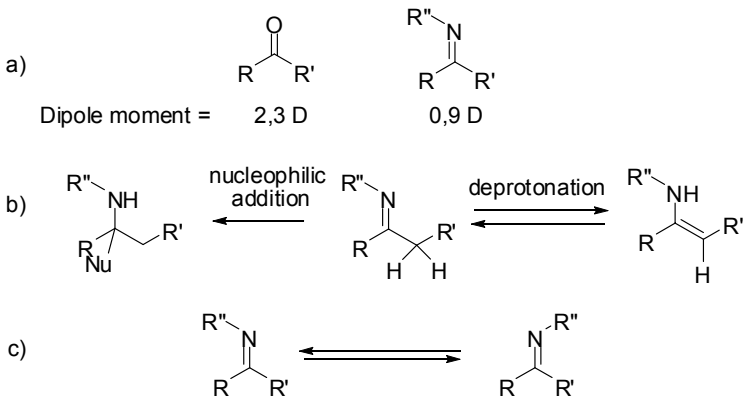


Scheme 4.1 *Nucleophilic addition to the C=N double bond.*

For example, probably the most convenient way to introduce an alkyl substituent at the α-carbon of an amine in an asymmetric fashion consists of the enantioselective addition of organometallic reagents to C=N double bonds.[6] The development of this reaction, however, has been limited in comparison to

the corresponding addition to carbonyl compounds, by several factors associated with the reactivity of imines. The poor electrophilicity of the azomethine carbon, compared to carbonyl compounds, makes imines less reactive toward nucleophilic attack (Scheme 4.2a); furthermore, enolizable imines show a high propensity to undergo deprotonation, rather than addition (Scheme 4.2b). Controlling stereoselectivity in this reaction is difficult due to the existence of *cis-trans* isomers (Scheme 4.2c).[7]



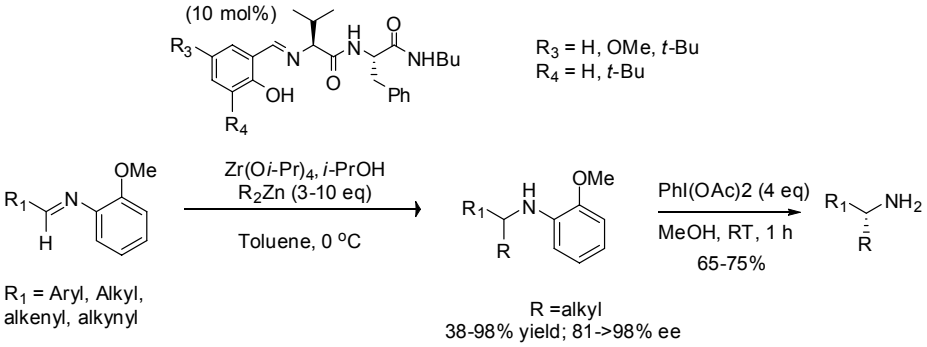
Scheme 4.2 *Some characteristic properties of imines.*

Although many procedures employing chiral auxiliaries[6a-e,8] and stoichiometric chiral ligands[6a-c,e,9] have been described in the literature, the development of catalytic versions of the organometallic addition to the C=N doube bond has been hampered by the ability of the nitrogen atom to bind to the catalyst (for example Lewis acids) strongly, interrupting the catalytic cycle. Only recently, highly enantioselective catalytic methods have appeared in literature.[6e,f,g]

High enantioselectivities for the addition of dialkylzinc reagents have been obtained with imine derivatives protected through *N*-alkylation[10,11] or activated via *N*-sulfonylation,[12,13] *N*-phosphonylation[14,15] or *N*-acylation.[16,17]

4.2 State of the art in the addition of organozinc reagents to imines

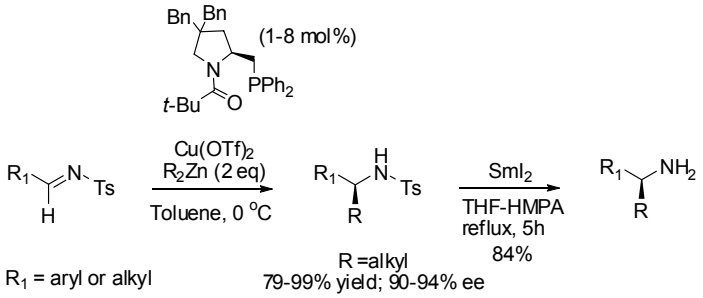
Hoveyda reported the first efficient catalytic method for the enantioselective addition of dialkylzinc reagents to a variety of *N*-*o*-methoxyphenyl alkyl/aryl-aldimines (Scheme 4.3).[10a-c] The aromatic substrates can be isolated whereas the aliphatic substrates are generated more conveniently *in situ* to circumvent formation of enamines and the corresponding homocoupling products (for example, aldol- and Mannich-type additions). The use of chiral Zr-dipeptide complexes as Lewis acid activators of the imino acceptors allows for the preparation of the corresponding *o*-anisidine amines with enantioselectivities exceeding 98%. Oxidative removal of the anisidoyl group affords the enantiomerically enriched amines without loss of enantioselectivity. The low yields observed for the aliphatic substrates were improved by using less Lewis acidic Hf-complexes.[10d]



Scheme 4.3 *Addition of alkylzinc reagents to N-o-anisidine aldimines.*

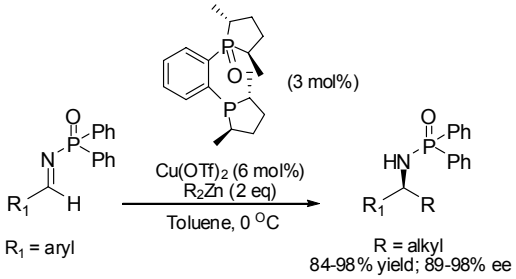
N-Sulfonylimines can undergo diethylzinc addition in high yields and with ee's up to 96% in the presence of $Cu(OTf)_2$ and amidophosphine ligands, under mild conditions, as described by Tomioka *et al*. (Scheme 4.4).[12] The best results in terms of both reactivity and enantioselectivity were obtained with *N*-tosylimines and *N*-mesylimines. Tuning of the steric features of the substituents on the pyrrolidine ring of the chiral ligand played a crucial role in achieving a

high level of enantioselection. Also in this case the procedure can be extended to asymmetric amine synthesis by deprotection of the *N*-sulfonylamide by SmI_2.



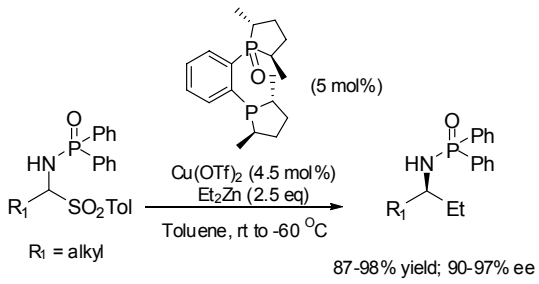
Scheme 4.4 *Addition of alkylzinc reagents to N-sulfonylimines.*

The state of the art for the dialkylzinc addition to *N*-diphenylphosphinoylimines is currently represented by the protocol developed by the Charette group[14] in which the use of a catalytic amount of $Cu(OTf)_2$ in combination with (*R*,*R*)-BozPHOS promotes the alkylation of several aromatic aldimines and ketimines in high yields and with high enantioselectivities (Scheme 4.5).



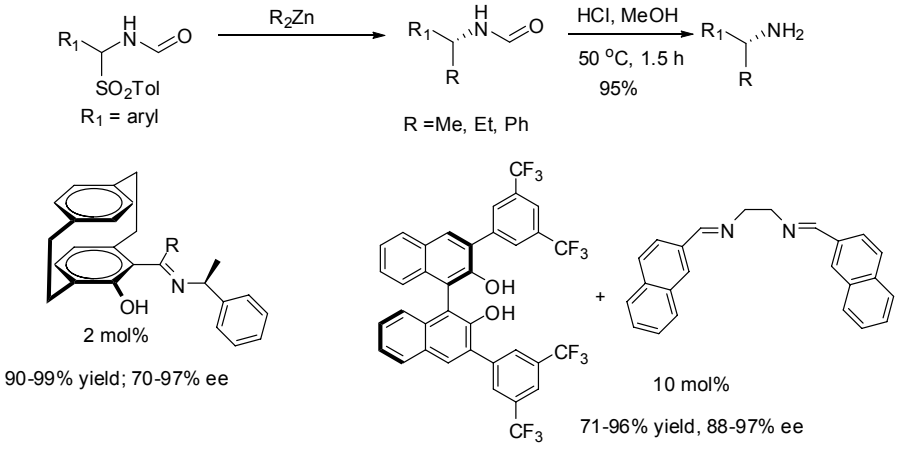
Scheme 4.5 *Addition of alkylzinc reagents to aromatic N-phosphinoylimines.*

Due to extensive decomposition of the *N*-diphenylphosphinoylimines derived from aliphatic aldehydes, bearing enolizable protons, sulfinate adducts of the starting materials were required as masked imines. Reaction of the adduct under standard conditions led to the desired addition product in high yield and with high enantioselectivity (Scheme 4.6).[14f] The use of a larger amount of Et_2Zn was necessary in order to form the imine *in situ*.



Scheme 4.6 *Addition of diethylzinc to alkyl N-phosphinoylimines generated in situ.*

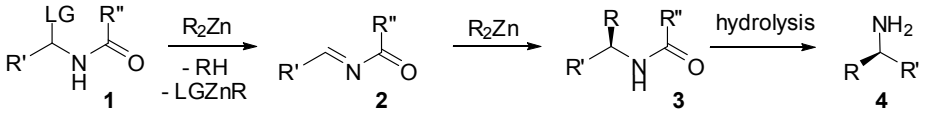
Finally, the scope of the addition of diorganozinc reagents to *N*-formylimines generated *in situ* has been investigated by Bräse[16] and Gong[17] using, respectively, [2,2]paracyclophane-based *N,O*-ligands and 3,3'-substituted optically active BINOLs in combination with racemic and achiral diimines as effective activators (Scheme 4.7).



Scheme 4.7 *Addition of diorganozinc reagents to N-formylimines.*

Although these methods provide access to chiral N-formylamines in high yields and with high enantioselectivities, they are restricted to the use of substrates derived from aryl aldehydes. Furthermore, the laborious synthesis of the chiral ligand or high catalyst loadings are required frequently. The use of N-formylimines as substrates for the synthesis of alkylated chiral amines, however, appears particularly attractive for several reasons. First, the product

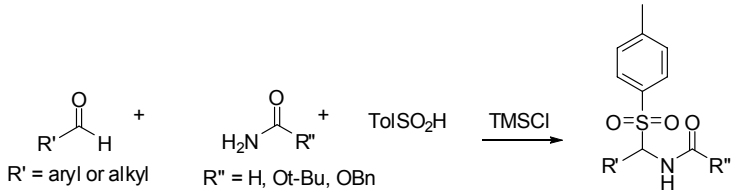
of the reaction is a formamide, which can be deprotected under acidic conditions and without loss of enantioselectivity. In order to circumvent practical problems arising from the inherent instability of acylimines, especially those derived from aliphatic aldehydes, it is possible to generate these substrates in situ from stable precursors. A detailed explanation of this strategy is presented in Scheme 4.8.



R = Me, Et, Ph
R' = aryl, alkyl
R" = H, OR

Scheme 4.8 *Addition of organozinc reagents to in situ generated imines.*

The starting material **1** is an imine adduct substituted at the α-carbon with a leaving group. Elimination of the leaving group under basic conditions generates the imine **2**, which can undergo nucleophilic attack to form the *N*-acylamine **3**. Deprotection of **3** affords the free α-chiral amine **4**. In the addition reaction of R_2Zn, the nucleophile acts as a base also generating the *N*-acylimine together with an equimolar amount of RH and of the adduct LGZnR. It is important that such a species does not inhibit the catalysis. Several leaving groups have been used to form *N*-acylimines, e.g. benzotriazolates,[18] succinimidates[19] and sulfinates.[16,17,20] In the addition reaction of diorganozinc reagents, sulfinate is often the leaving group of choice as its adduct with R_2Zn does not affect the addition reaction[14c] and as the corresponding α-amidosulfones are readily available via a one-pot condensation of the desired aldehyde with *p*-toluenesulfinic acid and an amide or a carbamate (Scheme 4.9).[21]



Scheme 4.9 *Synthesis of the starting material.*

We considered these features highly attractive in order to develop a short and practical catalytic, enantioselective route to chiral amines, starting from aromatic and aliphatic aldehydes, formamide and organometallic reagents, based on the use of readily available chiral phosphoramidite ligands[22] in combination with Cu(II) salts.

4.3 Copper-catalyzed addition of organozinc reagents using phosphoramidite ligands

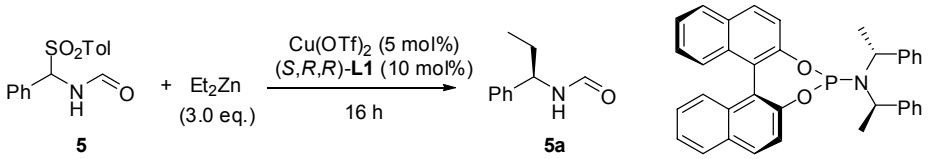
Initially, we investigated the reactivity of the α-amidosulfone **5** (Table 4.1), derived from the condensation of benzaldehyde, *p*-toluenesulfinic acid and formamide, in the copper/phosphoramidite-catalyzed addition of Et_2Zn.

For the optimization of the reaction conditions, 5 mol% of $Cu(OTf)_2$ and 10 mol% of the homochiral monodentate phosphoramidite (*S*,*R*,*R*)-**L1**[22,23] (2.0 equiv. with respect to Cu) were used.

4.3.1 Optimization of the reaction conditions

A preliminary screening, carried out at -30 °C, showed that the reaction proceeds to full conversion and with good enantioselectivity in several solvents (Table 4.1; entries 3-7). In *n*-hexane, because of the poor solubility of the substrate, the reaction proceeds at r.t. only (entry 1). The reaction temperature was decreased in order to obtain higher enantioselectivities. In DCM and THF full conversion was still achieved at -50 °C providing 73% and 96% ee, respectively (entries 11 and 12). A further decrease of the reaction temperature to -78 °C resulted in lower or no conversion.

Table 4.1 *Screening of solvents and temperature.*



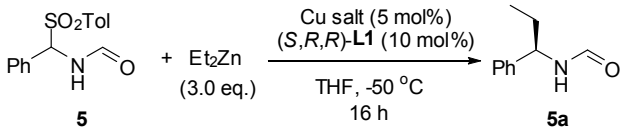
(*S*,*R*,*R*)-**L1**

Entry	T(°C)	solvent	conv(%)	ee(%)	Remarks
1	r.t.	hexane	100	73	36h
2	-30	hexane	-	-	no reaction
3	-30	Et_2O	70	90	
4	-30	toluene	60	90	
5	-30	DCM	100	65	
6	-30	EtOAc	100	90	
7	-30	THF	100	92	
8	-50	Et_2O	-	-	no reaction
9	-50	toluene	-	-	no reaction
10	-50	EtOAc	-	-	no reaction
11	-50	DCM	100	73	
12	-50	THF	100	96	
13	-60	THF	72	96	24h
14	-78	THF	<10	82	24h
15	-78	DCM	-	-	no reaction

The use of THF as the solvent gave the best results affording at -50 °C, product (*R*)-**5a** in quantitative yield and with 96% ee, hence it was used as solvent of choice for further investigations.

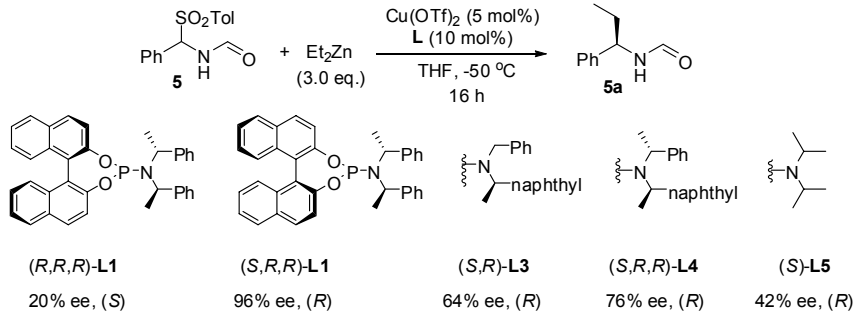
The screening of different copper sources showed no influence of the counter ion on the stereochemical outcome of the reaction. In addition, both Cu(II) and Cu(I) salts proved to be effective in the addition of diethylzinc to the α-amido sulfone **5** (Table 4.2).

Table 4.2 *Screening of copper salts.*



Entry	Cu salt	ee(%)
1	$Cu(OTf)_2$	96
2	$Cu(OAc)\cdot H_2O$	96
3	$Cu(acac)_2$	96
4	$CuBr\cdot SMe_2$	96
5	CuI	94
6	$CuCl_2$	95

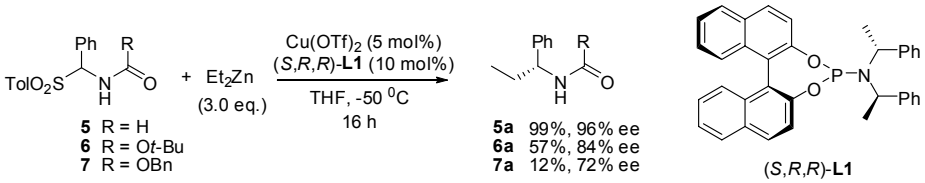
Next a number of chiral phosphoramidite ligands were screened. Phosphoramidite (*R*,*R*,*R*)-**L1**, a diastereoisomer of (*S*,*R*,*R*)-**L1**, afforded **5a** with 20% ee, indicating a mismatch combination of the binaphthol and chiral amine moieties. Moreover, the formation of the opposite enantiomer of **5a**, in this experiment, suggests that the binaphthol part is the dominant feature contributing to the chiral induction. Phosphoramidite ligands **L3**-**L5** gave full conversion of **5** to product **5a** at -50 °C in THF, however, with lower enantioselectivity in comparison to (*S*,*R*,*R*)-**L1** (Scheme 4.10). On the basis of these preliminary studies we concluded that (*S*,*R*,*R*)-**L1** is the ligand of choice.



Scheme 4.10. *Screening of phosphoramidite ligands for the addition of Et_2Zn to **5**.*

Further screening of the reaction conditions showed that it is possible to lower the catalyst loading to 2 mol% and the amount of diethylzinc to 2.5 equiv. without affecting the yield or the enantioselectivity. A decrease of the amount of catalyst to 1 mol% resulted in longer reaction times (full conversion only after 36 h).

Replacing the amide moiety for a carbamate reduced both the isolated yield and the enantioselectivity significantly (Scheme 4.11, substrates **6** and **7**).



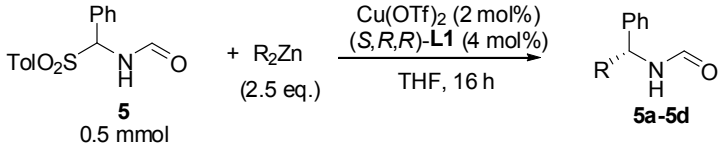
Scheme 4.11 *Screening of protecting groups.*

4.3.2 Organometallic reagent scope

Next the use of other commercially available organozinc reagents in the addition to the *N*-formylimine generated *in situ* from **5** was investigated. Using 2 mol% of the chiral Cu/phosphoramidite catalyst and 2.5 equiv. of the organozinc reagent (Table 4.3), *i*-Pr_2Zn and *n*-Bu_2Zn afforded compound **5b** and **5c** in high yield and 91% and 88% enantioselectivity, respectively (entries 2, 3).

The introduction of a methyl substituent was not possible at -50 °C because of the lower reactivity of Me_2Zn. At -30 °C, two products could be observed by TLC and detected by GS-MS: the expected product **5d** and benzaldehyde.[24]

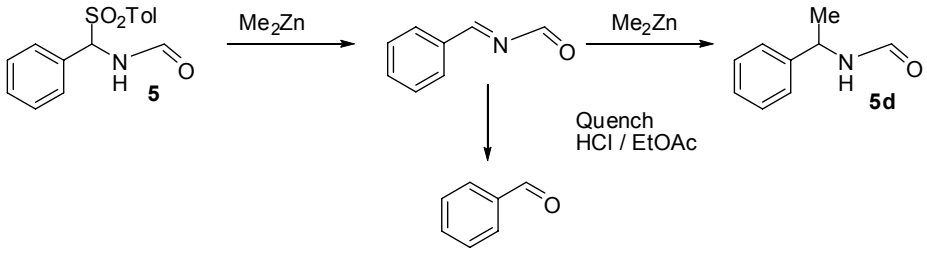
Table 4.3 *Addition of diorganozinc reagents to **5**.*



Entry	R_2Zn	T (°C)	Product	Yield (%)[a]	Ee (%)
1	Et_2Zn	-50	**5a**	99	96-(+)-(*R*)
2	*i*Pr_2Zn	-50	**5b**	97	91-(+)-(*R*)
3	*n*Bu_2Zn	-50	**5c**	92	88-(+)-(*R*)[b]
4	Me_2Zn	-50	**5d**	-	-
5	Me_2Zn	-30	**5d**	n.d.	27-(+)-(*R*)
6	Me_2Zn	-10	**5d**	99	10-(+)-(*R*)

[a] Isolated yield. [b] The absolute configuration of **5c** was tentatively assigned by analogy on the basis of the selectivity observed with the same catalyst (*S*,*R*,*R*)-**L1** in the addition of the other organozinc reagents to **5**.

The latter derives from the hydrolysis of the *in situ* generated imine during the quenching of the reaction mixture (aq. HCl, 1M), indicating that, using Me_2Zn, the rate-determining step is the addition reaction and not the formation of the imine (Scheme 4.12). Product **5d** could be isolated in quantitative yield carrying out the addition reaction at higher temperature (-10 °C), however, the enantioselectivity was low (entry 6).

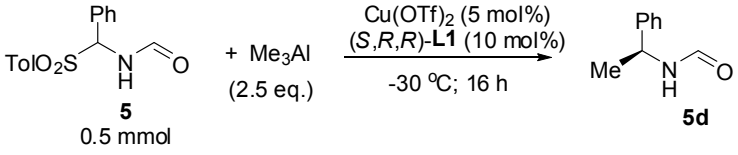


Scheme 4.12 *Addition of Me_2Zn to compound **5** at -30 °C.*

The methyl group is ubiquitous in biologically active compounds. Difficulties are however encountered frequently in the transfer of a methyl group in organometallic addition reactions. Hence, we made considerable efforts to achieve high enantioselectivity in the addition of methyl nucleophiles. Towards this goal, we investigated the use of Me_3Al as methyl source. [25]

The addition reaction of Me_3Al to α-amido sulfone **5** under standard conditions did not proceed at -50 °C. Although full conversion to product **5d** was reached in THF at -30 °C after overnight reaction, the product was obtained in racemic form (Table 4.4, entry 1). No enantioselectivity was observed in toluene either (entry 2), while better results were achieved in ethereal solvents. Thus, **5d** could be obtained with 80% enantioselectivity in *i*-Pr_2O (entry 6).

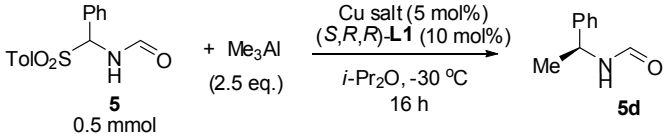
Table 4.4 *Solvent screening for the addition of Me_3Al to **5**.*

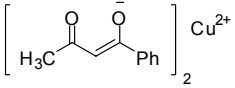
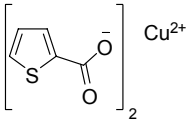
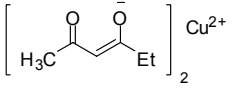
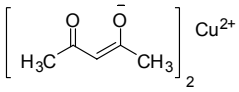
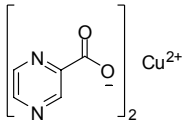
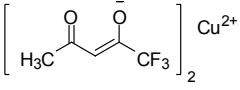
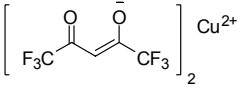


Entry	Solvent	Conv. (%)	ee(%)
1	THF	100	-
2	Toluene	100	-
3	Et_2O	>90	50
4	*n*-Bu_2O	≈50	70
5	*t*-BuOMe	100	65
6	*i*-Pr_2O	100	80

A further improvement was achieved using a different copper source. CuTC (TC = 2-thiophenecarboxylate) gave approximately the same enantioselectivity observed with $Cu(OTf)_2$, (Table 4.5, entry 2).

Table 4.5 *Copper salt screening for the addition of Me_3Al to **5**.*



Entry	Cu salt	ee(%)	Entry	Cu salt	ee(%)
1	$Cu(OTf)_2$	80	8		80
2		81	9		81
3	$CuBr{\cdot}SMe_2$	rac	10	$Cu(BF_4)_2{\cdot}6H_2O$	32
4	$Cu(OAc)_2{\cdot}H_2O$	84	11	CuSPh	rac
5		86	12		rac
6		78	13	$CuSO_4{\cdot}5H_2O$	rac
7		83	14	Cu(*L*-Proline)$_2$	rac

A higher level of stereocontrol (84% ee) was reached with $Cu(OAc)_2{\cdot}H_2O$ (entry 4), however the highest ee (86%) was obtained using $Cu(acac)_2$ (entry 5). The use of copper salts structurally related to $Cu(acac)_2$ did not lead to better results (entries 6-9). The enantioselectivity dropped dramatically using $Cu(BF_4)_2{\cdot}6H_2O$ (entry 10) and racemic product was obtained with $CuBr{\cdot}SMe_2$, CuSPh, Cu(2-piperazinecarboxylate)$_2$ and $CuSO_4{\cdot}5H_2O$ (entries 3, 11-13), confirming the importance of the counter ion for the formation of an efficient

catalyst. $Cu(acac)_2$ turned out to be the best choice leading to the desired product in 70% isolated yield and 86% ee (entry 5). When the catalyst loading was decreased to 2 mol% both lower isolated yield (44%) and lower enantioselectivity (67%) were obtained.

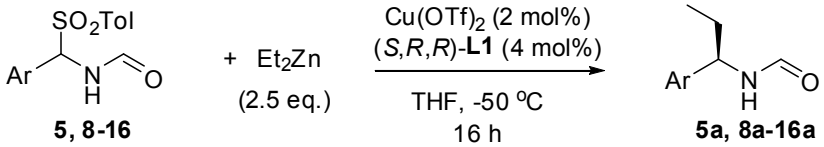
Interestingly, in contrast to the formation of (+)-(*R*)-**5d** using Me_2Zn, the application of Me_3Al resulted in the formation of (-)-(*S*)-**5d** using the same enantiomer of the phosphoramidite ligand (*S*,*R*,*R*)-**L1**. A rationalization for this experimental observation will be provided later in this chapter.

4.3.3 Substrate scope

The scope of *in situ* generated aromatic and aliphatic *N*-formylimines for the copper/phosphoramidite-catalyzed addition of Et_2Zn to aromatic α-amidosulfones was investigated next (Table 4.6). Electronic effects do not seem to play a major role: substitution at the *para* position of the aryl moiety with electron-donating and electron-withdrawing groups does not affect the enantioselectivity and the *N*-formylamines were isolated with ≥96% ee and near quantitative yield (entries 2-5). High enantioselectivities were obtained with *meta*-substituted substrates as well (entries 6 and 7). The introduction of a substituent in the *ortho* position resulted in a dramatic decrease in the ee to less than 50% (entries 8 and 9). We attribute this reduction in stereocontrol to steric effects of the *o*-substituent. Addition to the 2-naphthyl substituted sulfone **16** gave product **16a** in 80% ee.

α-Amidosulfones derived from aliphatic aldehydes showed lower reactivity in the addition reaction than their aromatic counterparts. Compound **17** was chosen as model substrate. No addition reaction was observed in THF, at -50 °C (Table 4.7, entry 1). An increase in temperature to -20 °C was necessary to achieve full conversion of the starting material after overnight reaction and the enantioselectivity observed was modest (entry 2). Further screening of solvents revealed that toluene and Et_2O provide better results compared to THF (entry 4).

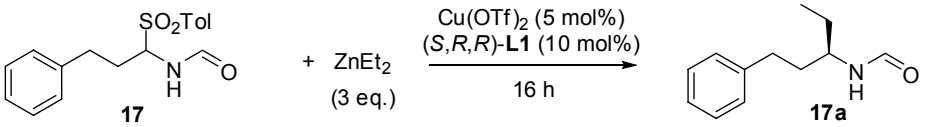
Table 4.6 *Cu-catalyzed addition of Et_2Zn to N-acyl imines generated in situ from aromatic α-amidosulfones.*



5, 8-16 **5a, 8a-16a**

Entry	Compound	Ar	Product	Yield (%)	ee (%)
1	**5**	Ph	**5a**	99	96-(+)-(*R*)
2	**8**	4-Cl-Ph	**8a**	94	97-(+)-(*R*)
3	**9**	4-Br-Ph	**9a**	94	99-(+)-(*R*)
4	**10**	4-MeO-Ph	**10a**	99	97-(+)-(*R*)
5	**11**	4-Me-Ph	**11a**	90	96-(+)-(*R*)
6	**12**	3-Me-Ph	**12a**	99	95-(+)-(*R*)
7	**13**	3-MeO-Ph	**13a**	96	95-(+)
8	**14**	2-MeO-Ph	**14a**	99	47-(-)
9	**15**	2-BnO-Ph	**15a**	99	45-(-)
10	**16**	2-naphthyl	**16a**	94	80-(+)

Table 4.7 *Solvent screening for the addition of Et_2Zn to **17**.*

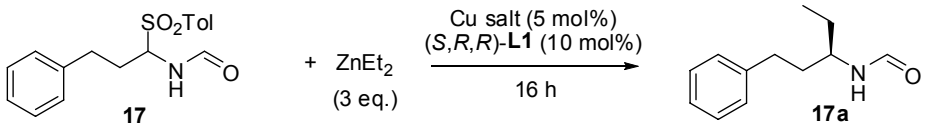


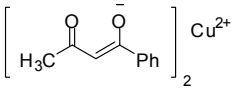
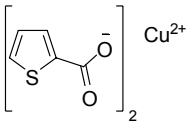
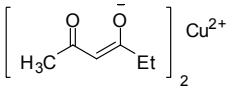
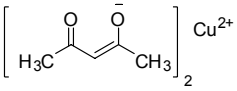
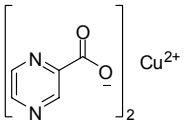
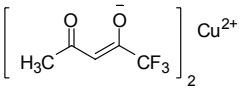
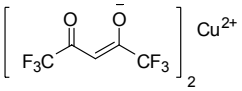
17 **17a**

Entry	Solvent	T(°C)	conv.%)	ee(%)
1	THF	-50	<10	-
2	THF	-20	100	17
3	Toluene	-20	100	37
4	Et_2O	-20	100	38
5	iPr_2O	-30	100	20

Several copper salts were tested in order to improve the enantioselectivity of the reaction. Using $Cu(OAc)_2 \cdot H_2O$, product **17a** was obtained with a strongly increased 66% ee (Table 4.8, entry 3).

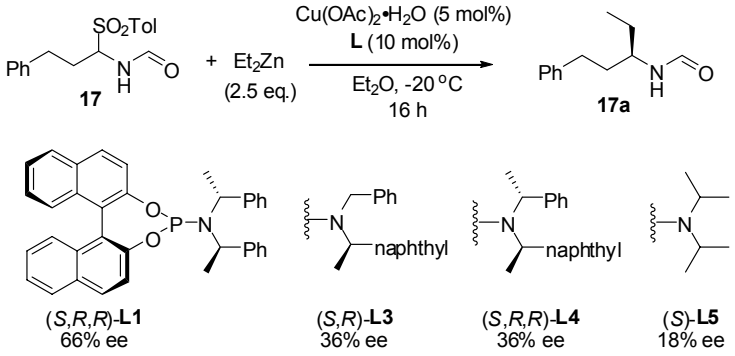
Table 4.8 *Screening of copper salt for the addition of Et_2Zn to **17**.*



Entry	Cu salt	ee(%)	Entry	Cu salt	ee(%)
1	$Cu(OTf)_2$	40	8		54
2		60	9		12
3	$CuBr \cdot SMe_2$	36	10	$Cu(BF_4)_2 \cdot 6H_2O$	54
4	$Cu(OAc)_2 \cdot H_2O$	66	11	CuSPh	rac
5		58	12		rac
6		48	13	$CuSO_4 \cdot 5H_2O$	rac
7		45			

Several phosphoramidite ligands were tested in order to improve the enantioselectivity for the addition of Et_2Zn to **17** also (Scheme 4.13). In this

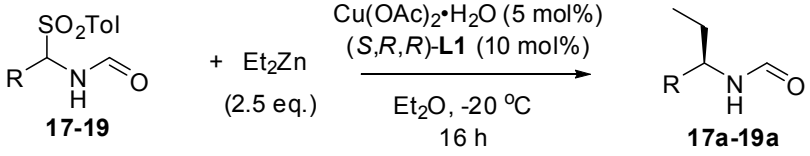
case, however, ligand (*S*,*R*,*R*)-**L1** proved again to be the most selective. Variation of the steric or chiral properties of the amine moiety in ligands **L3**-**L5** resulted, invariably, in a decrease in the enantioselectivity.



Scheme 4.13 *Ligand screening for the Et_2Zn addition to **17**.*

In summary, using (*S*,*R*,*R*)-**L1**, high yields and enantioselectivities varying between 45% and 70% were obtained for the Cu-catalyzed addition of diethylzinc to aliphatic substrates (Table 4.9).

Table 4.9 *Cu-catalyzed addition of Et_2Zn to N-acyl imines generated in situ from aliphatic α-amidosulfones.*



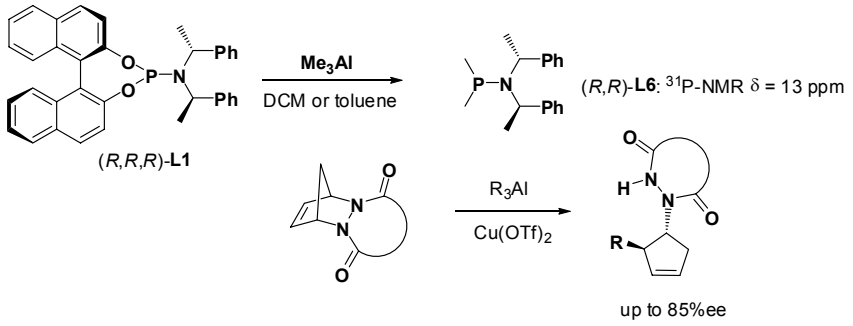
Entry	Compound	R	Product	Yield (%)	ee (%)
1	**17**	$PhCH_2CH_2$	**17a**	81	66-(+)
2	**18**	*c*-hexyl	**18a**	99	45-(+)
3	**19**	*n*-hexyl	**19a**	99	70-(+)

4.4 Studies on *in situ* ligand oxidation

Isolation of (*S*,*R*,*R*)-**L1** after the addition reaction of Et_2Zn to **5** carried out on 1.5 mmol scale in THF, at -50 °C was attempted in order to investigate the efficiency of recovery of the chiral phosphoramidite ligand. Ligand (*S*,*R*,*R*)-**L1** was recovered in 61% yield. It is possible that partial hydrolysis of the phosphoramidite occurs during the quenching of the reaction and during column chromatography over silica gel. Together with (*S*,*R*,*R*)-**L1**, a second compound containing phosphorus was isolated as a white foamy solid. The ^{1}H-NMR spectrum of this species appeared rather similar to that of (*S*,*R*,*R*)-**L1** while the ^{31}P-NMR spectrum showed one single absorption at 12.3 ppm. The spectroscopic data as well as HRMS analysis suggested that this new species was (*S*,*R*,*R*)-**L2** (Figure 4.1a,b).

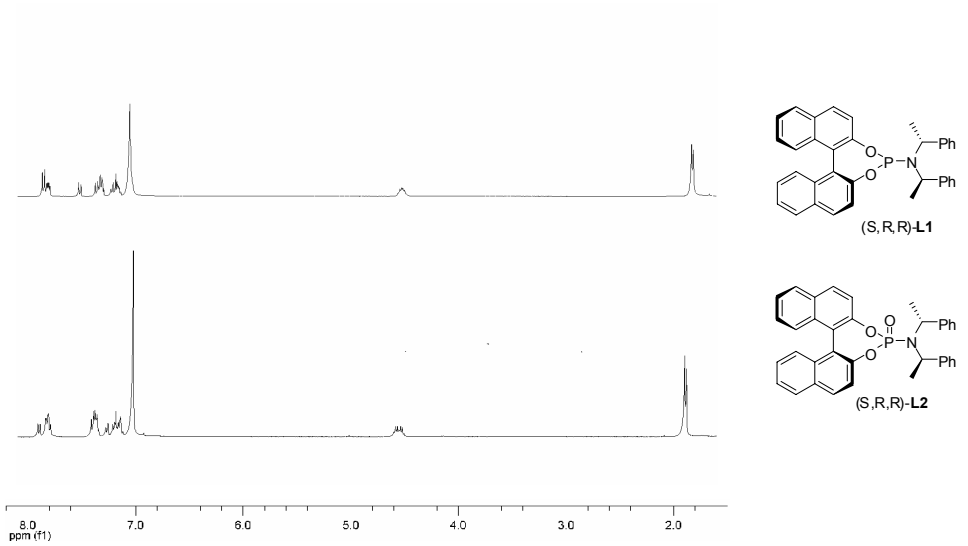
Further investigations revealed that the formation of the species (*S*,*R*,*R*)-**L2** could be detected after performing the addition reaction of both Me_3Al and Et_2Zn to substrate **5** in the solvents THF, Et_2O, *i*-Pr_2O, EtOAc and CH_2Cl_2. By contrast, if the reactions were performed in hexane, at room temperature, or in toluene, at -30 °C, the only phosphorous compound recovered was (*S*,*R*,*R*)-**L1**.

Modification of phosphoramidite ligands[26] during a reaction using organometallic reagents has been reported previously. Recently, Alexakis and Micouin[27] observed that, in the $Cu(OTf)_2$-catalyzed ring opening of meso bicyclic hydrazines, the phosphoramidite (*R*,*R*,*R*)-**L1** reacts with Me_3Al, in dichloromethane and toluene, leading to the corresponding aminophosphine, which is the actual ligand in the reaction (Scheme 4.14).

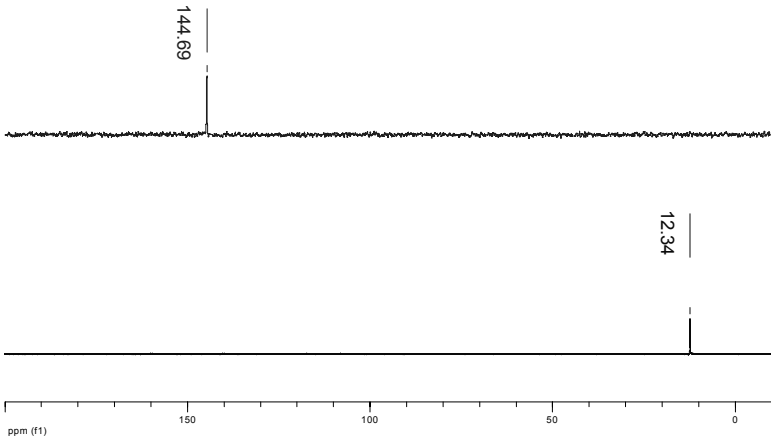


Scheme 4.14 *Phosphoramidite modification reported in the literature.*[27]

Figure 4.1 NMR spectra of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2**.

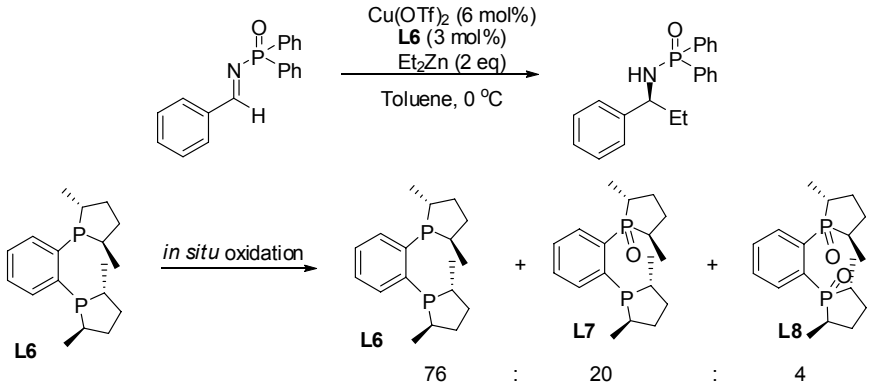


a) ^{1}H-NMR in $CDCl_3$, 400 MHz



b) ^{31}P-NMR in $CDCl_3$, 400 MHz

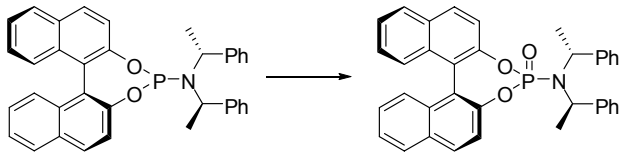
In our case, even though the chemical shift of the newly formed species (*S*,*R*,*R*)-**L2** in the ^{31}P-NMR spectrum would be consistent with the formation of the dimethylaminophosphine, the ^{1}H-NMR spectrum data rules out this possibility. The ^{1}H-NMR spectrum, in fact, clearly shows that the BINOL moiety is still present in (*S*,*R*,*R*)-**L2**. The substitution pattern is similar to (*S*,*R*,*R*)-**L1**: only minor shifts can be observed for the doublet corresponding to the methyl group and for the signal of the benzylic hydrogen; small differences are present in the aromatic region. The work of Charette et al.,[28] provided inspiration for the elucidation of the structure of (*S*,*R*,*R*)-**L2**. They found that, in the Cu-catalyzed addition of diorganozinc reagents to *N*-phosphonoylimines, an *in situ* oxidation of Me-Duphos by Cu(II) salts occurs, to produce the highly effective monoxide ligand (BozPHOS) and, to a lesser extent, the Me-Duphos bisoxide (Scheme 4.15). Furthermore, it was proven that in the bidentate ligand (BozPHOS), the cooperative effect of both donor groups, namely the phosphine and the hemilabile phosphinoxide moieties, is essential to reach high enantioselectivities.[28]



Scheme 4.15 *Ligand oxidation described by Charette.*[28]

Redox processes between phosphorous based ligands and transition metals have been reported previously.[29] Pd(II) salts, for example, can be reduced to Pd(0) in the presence of Ph_3P, producing $Ph_3P{=}O$ as the by-product.[30] Regarding this type of chemistry much less is known for copper. It has been reported that Cu(II) salts are reduced by 1,2-bis(diphenylphosphino)ethane to

produce several phosphine/phosphine oxide ligands,[31] however, to the best of our knowledge, no precedents for the Cu-catalyzed oxidation of phosphoramidite ligands are described in the literature. We decided to investigate the possibility of *in situ* oxidation of the phosphoramidite ligand (*S*,*R*,*R*)-**L1** to the corresponding phosphoric amide (*S*,*R*,*R*)-**L2** under the reaction conditions and its possible role in asymmetric catalysis (Scheme 4.16).



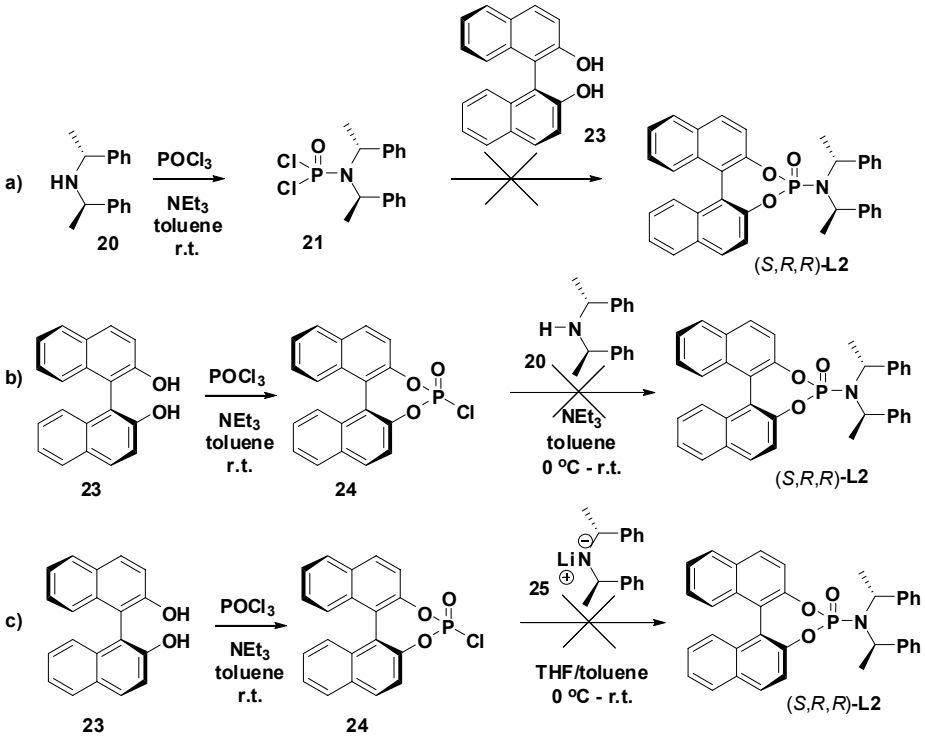
(*S*,*R*,*R*)-**L1** (*S*,*R*,*R*)-**L2**

Scheme 4.16 *In situ ligand oxidation.*

4.4.1 Synthesis of the phosphoric amide (*S*,*R*,*R*)-L2

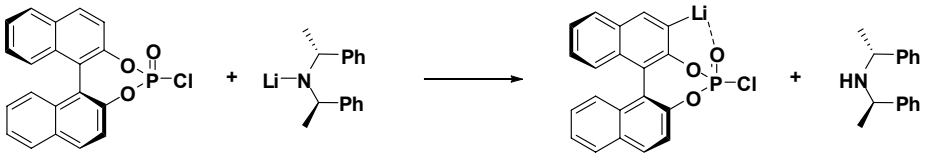
Several approaches for the synthesis of phosphoric amide (*S*,*R*,*R*)-**L2** were tried. At first, the use of procedures based on the synthesis of phosphoramidite (*S*,*R*,*R*)-**L1**[32] were investigated (Scheme 4.17).

The first attempt consisted of the synthesis of the phosphoroyl chloride **21** from $POCl_3$ and the chiral amine **20**, followed by substitution with (*S*)-BINOL **23** (Scheme 4.17a); however, the reaction did not proceed. Next the inverse procedure was used (Scheme 4.17b). The phosphoroyl chloride **24** was formed from $POCl_3$ and (*S*)-BINOL **23**.[33] Compound **24** is rather stable and was isolated and purified by column chromatography. In the second step of the synthesis the phosphoroyl chloride was reacted with the chiral amine **20** in presence of Et_3N. The reaction is known to work with non-sterically hindered secondary amines and cyclic aliphatic secondary amines like pyrrolidine and piperidine,[34] however, under these conditions, the bis(dimethyl-benzyl)amine **20** was recovered.



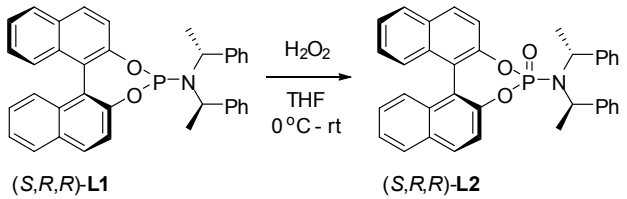
Scheme 4.17 *Attempts in the synthesis of (S,R,R)-**L2**.*

Sterically demanding amines undergo substitution on BINOL-based phosphorus chlorides successfully if the more reactive Li-amide is first formed.[32] In the case of the phosphoroyl chloride, however, this approach did not furnish the desired product either (Scheme 4.17c). It is possible that the formation of a stabilized carbanion, via coordination of the lithium to the P=O bond, promotes the deprotonation on the 3 position of the binaphthol moiety by the Li-amide rather than the substitution of the chloride (Scheme 4.18).



Scheme 4.18 *Reaction of the Li-amide with **24**.*

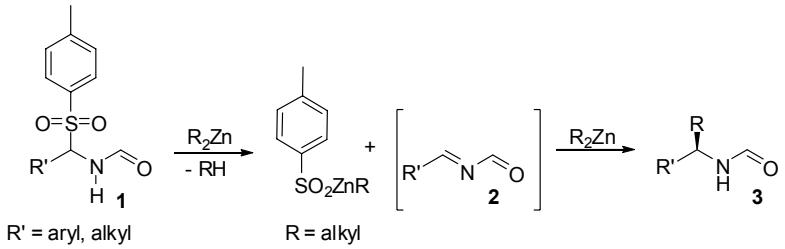
Finally, the phosphoric amide (*S*,*R*,*R*)-**L2** was synthesized, in quantitative yield, upon reaction of (*S*,*R*,*R*)-**L1** with hydrogen peroxide (Scheme 4.19). Characterization by ^{1}H-NMR and ^{31}P-NMR spectroscopy, HRMS and elemental analysis of the phosphoric amide synthesized and the isolated species (*S*,*R*,*R*)-**L2** confirmed that the two compounds are identical.



Scheme 4.19 *Synthesis of (S,R,R)-**L2**.*

4.4.2 Ligand oxidation

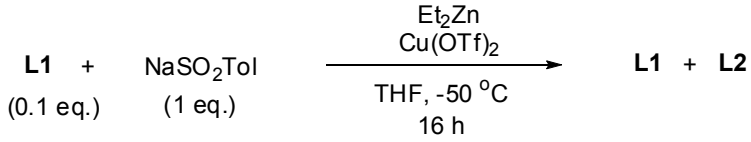
We hypothesized that the ligand oxidation, observed in the Cu-catalyzed addition of diorganozinc and organoaluminium reagents to *N*-formylimines could be due to the substrate itself. The *in situ* formation of the imine, in fact, generates 1 equivalent of the zinc-sulfinate adduct, which could act as an oxidizing agent (Scheme 4.20).



Scheme 4.20 *Formation of the zinc sulfinate adduct.*

To confirm this hypothesis, we investigated the effect that sulfinate, added as the sodium salt, has on ligand (*S*,*R*,*R*)-**L1**, under different conditions (Table 4.10).[35] If no sulfinate was present in the reaction mixture, no oxidation occurred (entry 1); when the sulfinate was added in a copper-free environment, with or without Et_2Zn, a small percentage (< 10%) of (*S*,*R*,*R*)-**L1** was oxidized to (*S*,*R*,*R*)-**L2** (entries 2 and 3). On the other hand, if both the sulfinate and a copper salt were added to the reaction mixture, complete oxidation of (*S*,*R*,*R*)-**L1** to the phosphoric amide was observed after overnight reaction, suggesting that the copper salt acts as a catalyst for the reaction (entry 4).

Table 4.10 *Effect of sulfinate on (S,R,R)-**L1**.*



Entry	$NaSO_2Tol$ (eq.)	Et_2Zn (eq.)	$Cu(OTf)_2$ (eq.)	L1 / L2 [a]
1	0	3	0.05	100 / 0
2	1	3	0	95 / 5
3	1	0	0	94 / 6
4	1	0	0.05	0 / 100

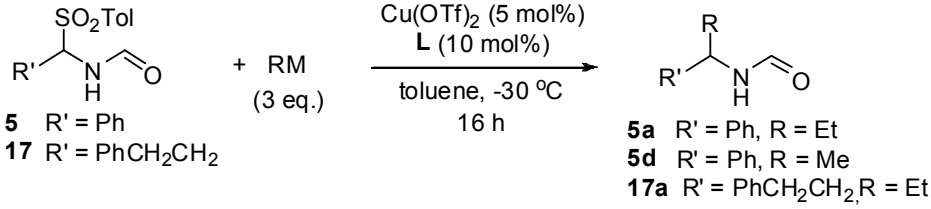
[a] The **L1** / **L2** ratio was determined by ^{31}P-NMR of the crude product after quenching with a saturated aqueous solution of NH_4Cl.

We were interested to see whether the chiral phosphoric amide (*S*,*R*,*R*)-**L2** was merely a by-product in the reaction or actually part of the active catalyst.

We mentioned earlier that no ligand modification was detected when the Me_3Al or Et_2Zn addition to compound **5** was performed in hexane or in toluene. This allowed us to analyze the activity and enantioselectivity of the species (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2**, used separately, from a mixture of the two (that would be formed inevitably *in situ*, when performing the reaction in THF, DCM or ethereal solvents, starting with (*S*,*R*,*R*)-**L1** alone).

The addition of Me_3Al and Et_2Zn to the α-amidosulfone **5** and the addition of Et_2Zn to the aliphatic α-amidosulfone **17** were carried out in toluene, at -30 °C, using 5 mol% of $Cu(OTf)_2$ and 10 mol% of the ligand (*S*,*R*,*R*)-**L1**, (*S*,*R*,*R*)-**L2** or their 1/1 mixture (5 mol% of (*S*,*R*,*R*)-**L1** plus 5 mol% of (*S*,*R*,*R*)-**L2**). The results are presented in Table 4.11. Entries 3, 6 and 9 demonstrate that the phosphoric amide (*S*,*R*,*R*)-**L2** is not an efficient chiral ligand by itself, affording product **5a** in full conversion but in racemic form. Moreover, low conversions of the starting material (< 10%) were observed for the addition of Et_2Zn to compound **17** and the addition of Me_3Al to compound **5**. No significant difference in the enantioselectivity was observed in the addition of diethylzinc to compound **5** in the presence of only (*S*,*R*,*R*)-**L1** or a 1/1 mixture of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** (entries 1, 2). The reaction proceeded to full conversion, overnight, and high ee's of 85% and 86%, respectively, were achieved for the product **5a**. However, the use of a 1/1 mixture of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** led to a slight improvement in the enantioselectivity of the addition of diethylzinc to the aliphatic α-amidosulfone **17** (entries 4 and 5).

Table 4.11 *Study on the effect of (S,R,R)-**L2** in toluene.*



5 R' = Ph
17 R' = $PhCH_2CH_2$

5a R' = Ph, R = Et
5d R' = Ph, R = Me
17a R' = $PhCH_2CH_2$, R = Et

Entry	Comp.	L	RM	Prod.	Conv. (%)	ee(%)
1	5	**L1**	Et_2Zn	**5a**	100	85
2	5	**L1**+**L2** (1/1)	Et_2Zn	**5a**	100	86
3	5	**L2**	Et_2Zn	**5a**	100	-
4	17	**L1**	Et_2Zn	**17a**	100	38
5	17	**L1**+**L2** (1/1)	Et_2Zn	**17a**	100	47
6	17	**L2**	Et_2Zn	**17a**	<10	-
7	5	**L1**	Me_3Al	**5d**	100	-
8	5	**L1**+**L2** (1/1)	Me_3Al	**5d**	100	52
9	5	**L2**	Me_3Al	**5d**	<10	-
10[a]	5	**L1**+**L2** (1/1)	Me_3Al	**5d**	100	60
11[a]	5	**L1**+HMPA (1/1)	Me_3Al	**5d**	100	50

[a] $Cu(acac)_2$ was used as copper source.

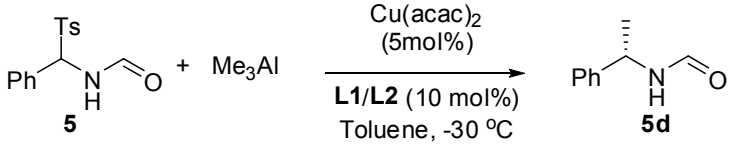
A striking improvement in the enantioselectivity was reached using Me_3Al in the formation of **5d**, that went from 0%, when (*S*,*R*,*R*)-**L1** was used as the only chiral species (entry 7), to 52% when both (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** were present in the reaction mixture (entry 8). These results suggest that the phosphoric amide (*S*,*R*,*R*)-**L2**, indeed, can have an effect on the enantioselectivity of the reaction.

We considered that (*S*,*R*,*R*)-**L2** could act as a chiral analogue of HMPA, whose strong coordinating properties are known to largely affect the regio- and stereochemical outcome of reactions involving organometallic species.[36] The

presence of a metal coordinating species might vary the structure of the actual catalyst, for example in terms of aggregation level, which is known to be strongly dependent on several factors, above all the solvent.[37] This observation prompted us to study the effect of the addition of HMPA in place of (*S*,*R*,*R*)-**L2** (Table 4.11, entry 11). Having observed a major influence of the phosphoric amide (*S*,*R*,*R*)-**L2** in the addition of Me_3Al to compound **5**, we decided to evaluate the effect of HMPA addition in the same reaction. $Cu(acac)_2$ was used instead of $Cu(OTf)_2$ because, from the screening of the copper salts for the Me_3Al addition (Table 4.5), it was proven to be the most effective. As shown in Table 4.11 (entries 10 and 11), HMPA seems to play a similar role compared to (*S*,*R*,*R*)-**L2**. With $Cu(acac)_2$ as copper source, the use of a 1/1 mixture of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** afforded the product **5d** with 60% ee, while the use of a 1/1 mixture of (*S*,*R*,*R*)-**L1** and HMPA gave **5d** with a slightly lower, but significant, 50% ee, suggesting that the effect that (*S*,*R*,*R*)-**L2** has on the enantioselectivity of the Me_3Al addition to **5** might not be due to its chiral properties but rather an additional (HMPA type) co-ligand effect.

We investigated the dependence of the enantioselectivity observed for **5d** as a function of the amount of phosphoric amide (*S*,*R*,*R*)-**L2** present in the reaction mixture. Keeping the total amount of (*S*,*R*,*R*)-**L1** plus (*S*,*R*,*R*)-**L2** fixed to 10 mol%, we varied the relative ratio of the two chiral species. As shown in Table 4.12 the highest ee (72%, entry 2) is obtained when a 75/25 mixture of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** is used. Interestingly, the formation of a similar ratio of (*S*,*R*,*R*)-**L1** to (*S*,*R*,*R*)-**L2** is detected by ^{31}P-NMR spectroscopy after the addition of Me_3Al to **5** in *i*-Pr_2O. Higher loadings of (*S*,*R*,*R*)-**L2** resulted in a decrease of the enantioselectivity (entries 3 and 4). Considering that the total amount of the species (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2** is kept constant to 10 mol% (2.0 equiv compared to copper), the reason for this decrease might be attributed to a decrease of the relative ratio between the chiral ligand (*S*,*R*,*R*)-**L1** and the copper salt.

Table 4.12 *Effect of (S,R,R)-**L2** loading.*



Entry	L1/L2	ee (%)
1	100/0	-
2	75/25	72
3	50/50	60
4	25/75	64
5	0/100	0

Further investigations are needed to clarify the exact role of (*S*,*R*,*R*)-**L2** in the Cu-catalyzed addition of organometallic reagents to N-formylimines generated *in situ* from α-amidosulfones.

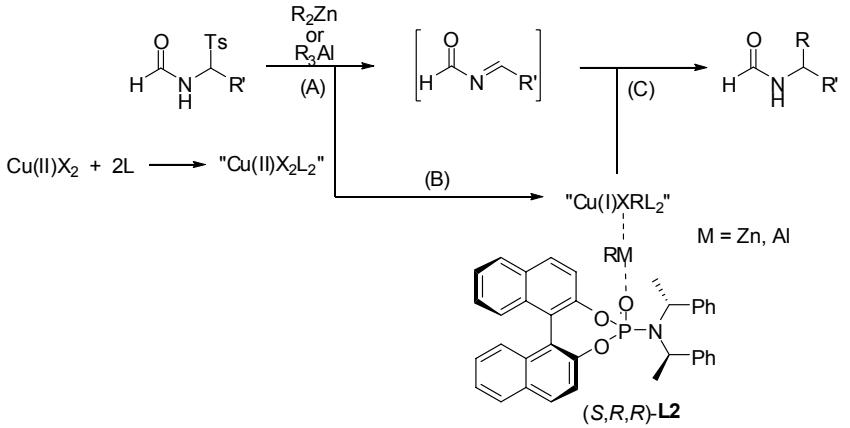
4.5 Conclusions

We showed that the copper/phosphoramidite-catalyzed addition of diorganozinc reagents and trimethylaluminum to *N*-acylimines generated *in situ* from aromatic and aliphatic α-amidosulfones furnishes optically active α-alkylamides in high yield and enantiomeric excess of up to 99%.

Beside providing a convenient method for the synthesis of optically active α-chiral amines, the development of this reaction offered several reflection points based on experimental observations. We mentioned that, in attempting to introduce a methyl substituent (*vide supra*), we observe opposite enantioselection in the formation of product **5d** switching from Me_2Zn to Me_3Al.

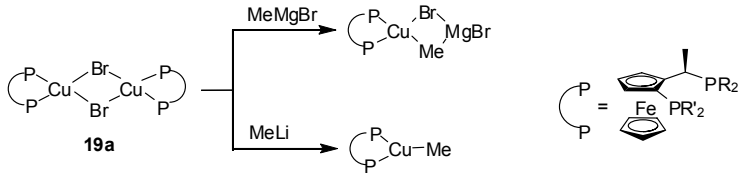
It is known that the organometallic reagent has multiple functions during the catalytic reaction. First of all, it acts as a base in order to generate *in situ* the actual substrate for the nucleophilic addition (Scheme 4.21, path (A)). The organometallic reagent is responsible for the reduction of the precatalytic copper(II) complex to a copper(I) active species[38] in which transmetallation of

the alkyl group “R” has occurred[39] (Scheme 4.21, path (B)). Then, the active catalyst can transfer the alkyl group to the *in situ* generated imine forming the final product (Scheme 4.21, path (C)).



Scheme 4.21 *Copper catalyzed organometallic addition to α-amido sulfones.*

A different stereochemical outcome of the reaction upon changing of the organometallic reagent suggests that the latter is involved in the structure of the active catalytic system, also. We assume that by switching from an organozinc to an organoaluminum reagent two different catalysts are formed, thereby changing the final outcome of the reaction. This assumption is in agreement with what was demonstrated for the copper catalyzed 1,4-addition of Grignard reagents[40] in which the addition of different organometallic species to a same precatalytic system, under the same conditions, leads to the formation of two different copper complexes (Scheme 4.22).



Scheme 4.22

A second striking experimental finding consists of the modification of the chiral ligand *in situ*. In particular, oxidation of the chiral phosphoramidite (*S*,*R*,*R*)-**L1** to the corresponding phosphoric amide (*S*,*R*,*R*)-**L2**, under the reaction conditions, was observed when performing the organometallic addition in THF, Et_2O, *i*Pr_2O, DCM and EtOAc, but not in hexane or toluene. A preliminary investigation into the effect of the chiral phosphoric amide (*S*,*R*,*R*)-**L2** shows that, under certain conditions, the presence of this species in the reaction mixture can improve the level of the enantioselectivity of the reaction. In the addition of Me_3Al to **5** in toluene, in fact, the presence of (*S*,*R*,*R*)-**L2** is essential to achieve enantioselectivity in the reaction, however, the same species does not seem to play a prominent role in the addition of organozinc reagents.

Assuming that the influence of (*S*,*R*,*R*)-**L2** is due to its coordinating properties (*vide supra*), it is plausible that such a coordination occurs to the metal, Zn or Al, of the organometallic species (Scheme 4.21). A stronger interaction with the more oxophilic aluminum atom can account for the marked effect on the stereochemical outcome of the Me_3Al addition reaction when the phosphoric amide is present.

Further mechanistic studies are required to clarify the actual role played by (*S*,*R*,*R*)-**L2**, however the advantage of readily available and stable starting materials as well as the easy deprotection of the α-alkylamides obtained make the new method a useful alternative to existing methods for the formation of optically active α-chiral amines.

4.6 Experimental section

General Methods.

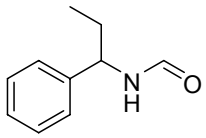
All reactions were performed in oven or flame dried glassware under an inert atmosphere of N_2 or argon and using standard Schlenk techniques. Toluene, THF and ether were distilled from sodium, *n*-hexane and CH_2Cl_2 from CaH_2. Dialkylzinc reagents: Me_2Zn (2 M in toluene), Et_2Zn (1 M in *n*-hexane), *i*-Pr_2Zn (1 M in toluene) and Me_3Al (1 M in *n*-heptane) were purchased from Aldrich, Bu_2Zn (1 M in *n*-heptane) was purchased from Fluka. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 TLC-plates F254 and visualized using UV or phosphomolybdic acid. Flash chromatography was carried out on silica gel (Aldrich, 230 – 400 mesh). ^{1}H NMR spectra were recorded at 300 or 400 MHz with $CDCl_3$ or DMSO-d^6 as solvent, ^{13}C NMR spectra were obtained at 50 or 100 MHz in $CDCl_3$ or DMSO-d^6 (Varian spectrometers). Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for hydrogen atoms, δ = 77.0 ppm for carbon atoms; DMSO-d^6, δ = 2.54 ppm for hydrogen atoms, δ = 40.45 ppm for carbon atoms). Optical rotations were recorded on Schmidt+Haench Polartronic MH8 instrument at 589 nm. Gas chromatography was performed on Hewlett-Packard HP 6890 Series GC System with flame ionization detector using chiral columns and HPLC analyses were performed on a Shimadzu LC-10AD VP instrument equipped with 6 parallel normal phase chiral columns, using a Chiralpak AD column (4.6 × 250 mm, 10 μm) and a diode array detector. Mass spectra were recorded on an JEOL JMS·600H mass spectrometer.

General procedure for the copper/phosphoramidite catalyzed addition of dialkylzinc reagents to aromatic α-amidosulfones.

$Cu(OTf)_2$ (3.6 mg, 0.010 mmol) and ligand (*S*,*R*,*R*)-**L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous THF (10 mL) and stirred for 30 min at room temperature. The mixture was cooled to -50 °C and the substrate (0.50 mmol) was added. A solution of a R_2Zn (1.25 mmol) in the indicated solvent was added dropwise and the reaction mixture was stirred for 16 h at -50 °C, then

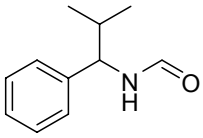
quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography.

(*R*)-(+)-*N*-(1-Phenyl-propyl)-formamide (5a).[16a]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **5a** in 99% isolated yield (Rf = 0.4) as a colorless oil which slowly solidified, m.p. = 56.8-58.8 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt(*S*) = 95.17 min (minor), Rt(*R*) = 95.75 min (major); 96% ee. $[\alpha]_D$ = + 136.1 (c 0.99, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.18 (s, 1H, C*H*O), 7.36-7.22 (m, 5H, H_{Ar}), 6.02 (s, br, 1H, N*H*), 4.96 (q, *J* = 7.8 Hz, 1H, C*H*), 1.92-1.80 (m, 2H, CH_2), 0.90 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 162.1, 141.0, 128.6, 127.5, 126.6, 54.2, 28.9, 10.6 ppm. Minor rotamer ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 12.0 Hz, 1H, C*H*O), 7.36-7.22 (m, 5H, H_{Ar}), 6.30 (s, br, 1H, N*H*), 4.37 (q, *J* = 7.2 Hz, 1H, C*H*), 1.92-1.80 (m, 2H, CH_2), 0.94 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 165.9, 140.8, 128.9, 127.9, 126.2, 59.1, 30.1, 10.5 ppm. HRMS calcd. for $C_{10}H_{13}NO$ 163.1004, found 163.0997.

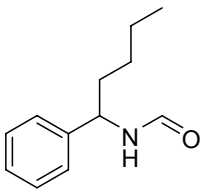
(*R*)-(+)-*N*-(1-Phenyl-2-methyl-propyl)-formamide (5b).[41]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **5b** in 97% isolated yield (Rf = 0.4) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt(*S*) = 97.42 min (minor), Rt(*R*) = 98.49 min (major); 91% ee. $[\alpha]_D$ = + 102.3 (c 1.07, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 3:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.15 (s, 1H, C*H*O), 7.34-7.18 (m, 5H, H_{Ar}), 6.69 (br s, 1H, N*H*), 4.79 (t, *J* = 8.5 Hz, 1H, C*H*), 2.09-1.95 (m, 1H, C*H*), 0.94 (d, *J* = 6.7 Hz, 3H, CH_3), 0.81 (d, *J* = 6.7 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.7, 141.0, 128.3, 127.1, 126.8, 57.8, 33.2, 19.6, 18.6 ppm. Minor rotamer ^{1}H-NMR (400

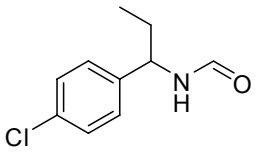
MHz, $CDCl_3$) δ = 8.08 (d, *J* = 11.7 Hz, 1H, C*H*O), 7.34-7.18 (m, 5H, H_{Ar}), 6.69 (s, br, 1H, N*H*), 4.15 (t, *J* = 7.2 Hz, 1H, C*H*), 2.09-1.95 (m, 1H, C*H*), 0.93 (d, *J* = 6.7 Hz, 3H, CH_3), 0.85 (d, *J* = 6.7 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 165.0, 141.0, 128.6, 127.4, 126.5, 62.9, 33. 8, 19.7, 18.2 ppm. HRMS calcd. for $C_{11}H_{15}NO$ 177.1154, found 177.1163.

(*R*)-(+)-*N*-(1-Phenyl-pentyl)-formamide (5c).



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **5c** in 92% isolated yield (Rf = 0.5) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt(*R*) = 108.43 min (major), Rt(*S*) = 106.70 min (minor); 88% ee. $[\alpha]_D$ = + 99.6 (c 1.09, $CHCl_3$).[42] The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.09 (s, 1H, C*H*O), 7.35-7.21 (m, 5H, H_{Ar}), 6.57 (br d, *J* = 7.5 Hz, 1H, N*H*), 4.98 (q, *J* = 7.7 Hz, 1H, C*H*), 1.80-1.74 (m, 2H, CH_2), 1.35-1.18 (m, 4H, CH_2), 0.86 (t, *J* = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.5, 142.0, 128.5, 127.2, 126.4, 52.1, 35.8, 28.2, 22.3, 13.8 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.09-8.06 (m, 1H, C*H*O), 7.35-7.21 (m, 5H, H_{Ar}), 6.76 (br t, *J* = 10.7 Hz, 1H, N*H*), 4.40 (q, *J* = 7.7 Hz, 1H, C*H*), 1.80-1.74 (m, 2H, CH_2), 1.35-1.18 (m, 4H, CH_2), 0.89 (t, *J* = 7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.5, 142.1, 128.7, 127.5, 126.0, 56.7, 36.9, 28.2, 22.2, 13.8 ppm. HRMS calcd. for $C_{12}H_{17}NO$ 191.1310, found 191.1320.

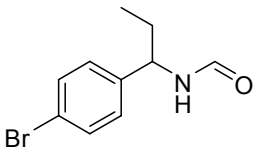
(*R*)-(+)-*N*-[1-(4-Chloro-phenyl)-propyl]-formamide (8a).[16a]



Purification by column chromatography (SiO_2; EtOAc/ *n*-pentane 1:1) afforded compound **8a** in 94% isolated yield (Rf = 0.28) as a colorless oil which slowly solidified, m.p. = 94.0-94.8 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 180 °C; Rt(*S*) = 117.57 min (minor), Rt(*R*) = 118.06 min (major); 97% ee. $[\alpha]_D$ = + 149.5 (c 1.06, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.14 (s, 1H, C*H*O), 7.31-7.25 (m, 2H, H_{Ar}), 7.19-7.15 (m, 2H, H_{Ar}), 6.54 (br d, *J* = 7.2 Hz,

1H, N*H*), 4.86 (q, *J* = 7.6 Hz, 1H, C*H*), 1.84-1.71 (m, 2H, CH_2), 0.92-0.84 (m, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.8, 140.0, 133.1, 128.7, 127.9, 53.3, 28.9, 10.5 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.31-7.25 (m, 2H, H_{Ar}), 7.19-7.15 (m, 2H, H_{Ar}), 7.06 (br t, *J* = 10.0 Hz, 1H, N*H*), 4.31 (q, *J* = 7.6 Hz, 1H, C*H*), 1.84-1.71 (m, 2H, CH_2), 0.92-0.84 (m, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.5, 140.2, 133.5, 129.0, 127.6, 57.7, 30.1, 10.5 ppm. HRMS calcd. for $C_{11}H_{12}ClNO$ 197.0607, found 197.0604. Elem. Anal. calcd. for $C_{11}H_{12}ClNO$: C 60.76%, H 6.12%, N 7.09%, found: C 60.60%, H 6.13, N 6.97%.

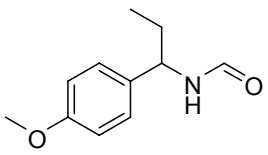
(*R*)-(+)-*N*-[1-(4-Bromo-phenyl)-propyl]-formamide (9a).[17b]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **9a** in 94% isolated yield (Rf = 0.43) as a white solid, m.p. = 100.6-101.7 °C. HPLC on Chiralpak AD column (*n*-heptane/propan-2-ol = 98:2, flow = 1.0 mL/min): Rt(*R*) = 47.21 min (major), Rt(*S*) = 51.64 min (minor); 99% ee. $[\alpha]_D$ = + 133.7 (c 0.92, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 8.13$ (s, 1H, C*H*O), 7.46-7.41 (m, 2H, H_{Ar}), 7.14-7.09 (m, 2H, H_{Ar}), 6.38 (br s, 1H, N*H*), 4.85 (q, *J* = 7.6 Hz, 1H, C*H*), 1.85-1.71 (m, 2H, CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.6, 140.7, 131.6, 128.2, 121.1, 53.1, 28.9, 10.5 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 11.8 Hz, 1H, C*H*O), 7.46-7.41 (m, 2H, H_{Ar}), 7.14-7.09 (m, 2H, H_{Ar}), 6.72 (br s, 1H, N*H*), 4.30 (q, *J* = 7.6 Hz, 1H, C*H*), 1.85-1.71 (m, 2H, CH_2), 0.91 (t, *J* = 7.3 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.5, 140.8, 131.8, 127.8, 121.4, 57.6, 30.1, 10.5 ppm. MS-EI calcd. for $C_{10}H_{12}BrNO$: 241 (27) $[M]^+$, 212 (100) $[M\text{-}Et]^+$. HRMS calcd. for C_8H_7BrNO [M-Et]: 211.9711, found 211.9708. Elem. Anal. calcd. for $C_{10}H_{12}BrNO_2$: C 49.61%, H 5.00%, N 5.79%, found: C 49.40%, H 5.10%, N 5.62%.

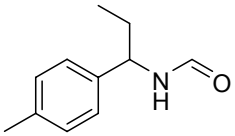
(*R*)-(+)-*N*-[1-(4-Methoxy-phenyl)-propyl]-formamide (10a).[16a]

Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 3:2) afforded compound **10a** in 99% isolated yield (Rf = 0.5) as a colorless oil which slowly solidified, m.p. = 73.0-74.4 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60



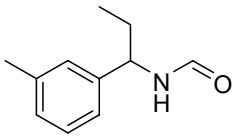
°C, 10 min.-1 °C/min till 180 °C; Rt(*S*) = 118.90 min (minor), Rt(*R*) = 119.23 min (major); 97% ee. $[\alpha]_D$ = + 141.9 (c 1.10, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 8.12$ (s, 1H, C*H*O), 7.18 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.87-6.82 (m, 2H, H_{Ar}), 6.54 (br s, 1H, N*H*), 4.87 (q, *J* = 7.7 Hz, 1H, C*H*), 3.76 (s, 3H, OCH_3), 1.85-1.71 (m, 2H, CH_2), 0.86 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.4, 158.7, 133.7, 127.6, 113.9, 55.2, 53.0, 28.9, 10.6 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.13 (d, *J* = 8.8 Hz, 2H, H_{Ar}), 6.87-6.82 (m, 2H, H_{Ar}), 6.54 (br s, 1H, N*H*), 4.23 (q, *J* = 7.6 Hz, 1H, C*H*), 3.77 (s, 3H, OCH_3), 1.85-1.71 (m, 2H, CH_2), 0.90 (t, *J* = 7.3 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.5, 158.8, 133.8, 127.2, 114.0, 57.5, 53.0, 30.2, 10.6 ppm. HRMS calcd. for $C_{11}H_{15}NO_2$ 193.1103, found 193.1102. Elem. Anal. calcd. for $C_{11}H_{15}NO_2$: C 68.37%, H 7.82%, N 7.25%, found: C 68.40%, H 7.90%, N 7.07%.

(*R*)-(+)-*N*-[1-(4-Methyl-phenyl)-propyl]-formamide (11a).[16a]



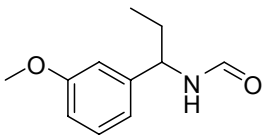
Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **11a** in 90% isolated yield (Rf = 0.43) as a colorless oil which slowly solidified, m.p. = 67.0-68.8 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 180 °C; Rt(*S*) = 110.45 min (minor), Rt(*R*) = 111.13 min (major); 96% ee. $[\alpha]_D$ = + 149.8 (c 1.05, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 3.3:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 8.16$ (s, 1H, C*H*O), 7.17-7.10 (m, 4H, H_{Ar}), 6.05 (s, br, 1H, N*H*), 4.91 (q, *J* = 7.7 Hz, 1H, C*H*), 2.32 (br s, 3H, CH_3), 1.88-1.74 (m, 2H, CH_2), 0.89 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.4, 138.5, 137.1, 129.3, 126.4, 53.4, 29.0, 21.0, 10.6 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.17-7.10 (m, 4H, H_{Ar}), 6.29 (s, br, 1H, N*H*), 4.31 (q, *J* = 7.5 Hz, 1H, C*H*), 2.33 (br s, 3H, CH_3), 1.88-1.74 (m, 2H, CH_2), 0.92 (t, *J* = 7.3 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.4, 138.7, 137.4, 129.5, 126.0, 57.8, 30.2, 21.0, 10.6 ppm. HRMS calcd. for $C_{11}H_{15}NO$ 177.1154, found 177.1161. Elem. Anal. calcd. for $C_{11}H_{15}NO$: C 74.54%, H 8.53%, N 7.90%, found: C 74.29%, H 8.60%, N 7.75%.

(*R*)-(+)-*N*-[1-(3-Methyl-phenyl)-propyl]-formamide (12a).[16a]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **12a** in 99% isolated yield (Rf = 0.47) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min., 1 °C/min till 180 °C; Rt(*S*) = 99.91 min (minor), Rt(*R*) = 100.77 min (major); 95% ee. $[\alpha]_D$ = + 128.8 (c 0.905, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 3:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H, C*H*O), 7.24-7.17 (m, 1H, H_{Ar}), 7.09-7.01 (m, 3H, H_{Ar}), 6.56 (br s, 1H, N*H*), 4.88 (q, *J* = 7.7 Hz, 1H, C*H*), 2.31 (s, 3H, CH_3), 1.87-1.72 (m, 2H, CH_2), 0.88 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.6, 141.6, 138.0, 128.3, 128.0, 127.3, 123.3, 53.6, 29.0, 21.3, 10.6 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.08 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.24-7.17 (m, 1H, H_{Ar}), 7.09-7.01 (m, 3H, H_{Ar}), 6.69 (br s, 1H, N*H*), 4.32-4.26 (m, 1H, C*H*), 2.33 (s, 3H, CH_3), 1.87-1.72 (m, 2H, CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.6, 141.7, 138.4, 128.6, 128.2, 126.8, 123.0, 58.1, 30.1, 21.3, 10.6 ppm. HRMS calcd. for $C_{11}H_{15}NO$ 177.1154, found 177.1163.

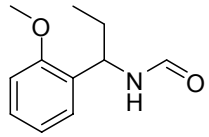
(+)-*N*-[1-(3-Methoxy-phenyl)-propyl]-formamide (13a).[43]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **13a** in 96% isolated yield (Rf = 0.30) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min., 1 °C/min till 180 °C; Rt = 121.75 min (minor), Rt = 122.98 min (major); 95% ee. $[\alpha]_D$ = + 116.1 (c 1.025, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 1H, C*H*O), 7.26-7.20 (m, 1H, H_{Ar}), 6.85-6.76 (m, 3H, H_{Ar}), 6.44 (br s, 1H, N*H*), 4.89 (q, *J* = 7.7 Hz, 1H, C*H*), 3.76 (s, 3H, OCH_3), 1.84-1.73 (m, 2H, CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.6, 159.6, 143.2, 129.6, 118.7, 112.4, 112.4, 55.1, 53.6, 29.0, 10.6 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.08 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.26-7.20 (m, 1H, H_{Ar}), 6.85-6.76 (m, 3H, H_{Ar}), 6.44 (br s, 1H, N*H*), 4.29 (q, *J* = 7.6 Hz, 1H, C*H*), 3.77 (s, 3H, OCH_3), 1.84-1.73 (m, 2H, CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-

NMR (100 MHz, $CDCl_3$) δ = 164.6, 159.8, 143.4, 129.8, 118.3, 112.6, 112.0, 58.1, 55.1, 30.1, 10.6 ppm. HRMS calcd. for $C_{11}H_{15}NO_2$ 193.1103, found 193.1102.

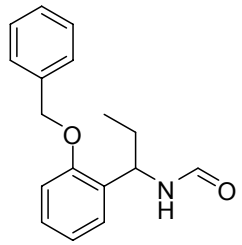
(–)-*N*-[1-(2-Methoxy-phenyl)-propyl]-formamide (14a).



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **14a** in 99% isolated yield (Rf = 0.31) as a white solid. Mp = 122.4-124.2 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 111.15 min (major), Rt = 112.39 min (minor); 47% ee. $[\alpha]_D$ = - 47.8 (c 0.98, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 2.5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.16 (s, 1H, C*H*O), 7.26-7.21 (m, 1H, H_{Ar}), 7.71-7.11 (m, 1H, H_{Ar}), 6.93-6.87 (m, 2H, H_{Ar}), 6.73 (br s, 1H, N*H*), 5.10 (q, *J* = 8.1 Hz, 1H, C*H*), 3.84 (s, 3H, OCH_3), 1.87-1.78 (m, 2H, CH_2), 0.85 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.3, 156.9, 129.0, 128.8, 128.4, 120.7, 110.9, 55.2, 52.0, 28.2, 11.0 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 12.0 Hz, 1H, C*H*O), 7.26-7.21 (m, 1H, H_{Ar}), 7.71-7.11 (m, 1H, H_{Ar}), 6.93-6.87 (m, 2H, H_{Ar}), 6.54 (br s, 1H, N*H*), 4.45 (q, *J* = 8.2 Hz, 1H, C*H*), 3.82 (s, 3H, OCH_3), 1.87-1.78 (m, 2H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.1, 156.4, 129.3, 128.7, 127.5, 120.7, 110.8, 55.7, 52.0, 28.6, 11.0 ppm. HRMS calcd. for $C_{11}H_{15}NO_2$ 193.1103, found 193.1102. Elem. Anal. calcd. for $C_{11}H_{15}NO_2$: C 68.37%, H 7.82%, N 7.25%, found: C 68.45%, H 7.89%, N 7.04%.

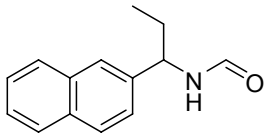
(–)-*N*-[1-(2-Benzyloxy-phenyl)-propyl]-formamide (15a).

Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **15a** in 99% isolated yield (Rf = 0.44) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 122.34 min (major), Rt = 143.18 min (minor); 45% ee. $[\alpha]_D$ = - 11.7 (c 1.07, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 2.5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.10 (br s, 1H, C*H*O), 7.44-7.33 (m, 5H, H_{Ar}), 7.27-7.17



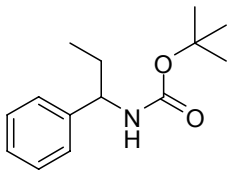
(m, 2H, H_{Ar}), 6.97-6.91 (m, 2H, H_{Ar}), 6.73 (br d, *J* = 9.3 Hz, 1H, N*H*), 5.11 (s, 2H, CH_2), 5.16 (q, *J* = 8.1 Hz, 1H, C*H*), 1.92-1.80 (m, 2H, CH_2), 0.86 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.4, 156.0, 136.5, 129.7, 129.1, 128.6, 128.4, 128.0, 127.3, 127.2, 120.9, 112.1, 70.1, 52.0, 28.2, 11.0 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, *J* = 12.0 Hz, 1H, C*H*O), 7.44-7.33 (m, 5H, H_{Ar}), 7.27-7.17 (m, 2H, H_{Ar}), 6.97-6.91 (m, 2H, H_{Ar}), 6.78 (br m, 1H, N*H*), 5.09 (s, 2H, CH_2), 4.61-4.55 (m, 1H, C*H*), 1.92-1.80 (m, 2H, CH_2), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.5, 155.5, 136.3, 129.7, 129.1, 128.6, 128.4, 128.0, 127.3, 127.2, 121.0, 112.0, 70.1, 54.7, 28.5, 10.9 ppm. HRMS calcd. for $C_{17}H_{19}NO_2$ 269.1416, found 269.1423.

(+)-*N*-(1-Naphthyl-propyl)-formamide (16a).



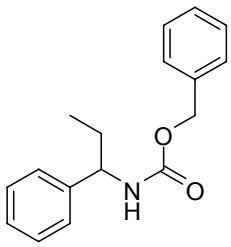
Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **16a** in 94% isolated yield (Rf = 0.29) as a colorless oil which slowly solidified, m.p. = 85.2-86.7 °C. HPLC on Chiralpak AD column (heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): t_R 15.88 min (major), t_R 20.08 min (minor). 80% ee. $[\alpha]_D$ = + 138.4 (c 1.00, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 3:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.19 (s, 1H, C*H*O), 7.83-7.78 (m, 3H, H_{Ar}), 7.72 (s, 1H, H_{Ar}), 7.50-7.44 (m, 2H, H_{Ar}), 7.38 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.28 (br d, *J* = 6.5 Hz, 1H, N*H*), 5.11 (q, *J* = 7.7 Hz, 1H, C*H*), 1.97-1.84 (m, 2H, CH_2), 0.97-0.90 (m, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.6, 138.8, 133.2, 132.7, 128.5, 127.8, 127.5, 126.2, 125.8, 125.3, 124.6, 53.7, 28.9, 10.7 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.83-7.78 (m, 3H, H_{Ar}), 7.67 (s, 1H, H_{Ar}), 7.50-7.44 (m, 2H, H_{Ar}), 7.32 (d, *J* = 8.5 Hz, 1H, H_{Ar}), 6.65 (br t, *J* = 11.2 Hz, 1H, N*H*), 4.49 (q, *J* = 7.6 Hz, 1H, C*H*), 1.97-1.84 (m, 2H, CH_2), 0.97-0.90 (m, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.7, 139.0, 133.1, 132.7, 128.8, 127.8, 127.6, 126.4, 126.1, 125.0, 124.0, 58.2, 30.0, 10.7 ppm. HRMS calcd. for $C_{14}H_{15}NO$ 213.1154, found 213.1155. Elem. Anal. calcd. for $C_{14}H_{15}NO$: C 78.84%, H 7.09%, N 6.57%, found: C 78.56%, H 7.12%, N 6.51%.

(+)- (1-Phenyl-propyl)-carbamic acid *tert*-butyl ester (6a).[44]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 2:98) afforded compound **6a** in 57% isolated yield (Rf = 0.38) as a colorless oil which slowly solidified. HPLC on Chiralpak AD column, 4.6 × 250 mm, 10 μm, (heptane/propan-2-ol = 99:1, flow = 1.0 mL/min): Rt = 11.12 min (major), Rt = 12.28 min (minor); 84% ee. $[\alpha]_D$ = + 44.0 (c 0.91, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.34-7.30 (m, 2H, H_{Ar}), 7.26-7.22 (m, 3H, H_{Ar}), 4.84 (br s, 1H, N*H*), 4.53 (br s, 1H, C*H*), 1.78-1.75 (m, 2H, CH_2), 1.42 (s, 9H, C(CH_3)$_3$), 0.89 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 155.3, 142.8, 128.4, 127.0, 126.3, 79.3, 56.31, 29.8, 28.3, 10.6 ppm. HRMS calcd. for $C_{14}H_{21}NO_2$ 235.1572, found 235.1577. Elem. Anal. calcd. for $C_{14}H_{21}NO_2$: C 71.46%, H 8.99%, N 5.95%, found: C 71.32%, H 9.02%, N 5.85%.

(+)- (1-Phenyl-propyl)-carbamic acid benzyl ester (7a).[45]

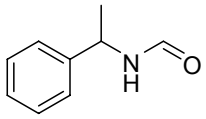


Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:9) afforded compound **7a** in 12% isolated yield (Rf = 0.64) as a colorless oil. HPLC on Chiralpak AD column, 4.6 × 250 mm, 10 μm, (heptane/propan-2-ol = 95:5, flow = 1.0 mL/min): Rt = 13.27 min (major), Rt = 15.64 min (minor); 49% ee. $[\alpha]_D$ = + 16.4 (c 0.78, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.35-7.26 (m, 10H), 5.13-5.03 (m, 3H), 4.62-4.62 (br m, 1H), 1.83-1.77 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 155.7, 142.3, 136.4, 128.5, 128.5, 128.1, 127.3, 126.4, 66.7, 56.9, 29.6, 10.6 ppm. HRMS calcd. for $C_{17}H_{19}NO_2$ 269.1416, found 269.1407.

Procedure for the copper/phosphoramidite catalyzed addition of trimethylaluminum to 1. $Cu(acac)_2$ (6.6 mg, 0.025 mmol) and ligand **(*S*,*R*,*R*)-L1** (27.0 mg, 0.050 mmol) were dissolved in anhydrous *i*Pr_2O (10 mL) and the mixture stirred for 45 min at room temperature. The mixture was cooled to -30 °C and substrate **5** (0.50 mmol) was added. A 1M solution of Me_3Al in heptane (1.25 mmol) was added dropwise and the reaction mixture was stirred for 16 h at -30 °C, then quenched with 1M aq. HCl (10 mL) and extracted with EtOAc (3

x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography.

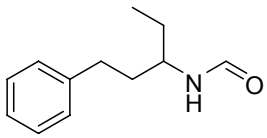
(*S*)-(–)-*N*-(1-Phenyl-ethyl)-formamide (5d).[46]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 3:2) afforded compound **5d** in 70% isolated yield (Rf = 0.37) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 89.32 min (major), Rt = 91.05 min (minor); 85% ee. $[\alpha]_D$ = - 102.3 (c 1.05, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.09 (br s, 1H, C*H*O), 7.37-7.23 (m, 5H, H_{Ar}), 6.32 (br s, 1H, N*H*), 5.20-5.13 (m, 1H, C*H*), 1.48 (d, *J* = 6.9 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.3, 142.6, 128.6, 127.4, 126.0, 47.5, 21.7 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.12 (br s, 1H, C*H*O), 7.37-7.23 (m, 5H, H_{Ar}), 6.44 (br s, 1H, N*H*), 4.69-4.61 (m, 1H, C*H*), 1.53 (d, *J* = 6.9 Hz, 3H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.2, 142.6, 128.8, 127.6, 125.7, 51.6, 23.5 ppm. HRMS calcd. for $C_9H_{11}NO$ 149.0841, found 149.0847.

General procedure for the copper/phosphoramidite catalyzed addition of diethylzinc to aliphatic α-amido sulfones. $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 0.010 mmol) and ligand (***S***,***R***,***R***)-**L1** (10.8 mg, 0.020 mmol) were dissolved in anhydrous Et_2O (10 mL) and the mixture stirred for 45 min at r.t. The mixture was cooled to -20 °C and the substrate (0.50 mmol) was added. A 1M solution of a Et_2Zn in hexane (1.25 mmol) was added dropwise and the reaction mixture was stirred for 16 h at -20 °C, then quenched with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography.

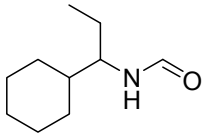
(+)-*N*-(1-Ethyl-3-phenyl-propyl)-formamide (17a).



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 6:4) afforded compound **17a** in 81% isolated yield (Rf = 0.44) as a colorless oil which slowly solidified, m.p. = 46.8-48.1 °C. Chiral GC - CP

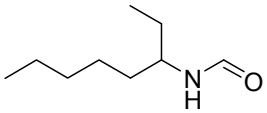
Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 111.79 min (minor), Rt = 112.76 min (major); 66% ee. $[\alpha]_D$ = + 16.5 (c 0.935, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 2.2:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.20 (s, 1H, C*H*O), 7.30-7.25 (m, 2H, H_{Ar}), 7.21-7.14 (m, 3H, H_{Ar}), 5.83 (d, *J* = 7.9 Hz, 1H, N*H*), 4.03-3.94 (m, 1H, C*H*), 2.79-2.54 (m, 2H, CH_2), 1.91-1.79 (m, 1H, CH_2), 1.76-1.54 (m, 2H, CH_2), 1.40-1.38 (m, 1H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 161.0, 141.6, 128.3, 128.2, 125.8, 49.3, 36.4, 32.2, 27.8, 10.0 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 11.9 Hz, 1H, C*H*O), 7.30-7.25 (m, 2H, H_{Ar}), 7.21-7.14 (m, 3H, H_{Ar}), 6.22 (t, *J* = 10.9 Hz, 1H, N*H*), 3.20-3.11 (m, 1H, C*H*), 2.79-2.54 (m, 2H, CH_2), 1.91-1.79 (m, 1H, CH_2), 1.76-1.54 (m, 2H, CH_2), 1.40-1.38 (m, 1H, CH_2), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.5, 140.8, 128.4, 128.3, 126.0, 53.6, 36.8, 31.9, 29.0, 10.2 ppm. HRMS calcd. for $C_{12}H_{17}NO$ 191.1310, found 191.1319. Elem. Anal. calcd. for $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32, found: C 74.88, H 8.93, N 7.20.

(+)-*N*-(1-Cyclohexyl-propyl)-formamide (18a).



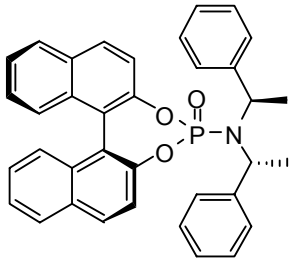
Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **18a** in 99% isolated yield (Rf = 0.38) as a colorless oil which slowly solidified, m.p. = 58.0-58.6 °C. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 91.98 min (minor), Rt = 93.23 min (major); 45% ee. $[\alpha]_D$ = + 13.5 (c 0.90, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 1.6:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.20 (s, 1H, C*H*O), 5.64 (br s, 1H, N*H*), 3.80-3.72 (m, 1H, C*H*), 1.75-1.54 (m, 6H), 1.40-0.93 (m, 7H), 1.01-0.85 (m, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 161.1, 53.8, 41.3, 29.6, 28.2, 26.3, 26.1, 24.6, 10.4 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 11.9 Hz, 1H, C*H*O), 6.01 (br s, 1H, N*H*), 2.96-2.88 (m, 1H, C*H*), 1.75-1.54 (m, 6H), 1.40-0.93 (m, 7H), 1.01-0.85 (m, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 164.7, 59.5, 42.0, 29.9, 27.8, 26.2, 26.0, 26.0, 25.4, 10.6 ppm. HRMS calcd. for $C_{10}H_{19}NO$ 169.1467, found 169.1471. Elem. Anal. calcd. for $C_{10}H_{19}NO$: C 70.96%, H 11.31%, N 8.28%, found: C 71.04%, H 11.27%, N 8.05%.

(+)-*N*-(1-Ethyl-*n*-hexyl)-formamide (19a).[47]



Purification by column chromatography (SiO_2; EtOAc/*n*-pentane 1:1) afforded compound **19a** in 99% isolated yield (Rf = 0.44) as a colorless oil. Chiral GC - CP Chiralsil Dex CB, 25m×0.25mm×0.25μm, He-flow: 1mL/min, oven: 60 °C, 10 min.-1 °C/min till 150 °C-10 °C/min till 180 °C; Rt = 72.77 min (minor), Rt = 74.77 min (major); 70% ee. $[\alpha]_D$ = + 7.4 (c 0.96, $CHCl_3$). The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 2:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.16 (s, 1H, C*H*O), 5.62 (br s, 1H, N*H*), 3.91-3.84 (m, 1H, C*H*), 1.58-1.19 (m, 10H), 0.91-0.82 (m, 6H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.9, 49.5, 34.5, 31.6, 27.8, 25.4, 22.5, 13.9, 10.1 ppm. Minor rotamer ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 11.9 Hz, 1H, C*H*O), 5.89 (br s, 1H, N*H*), 3.18-3.10 (m, 1H, C*H*), 1.58-1.19 (m, 10H), 0.91-0.82 (m, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.3, 54.5, 35.5, 31.4, 28.9, 25.5, 22.5, 13.9, 10.3 ppm. HRMS calcd. for $C_9H_{19}NO$ 157.1467, found 157.1468.

***O*,*O*'-(*S*)-(1,1'-Dinaphthyl-2,2'diyl)-*N*,*N*-di-(*R*,*R*)-1-phenylethylphosphoricamide (*S*,*R*,*R*)-L2.**

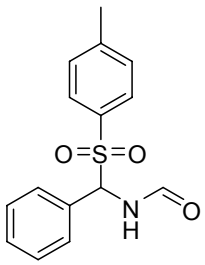


Phosphoramidite (*S*,*R*,*R*)-**L1** (770 mg, 1.43 mmol) was dissolved in 25 mL of THF. The solution was cooled down to 0 °C and 5 mL of a solution of H_2O_2 30% in water were added. Formation of a white precipitate was observed. The reaction mixture was warmed up to r.t. and stirred overnight. The reaction mixture was treated with a saturated aqueous solution of Na_2SO_3 (15 mL) and extracted (2 × 10 mL) with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 788 mg (1.42 mmol) of (*S*,*R*,*R*)-**L2** as a white solid, m.p = 184.8-185.0 °C. Yield 99%. $[\alpha]_D$ = + 384.1 (c 1.01, $CHCl_3$).^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.03-8.00 (m, 1H), 7.95-7.90 (m,3H), 7.53-7.44 (m, 4H), 7.39-7.24 (m, 4H), 7.12 (br s, 10H), 4.65-4.52 (m, 2H), 1.83 (d, *J* = 7.1 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.3, 149.0, 148.9, 146.6, 146.6, 141.2, 141.2, 132.5, 132.3, 131.7, 131.1, 131.0, 130.5, 128.4, 128.1, 128.0, 127.7, 127.4, 127.0, 126.9, 126.4, 126.3, 125.4, 121.7, 121.7, 120.4, 120.3, 54.7, 54.6, 20.3 ppm. ^{31}P-NMR (95 MHz, $CDCl_3$) δ = 12.34

ppm. HRMS calcd. for $C_{36}H_{30}NO_3P$ 555.1963, found 555.1932. Elem. Anal. calcd. for $C_{36}H_{30}NO_3P$: C 77.82%, H 5.44%, N 2.52%, found: C 77.50%, H 5.71%, N 2.55%.

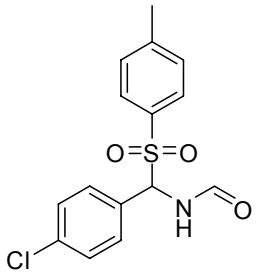
Characterization of the starting materials. All the starting materials were synthesized according to literature procedures.[21]

***N*-[Phenyl(toluene-4-sulfonyl)methyl]formamide (5).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.75 (d, *J* = 10.8 Hz, 1H, N*H*), 7.95 (s, 1H), 7.71- 7.69 (m, 2H), 7.56-7.52 (m, 2H), 7.47-7.34 (m, 5H), 6.37 (d, *J* = 10.4 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 161.0, 145.5, 134.1, 131.0, 130.3, 130.1, 129.8, 129.0, 126.2, 70.9, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.40 (t, *J* = 10.6 Hz, 1H), 7.88 (d, *J* = 10.4 Hz, 1H), 7.71- 7.69 (m, 2H), 7.56-7.52 (m, 2H), 7.47-7.34 (m, 5H), 6.25 (d, *J* = 10.8 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.7, 145.5, 134.1, 131.0, 130.4, 130.1, 130.0, 128.8, 126.2, 76.6, 21.8 ppm. M.p. = 144.9-145.2 °C. MS-EI for $C_{15}H_{15}NO_3S$: 104 (100), 133 (63.3) [M-SO_2Tol], 156 (42.5) [SO_2Tol]; MS-CI: 307 [M+NH_4^+], 290 [M+H^+]. Elem. Anal. calcd. for $C_{15}H_{15}NO_3S$: C 62.26%, H 5.23%, N 4.84%, found: C 62.25%, H 5.22%, N 4.88%.

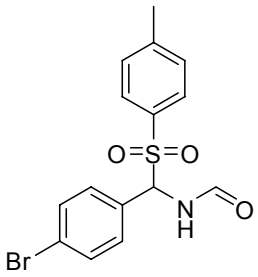
***N*-[4-Chloro-phenyl(toluene-4-sulfonyl)methyl]formamide (8).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9. 76 (d, *J* = 10.0 Hz, 1H), 7.93 (s, 1H), 7.72-7.70 (m, 2H), 7.62-7.51 (m, 2H), 7.57-7.46 (m, 2H), 7.44-7.39 (m, 2H), 6.45 (d, *J* = 10.4 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 160.9, 145.6, 135.1, 133.9, 131.9, 130.3, 130.0, 129.9, 129.0, 70.1, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.44 (t, *J* = 10.6 Hz, 1H), 7.85 (d, *J* = 10.4 Hz, 1H), 7.72-7.70 (m, 2H), 7.62-7.51 (m,

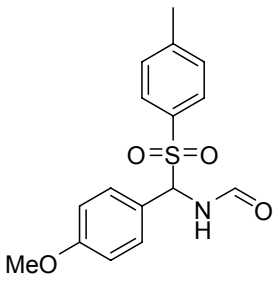
2H), 7.57-7.46 (m, 2H), 7.44-7.39 (m, 2H), 6.31 (d, *J* = 10.4 Hz, 1H), 2.39 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.4, 145.9, 135.0, 133.0, 131.7, 130.5, 130.1, 129.9, 129.0, 75.8, 21.8 ppm. M.p. = 122.6-124.9 °C. MS-EI for $C_{15}H_{14}ClNO_3S$: 92 (94.5), 138 (100), 156 (19.7) [SO_2Tol],167 (15.7) [M-SO_2Tol]; MS-CI: 324 [M+H^+], 341[M+NH_4^+]. Elem. Anal. calcd. for $C_{15}H_{14}ClNO_3S$: C 55.64%, H 4.36%, N 4.33%, found: C 55.79%, H 4.39%, N 4.34%.

***N*-[4-Bromo-phenyl(toluene-4-sulfonyl)methyl]formamide (9).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.76 (d, *J* = 10.5 Hz, 1H), 7.94-7.40 (m, 9H), 6.42 (d, *J* = 10.6 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 161.0, 145.7, 133.8, 132.2, 132.0, 130.3, 129.9, 123.8, 70.2, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.43 (t, *J* = 10.5 Hz, 1H), 7.94-7.40 (m, 9H), 6.28 (d, *J* = 10.7 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.5, 145.9, 133.0, 133.0, 132.0, 130.5, 124.9, 123.8, 75.9, 21.8 ppm. M.p. = 124.5-125.6 °C. Elem. Anal. calcd. for $C_{15}H_{14}BrNO_3S$: C 48.92%, H 3.83%, N 3.80%, found: C 49.01%, H 3.88%, N 3.84%.

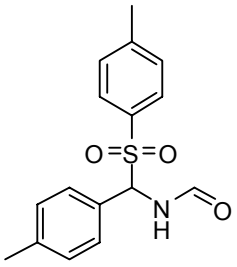
***N*-[4-Methoxy-phenyl(toluene-4-sulfonyl)methyl]formamide (10).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.70 (d, *J* = 10.6 Hz, 1H), 7.92 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.49-7.44 (m, 2H), 7.41-7.37 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.30 (d, *J* = 10.6 Hz, 1H), 3.75 (s, 3H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 160.8, 160.7, 145.4, 134.2, 131.5, 130.3, 129.8, 122.6, 114.4, 70.4, 55.9, 21.82 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.34 (t, *J* = 9.3 Hz, 1H), 7.85 (d, *J* = 10.4 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.49-7.44 (m, 2H), 7.41-7.37 (m, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 6.17 (d, *J* = 10.7 Hz, 1H), 3.73 (s, 3H), 2.27 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.6, 160.7, 145.5, 133.4,

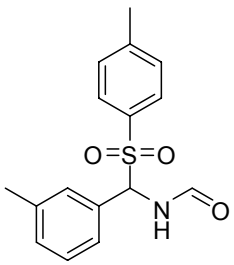
131.3, 130.4, 129.9, 122.8, 114.3, 76.1, 55.9, 21.8 ppm. M.p. = 127.6-128.9 °C. MS-EI for $C_{16}H_{17}NO_4S$: 92 (100), 134 (89.2), 163 (54.8) [M-SO_2Tol], 156 (26.7) [SO_2Tol]; MS-CI: 320 [M+H^+]. Elem. Anal. calcd. for $C_{16}H_{17}NO_4S$: C 60.17%, H 5.37%, N 4.39%, found: C 60.18%, H 5.35%, N 4.37%.

***N*-[4-Methyl-phenyl(toluene-4-sulfonyl)methyl]formamide (11).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.70 (d, *J* = 10.0 Hz, 1H), 7.92 (s, 1H), 7.68 (d, br, *J* = 6.4 Hz, 2H), 7.41-7.39 (m, 4H), 7.20 (d, *J* = 6.8 Hz, 2H), 6.30 (d, *J* = 10.8 Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 160.9, 145.4, 139.7, 134.2, 130.3, 130.0, 129.8, 129.5, 127.9, 70.7, 21.8, 21.5 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.33 (t, *J* = 9.8 Hz, 1H), 7.86 (d, *J* = 10.8 Hz, 1H), 7.55 (d, br, *J* = 6.4 Hz, 2H), 7.41-7.39 (m, 2H), 7.33 (d, br, *J* = 6.4 Hz, 2H), 7.14 (d, *J* = 6.8 Hz, 2H), 6.18 (d, *J* = 10.8 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.6, 145.6, 139.6, 133.4, 130.4, 129.9, 129.9, 129.4, 128.0, 76.4, 21.8, 21.5 ppm. M.p. = 143.3-144.0 °C. MS-EI for $C_{16}H_{17}NO_3S$: 91 (100), 118 (91.6), 147 (42.5) [M-SO_2Tol], 156 (27.9) [SO_2Tol]; MS-CI: 321 [M+NH_4^+], 304 [M+H^+]. Elem. Anal. calcd. for $C_{16}H_{17}NO_3S$: C 63.34%, H 5.65%, N 4.62%, found: C 62.98%, H 5.66%, N 4.66%.

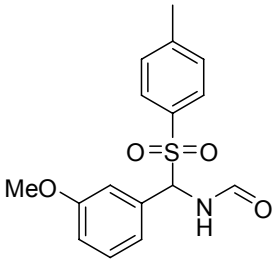
***N*-[3-Methyl-phenyl(toluene-4-sulfonyl)methyl]formamide (12).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.77 (d, *J* = 10.6 Hz, 1H), 7.92 (s, 1H), 7.69 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 2H), 7.48-7.09 (m, 6H), 6.28 (d, *J* = 10.5 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) = 160.9, 145.5, 138.2, 134.1, 130.8, 130.6, 130.3, 129.8, 128.9, 127.3, 126,2, 70.9, 21.8, 21.6 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.34$ (t, *J* = 10.6 Hz, 1H), 7.85 (d, *J* = 10.4 Hz, 1H), 7.56 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 2H), 7.48-7.09 (m, 6H), 6.20 (d, *J* = 10.6 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) = 165.5, 145.6, 138.0, 133.3, 130.9, 130.7, 130.4, 129.9, 128.7,

127.0, 126.2, 76.5, 21.8, 21.6 ppm. M.p. = 114.2-115.1 °C. Elem. Anal. calcd. for $C_{16}H_{17}NO_3S$: C 63.34%, H 5.65%, N 4.62%, found: C 63.23%, H 5.63%, N 4.65%.

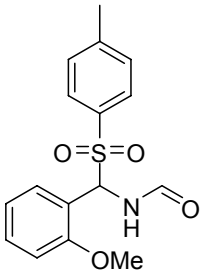
***N*-[3-Methoxy-phenyl(toluene-4-sulfonyl)methyl]formamide (13).**



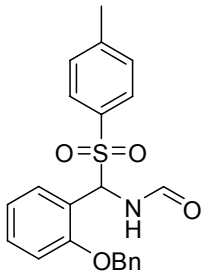
The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 5:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.72 (d, *J* = 10.0 Hz, 1H), 7.95 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.12-6.92 (m, 3H), 6.35 (d, *J* = 10.8 Hz, 1H), 3.72 (s, 3H), 2.39 (s, 3H) ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.38$ (t, *J* = 10.6 Hz, 1H), 7.88 (d, *J* = 10.4 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.12-6.92 (m, 3H), 6.21 (d, *J* = 10.8 Hz, 1H), 3.67 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C-NMR major rotamer + minor rotamer (50 MHz, DMSO-*d*^{6}) δ = 165.5, 160.9, 159.7, 159.6, 145.6, 145.5, 134.1, 133.3, 132.4, 130.4, 130.3, 130.0, 129.8, 122.4, 115.8, 115.7, 115.2, 76.6, 70.9, 55.9, 21.8 ppm. M.p. = 116.3-116.9 °C. Elem. Anal. calcd. for $C_{16}H_{17}NO_4S$: C 60.17%, H 5.37%, N 4.39%, found: C 60.08%, H 5.35%, N 4.17%.

***N*-[2-Methoxy-phenyl(toluene-4-sulfonyl)methyl]formamide (14).**

The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 10:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.72 (d, *J* = 9.9 Hz, 1H), 8.06 (br s, 1H), 7.58-7.52 (m, 3H), 7.46-7.36 (m, 3H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 10.7 Hz, 1H), 3.57 (s, 3H), 2.39 (s, 3H) ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.30$ (t, *J* = 10.6 Hz, 1H), 8.14 (d, *J* = 10.4 Hz, 1H), 7.68-7.66 (m, 1H), 7.58-7.52 (m, 2H), 7.46-7.36 (m, 3H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.22 (d, *J* = 10.8 Hz, 1H), 3.44 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C-NMR major rotamer + minor rotamer (50 MHz, DMSO-*d*^{6}) δ = 165.4, 160.4, 156.8, 156.3, 144.7, 144.6, 133.7, 132.9, 131.0, 129.4, 129.2, 129.1, 128.8, 120.3, 118.9, 118.5, 111.0, 110.8, 63.8, 55.5, 55.3, 21.0 ppm. M.p. = 134.6-135.5 °C. Elem. Anal. calcd. for $C_{16}H_{17}NO_4S$: C 60.17%, H 5.37%, N 4.39%, found: C 60.11%, H 5.36%, N 4.21%.

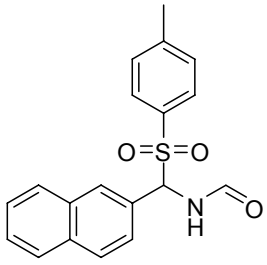


***N*-[2-Benzyloxy-phenyl(toluene-4-sulfonyl)methyl]formamide (15).**



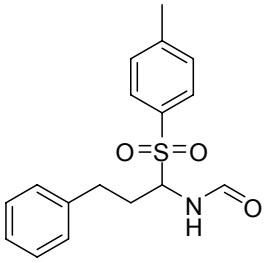
The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 7:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.77 (d, *J* = 10.7 Hz, 1H), 8.00 (br s, 1H), 7.60 (br d, *J* = 7.9 Hz, 1H), 7.54-7.52 (m, 2H), 7.47-7.27 (m, 7H), 7.06 (t, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 10.7 Hz, 1H), 5.10 (d, *J* = 12.1 Hz, 1H), 4.95 (d, *J* = 12.1 Hz, 1H), 2.36 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 161.1, 156.9, 145.5, 137.5, 134.6, 131.7, 130.3, 130.0, 129.4, 129.1, 128.6, 127.9, 121.4, 119.8, 113.2, 70.4, 64.2, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.34$ (t, *J* = 10.7 Hz, 1H), 8.00 (br s, 1H), 7.68 (br d, *J* = 7.8 Hz, 1H), 7.54-7.52 (m, 2H), 7.47-7.27 (m, 7H), 7.00 (t, *J* = 7.7 Hz, 2H), 6.25 (d, *J* = 10.8 Hz, 1H), 5.03 (d, *J* = 12.4 Hz, 1H), 4.83 (d, *J* = 12.4 Hz, 1H), 2.36 (s, 3H) ppm. M.p. = 131.6-132.0 °C. Elem. Anal. calcd. for $C_{22}H_{21}NO_4S$: C 66.82%, H 5.35%, N 3.54%, found: C 66.78%, H 5.31%, N 3.60%.

***N*-[2-Naphtyl(toluene-4-sulfonyl)methyl]formamide (16).**



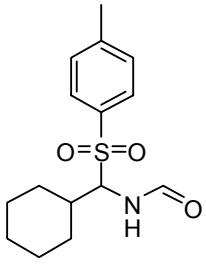
The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.92 (d, *J* = 10.6 Hz, 1H), 8.10-7.83 (m, 5H), 7.76-7.67 (m, 2H), 7.62-6.97 (m, 5H), 6.56 (d, *J* = 10.5 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 161.0, 145.6, 134.1, 133.8, 132.9, 130.4, 129.8, 128.7, 128.5, 128.5, 128.3, 127.8, 127.4, 127.1, 126.2, 125.2, 71.0, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) $\delta = 9.54$ (d, *J* = 10.6 Hz, 1H), 8.10-7.83 (m, 5H), 7.76-7.67 (m, 2H), 7.62-6.97 (m, 5H), 6.44 (d, *J* = 10.7 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-*d*^{6}) δ = 165.6, 145.7, 133.7, 133.3, 132.8, 130.5, 130.0, 128.8, 128.6, 128.5, 128.3, 127.8, 127.4, 127.0, 126.2, 125.2, 76.7, 21.5 ppm. M.p. = 135.3-135.7 °C. Elem. Anal. calcd. for $C_{19}H_{17}NO_3S$: C 67.24%, H 5.05%, N 4.13%, found: C 66.82%, H 5.08%, N 4.05%.

***N*-[(3-Phenyl)propyl(toluene-4-sulfonyl)methyl]formamide (17).**



The ^{1}H- and ^{13}C-NMR spectra (DMSO-*d*^{6}) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 9.02 (d, *J* = 10.0 Hz, 1H), 7.98 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.28-7.24 (m, 2H), 7.19-7.12 (m, 3H), 5.06 (dt, J_1 = 10.4 Hz, J_2 = 2.6 Hz, 1H), 2.72-2.63 (m, 1H), 2.56-2.51 (m, 1H), 2.37 (s, 3H), 2.31-2.21 (m, 1H), 1.95-1.80 (m, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-*d*^{6}) δ = 161.6, 145.4, 140.8, 134.0, 130.4, 129.8, 129.1, 129.0, 126.9, 67.5, 31.3, 29.0, 21.8 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, DMSO-*d*^{6}) δ = 8.64 (t, *J* = 10.2 Hz, 1H), 7.78 (d, *J* = 10.8 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.28-7.24 (m, 2H), 7.19-7.12 (m, 3H), 4.86 (dt, J_1 = 10.4 Hz, J_2 = 2.8 Hz, 1H), 2.72-2.63 (m, 1H), 2.56-2.51 (m, 1H), 2.39 (s, 3H), 2.31-2.21 (m, 1H), 1.95-1.80 (m, 1H) ppm. ^{13}C-NMR (100 MHz, DMSO-*d*^{6}) δ = 165.9, 145.7, 140.9, 133.0, 130.7, 130.0, 129.2, 128.9, 126.9, 73.2, 31.5, 29.0, 21.8 ppm. M.p. = 137.1-143.5 °C. Elem. Anal. calcd. for $C_{17}H_{19}NO_3S$: C 64.33%, H 6.03%, N 4.41%, found: C 64.60%, H 6.05%, N 4.37%.

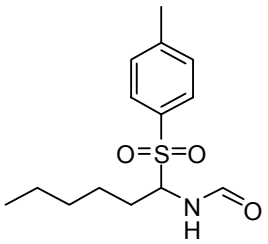
***N*-[Cyclohexyl(toluene-4-sulfonyl)methyl]formamide (18).**



The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 7:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.02 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.36-7.29 (m, 2H), 6.77 (d, *J* = 10.8 Hz, 1H), 5.13 (dd, J_1 = 11.0 Hz, J_2 = 3.7 Hz, 1H), 244-2.40 (m, 4H), 2.13-2.09 (m, 1H), 1.76-1.65 (m, 4H), 1.39-1.06 (m, 5H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 160.30, 145.1, 134.3, 129.8, 128.7, 70.7, 36.5, 30.5, 27.2, 25.9, 25.6, 25.5, 21.6 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 11.2 Hz, 1H), 7.36-7.29 (m, 2H), 6.55 (t, *J* = 11.1 Hz, 1H), 4.15 (dd, J_1 = 11.3 Hz, J_2 = 3.5 Hz, 1H), 244-2.40 (m, 4H), 2.13-2.09 (m, 1H), 1.76-1.65 (m, 4H), 1.39-1.06 (m, 5H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) δ = 163.8, 145.7, 133.2, 130.2, 129.1, 70.7, 36.2, 30.6, 27.0, 25.9, 25.6, 25.5, 21.6 ppm. M.p. = 105.4-105.5 °C. Elem. Anal.

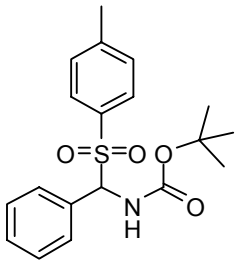
calcd. for $C_{15}H_{21}NO_3S$: C 60.99%, H 7.17%, N 4.74%, found: C 61.36%, H 7.22%, N 4.55%.

***N*-[Hexyl(toluene-4-sulfonyl)methyl]formamide (19).**



The ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) show a 7:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.92 (s, 1H), 7.69-7.65 (m, 2H), 7.37 (d, J = 10.4 Hz, 1H), 7.29-7.23 (m, 2H), 5.17 (dt, J_1 = 10.8 Hz, J_2 = 2.9 Hz, 1H), 2.32 (s, 3H), 2.09-2.03 (m, 1H), 1.74-1.60 (m, 1H), 1.36-1.17 (m, 6H), 0.78-0.75 (m, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.8, 145.0, 132.9, 129.5, 128.9, 67.2, 30.7, 26.1, 24.5, 21.9, 21.3, 13.5 ppm. Minor rotamer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, J = 11.2 Hz, 1H), 7.69-7.65 (m, 2H), 7.29-7.23 (m, 2H), 7.10 (t, J = 10.6 Hz, 1H), 4.40 (dt, J_1 = 10.6 Hz, J_2 = 2.9 Hz, 1H), 2.32 (s, 3H), 2.09-2.03 (m, 1H), 1.74-1.60 (m, 1H), 1.36-1.17 (m, 6H), 0.78-0.75 (m, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 164.7, 145.5, 131.5, 129.9, 129.2, 73.2, 30.6, 26.5, 24.7, 21.9, 21.3, 13.5 ppm. M.p. = 73.5-74.6 °C. Elem. Anal. calcd. for $C_{14}H_{21}NO_3S$: C 59.34%, H 7.47%, N 4.94%, found: C 59.58%, H 7.52%, N 4.91%.

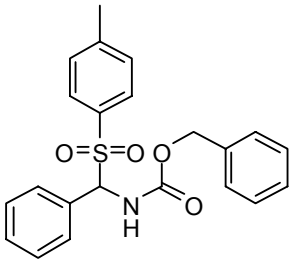
***N*-[Phenyl(toluene-4-sulfonyl)methyl]tert-butoxycarbamate (6).**



^{1}H-NMR (400 MHz, DMSO-d^6) δ = 8.64 (d, J = 10.8 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.62-7.59 (m, 2H), 7.41-7.36 (m, 5H), 5.93 (d, J = 10.8 Hz, 1H), 2.35 (s, 3H), 1.16 (s, 9H) ppm. ^{13}C-NMR (50 MHz, DMSO-d^6) δ = 159.6, 149.9, 139.4, 135.8, 135.3, 134.9, 134.7, 133.5, 84.7, 79.8, 33.2, 26.5 ppm. M.p. = 163.3-164.5 °C. Elem. Anal. calcd. for $C_{19}H_{23}NO_4S$: C 63.13%, H 6.41%, N 3.88%, found: C 63.10%, H 6.42%, N 3.74%.

***N*-[Phenyl(toluene-4-sulfonyl)methyl]benzyloxycarbamate (7).**

^{1}H-NMR (400 MHz, DMSO-d^6) δ = 9.14 (d, J = 10.8 Hz, 1H), 7.67-7.58 (m, 4H), 7.40-7.43 (m, 7H), 7.20-7.09 (m, 3H), 6.01 (d, J = 10.7 Hz, 1H), 4.90 (d, J = 12.6 Hz, 1H), 4.83 (d, J = 10.6 Hz, 1H), 2.38 (s, 3H) ppm. ^{13}C-NMR (50 MHz, DMSO-d^6) δ = 155.9, 145.3, 137.5, 137.0, 134.4, 131.1, 130.3, 130.2, 130.0, 129.8, 129.0, 128.8, 128.6, 128.3, 125.0, 75.5, 66.7, 21.9 ppm. M.p. = 163.3-164.5 °C.



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