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Catalytic Enantioselective Addition of Organometallic Reagents to *N*-Formylimines Using Monodentate Phosphoramidite Ligands

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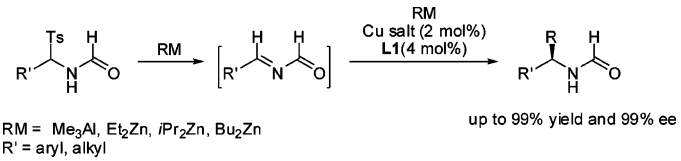

The asymmetric synthesis of protected amines via the copper/phosphoramidite-catalyzed addition of organozinc and organoaluminum reagents to *N*-acylimines, generated in situ from aromatic and aliphatic α-amidosulfones, is reported. High yields of optically active *N*-formyl-protected amines and enantioselectivities 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 and the effect on the catalytic addition reaction is presented.

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 addition of organometallic reagents to C═N double bonds is one of the most powerful methods to form optically active α-chiral amines.[5] 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 makes these substrates less reactive toward nucleophilic attack; moreover, enolizable imines show a high tendency to undergo deprotonation, rather than addition. The control of stereoselectivity in this reaction is difficult because of the cis−trans isomerization about the C═N double bond.[6] Although many procedures employing chiral auxiliaries[5a−e,7] and stoichiometric chiral ligands[5a−c,e,8] are described in the literature, the development of catalytic versions of this reaction has been hampered by the capability of the nitrogen of the imine or the product of the nucleophilic addition to strongly bind the catalyst (for example, Lewis acids),

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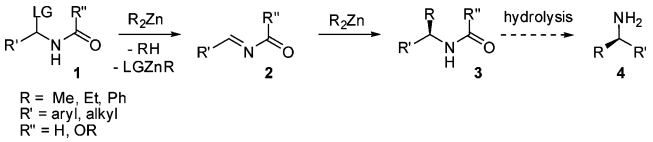
interrupting the cycle. Only recently, highly enantioselective catalytic methods have appeared in the literature.[5e,f,g] The highest enantioselectivities for the addition of dialkylzinc reagents have been obtained on imine derivatives activated through *N*-alkylation,[9,10] *N*-sulfonylation,[11,12] *N*-phosphonylation,[13,14] and *N*-acylation.[15,16]

Hoveyda reported the first efficient catalytic method for the enantioselective addition of dialkylzinc reagents to a variety of *N*-*o*-methoxyphenyl alkyl/aryl-aldimines.[9a−c] The use of chiral Zr-dipeptide complexes as Lewis acid activators of the imino acceptors allows the corresponding *o*-anisidine amines to be obtained with enantioselectivities exceeding 98%. The low yields observed for the aliphatic substrates were improved using less Lewis acidic Hf-complexes.[9d] *N*-Sulfonylimines can also undergo diethylzinc addition in high yields and with ee values up to 96% in the presence of $Cu(OTf)_2$ and amidophosphine ligands, under mild conditions, as described by Tomioka et al.[11] The state of the art for the dialkylzinc addition to *N*-diphenylphosphinoylimines is currently represented by the protocol developed by Charette group[13] in which the use of a catalytic amount of $Cu(OTf)_2$ in combination with (*R*,*R*)-BozPHOS promotes the alkylation of several aromatic and aliphatic aldimines as well as aromatic ketimines in high yields and with high enantioselectivities. Finally, the scope of the addition of diorganozinc reagents to *N*-acylimines has been successfully investigated by Bräse[15] and Gong[16] 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. Although the latter methods provide access to chiral *N*-acylamines in high yields and with high enantioselectivities, they are restricted to the use of substrates derived from aryl aldehydes. Moreover, laborious synthesis of the chiral ligand or high catalyst loading is frequently required. 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 that can be deprotected under mild hydrolytic conditions and without loss of enantioselectivity. Moreover, in order to prevent practical problems arising from the inherent instability of imines, especially those derived from aliphatic aldehydes, it is possible to generate these *N*-formyl substrates in situ, from stable precursors (Scheme 1).

SCHEME 1. Addition of Organozinc Reagents to in Situ Generated Imines



The starting material **1** is an imine adduct substituted on 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** under mild conditions affords the free α-chiral amine **4**. In the addition reaction of R_2Zn, the nucleophile acts also as a base generating the *N*-acylimine together with an equimolar amount of RH and of the adduct LGZnR. Clearly, it is important that such a species does not inhibit the catalytic process. Several leaving groups have been used to form *N*-acylimines, for example, benzotriazolates,[17] succinimidates,[18] and sulfinates.[15,16,19] In the addition reaction of diorganozinc reagents, the sulfinate is often the leaving group of choice because its adduct with R_2Zn does not affect the addition reaction[13c] and because 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.[20]

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[21] in combination with Cu(II) salts.

Results and Discussion

Initially, we investigated the reactivity of the α-amidosulfone **5**, derived from the condensation of benzaldehyde, *p*-toluenesulfinic acid, and formamide, in the copper/phosphoramidite-catalyzed addition of Et_2Zn (Scheme 2). For the optimization of the reaction conditions, 5 mol % of $Cu(OTf)_2$ and 10 mol %

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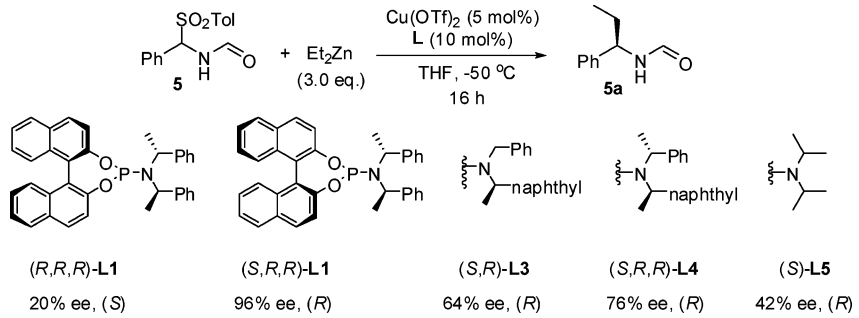
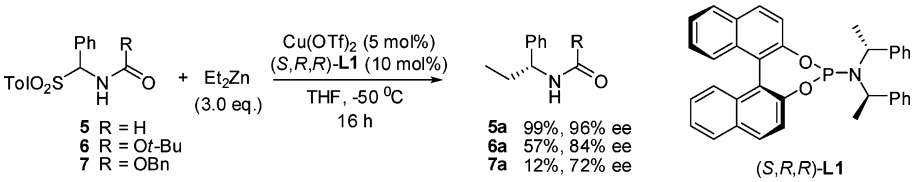
SCHEME 2. Screening of Ligands for the Addition of Et_2Zn to 5



SCHEME 3. Screening of Protecting Groups



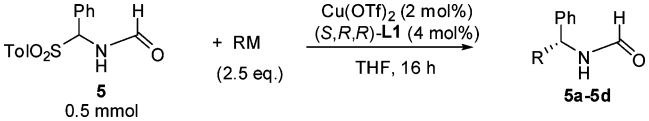
of the homochiral monodentate phosphoramidite (*S*,*R*,*R*)-**L1**[21,22] (2 equiv with respect to Cu) were used. The screening of a number of solvents (see the Supporting Information, A1) showed that THF gave the best results, affording, at −50 °C, product (*R*)-**5a** in quantitative yield and with 96% ee. Phosphoramidite ligands **L3**−**L5** also gave full conversion of **5** to product **5a** at −50 °C in THF, however, with lower enantioselectivity in comparison to (*S*,*R*,*R*)-**L1**. 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. On the basis of these preliminary studies we concluded that (*S*,*R*,*R*)-**L1** was the ligand of choice.

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 enantioselectivity. A decrease of the amount of catalyst to 1 mol % resulted in longer reaction times (full conversion after 36 h). Replacing the amide moiety for a carbamate was deleterious for both the isolated yield and the enantioselectivity (Scheme 3, substrates **6** and **7**).

Next, the scope 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 1), iPr$_2$Zn and nBu$_2$Zn afforded compound **5b** and **5c** in high yield and 91% and 88% enantioselectivity, respectively (entries 2 and 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 on TLC: the expected product **5d** and benzaldehyde.[23] The latter derives from the hydrolysis of the in situ generated imine during the quenching of the reaction mixture (aq HCl, 1 M), indicating that, using Me_2Zn, which has low reactivity compared to the other zinc reagents, the rate-determining step is the addition reaction and not the formation of the imine. 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).

TABLE 1. Addition of Diorganozinc Reagents and Trimethylaluminum to 5



entry	RM	*T* (°C)	product	yield (%)[a]	ee (%)
1	Et_2Zn	−50	**5a**	99	96-(+)-(*R*)
2	iPr$_2$Zn	−50	**5b**	97	91-(+)-(*R*)
3	nBu$_2$Zn	−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*)
7[c]	Me_3Al	−30	*ent*-**5d**	70	86-(−)-(*S*)

[a] Isolated yield. [b] The absolute configuration of **5c** was assigned 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**. [c] 5 mol % of $Cu(acac)_2$, 10 mol % of (*S*,*R*,*R*)-**L1**, i-Pr$_2$O.

Because the methyl group is ubiquitous in biologically active compounds and difficulties are frequently encountered in the transferring of a methyl group in organometallic addition reactions, we made considerable efforts to achieve high enantioselectivity in the addition of methyl nucleophiles. Toward this goal, we investigated the use of Me_3Al as the methyl source. Optimization of the solvent, Cu salt, and temperature (see the Supporting Information, A2) led to the formation of product **5d** in 70% yield and 86% ee, using $Cu(acac)_2$ as copper salt in iPr$_2$O, at −30 °C (entry 7). 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**.[24]

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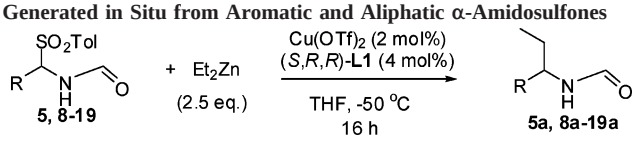
(23) Formation of benzaldehyde was detected by GC-MS as well. The formation of benzaldehyde in the addition of Me_2Zn to the aromatic model substrate in THF, at −30 °C, was detected by GC-MS. We did not detect the aldehyde in the addition of the other organozinc reagents or Me_3Al, indicating that in such cases the imine formation is the rate-determining step. However, considering the lower reactivity of Me_2Zn, we believe that the rate of the addition decreases to a large extent, becoming slower than the imine formation.

TABLE 2. Cu-Catalyzed Addition of Et_2Zn to *N*-Acyl Imines Generated in Situ from Aromatic and Aliphatic α-Amidosulfones



entry	compd	R	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-OMe-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-OMe-Ph	**13a**	96	95-(+)
8	**14**	2-OMe-Ph	**14a**	99	47-(−)
9	**15**	2-OBn-Ph	**15a**	99	45-(−)
10	**16**	2-naphthyl	**16a**	94	80-(+)
11[a]	**17**	$PhCH_2CH_2$	**17a**	81	66-(+)
12[a]	**18**	*c*-hexyl	**18a**	99	45-(+)
13[a]	**19**	*n*-hexyl	**19a**	99	70-(+)

[a] Reaction conditions: $Cu(OAc)_2 \cdot H_2O$ (5 mol %), (*S*,*R*,*R*)-**L1** (10 mol %) in iPr_2O at −20 °C.

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 2). 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 depletion of stereocontrol to steric effects of the ortho 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 the model substrate. No addition reaction was observed in THF, at −50 °C. An increase of the temperature to −20 °C was necessary to achieve full conversion of the starting material after overnight reaction and the enantioselectivity observed was modest. Further screening of solvents revealed that toluene and Et_2O provide better results compared to THF. Several copper salts were tested to improve the enantioselectivity of the reaction and, using $Cu(OAc)_2 \cdot H_2O$, product **17a** was obtained with 66% ee.

Different phosphoramidite ligands were tested to improve the enantioselectivity for the addition of Et_2Zn to **17** (see the Supporting Information, A3). Also in this case, however, ligand (*S*,*R*,*R*)-**L1** was proven to be the best one. Variation of the steric or chiral properties of the amine moiety in ligands **L3**−**L5** determined, invariably, a decrease in the enantioselectivity.

(24) In analogy with organocuprate and zincate chemistry, we suppose that the organometallic species is involved in the structure of the active catalytic system. We assume that by switching from an organozinc to an organoaluminum reagent we probably form two different catalysts, thereby changing the stereochemical outcome of the reaction. This assumption is in agreement with what was demonstrated by our group for the copper-catalyzed 1,4-addition of Grignard reagents. For reference see: (a) Mori, S.; Nakamura, E. *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: New York, 2002. (b) Harutyunyan, S. R.; Lopez, F.; Browne, W. R.; Correa, A.; Pena, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Soc. Chem.* **2006**, *128*, 9103.

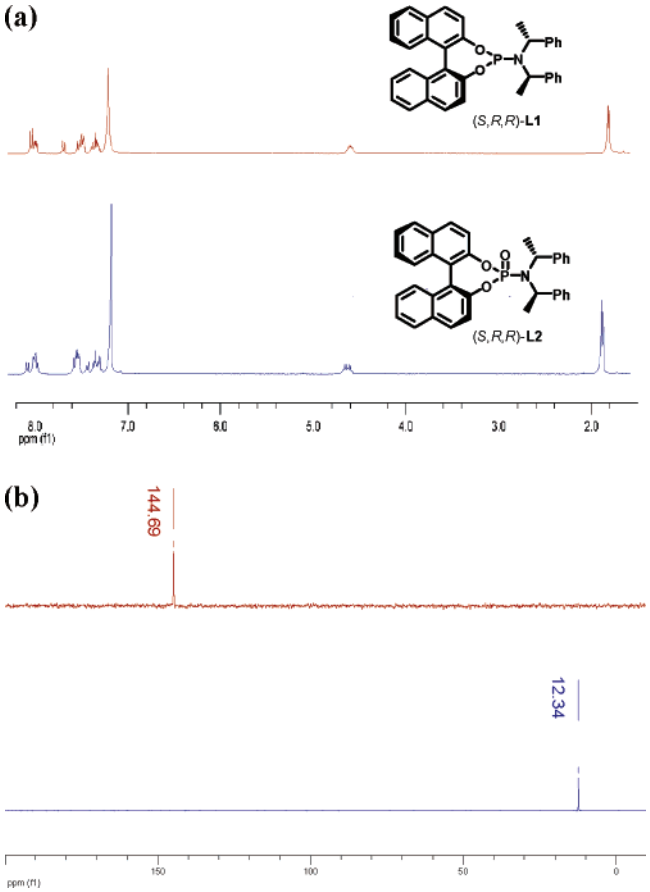


FIGURE 1. NMR spectra of (*S*,*R*,*R*)-**L1** and (*S*,*R*,*R*)-**L2**: (a) ^1H NMR in $CDCl_3$, 400 MHz; (b) ^{31}P NMR in $CDCl_3$, 400 MHz. (*S*,*R*,*R*)-**L1** δ = 144.7 ppm; (*S*,*R*,*R*)-**L2** δ = 12.3 ppm.

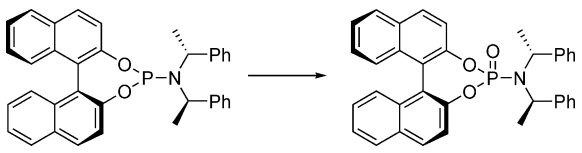
In summary, with use of (*S*,*R*,*R*)-**L1**, high yields and enantioselectivities between 45% and 70% were obtained for the Cu-catalyzed addition of diethylzinc to aliphatic substrates (entries 11−13).

Studies on in Situ Ligand Oxidation. To investigate the efficiency of recovery of the chiral phosphoramidite ligand, we tried to isolate (*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. 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 on silica gel. Together with (*S*,*R*,*R*)-**L1**, a second compound containing phosphorus was isolated as a white foamy solid. The ^1H NMR of this species looked rather similar to that of (*S*,*R*,*R*)-**L1** while the ^{31}P NMR showed one single absorption at 12.3 ppm. The spectroscopic data as well as HRMS analysis suggest that this new species is (*S*,*R*,*R*)-**L2** (Figure 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, iPr_2O, EtOAc, and DCM. In contrast, if the reactions were performed in hexane, at room temperature, or in toluene, at −30 °C, the only phosphorus compound recovered was (*S*,*R*,*R*)-**L1**.

Modification of phosphoramidite ligands during a reaction with organometallic reagents has been previously reported in the literature. Recently, Alexakis and Micouin[25] observed that, in the $Cu(OTf)_2$-catalyzed ring opening of meso bicyclic

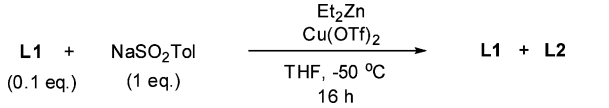
SCHEME 4. In Situ Ligand Oxidation



hydrazines, the phosphoramidite (*R*,*R*,*R*)-**L1** reacts with Me_3-Al, in dichloromethane and toluene, leading to the corresponding aminophosphine, which is the actual ligand in the reaction. In our case, even though the chemical shift of the newly formed species (*S*,*R*,*R*)-**L2** in the ^{31}P NMR would be consistent with the formation of the dimethylaminophosphine, the ^1H NMR data rule out this possibility. The ^1H NMR, in fact, clearly shows that the BINOL moiety is still present in (*S*,*R*,*R*)-**L2**; moreover the substitution pattern is very 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.[26] provided inspiration for the elucidation ofthe (*S*,*R*,*R*)-**L2** structure. They found that, in the Cu-catalyzed addition of diorganozinc reagents to *N*-phosphonoylimines, an in situ oxidation of Me-Duphos occurs by Cu(II) salts, to produce the highly effective monoxide ligand (BozPHOS) and, in minor extent, the Me-Duphos bisoxide. Redox processes between phosphorus-based ligand and transition metals had been previously reported.[27] Pd(II) salts, for example, can be reduced to Pd(0) in the presence of Ph_3P, producing $Ph_3P{=}O$ as the byproduct.[28] Much less is known about this type of chemistry 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;[29] 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 the possible role in asymmetric catalysis (Scheme 4).

The phosphoric amide could be easily synthesized, in quantitative yield, upon reaction of (*S*,*R*,*R*)-**L1** with hydrogen peroxide. Characterization by ^1H NMR, ^{31}P NMR, and HRMS and elemental analysis of the synthesized phosphoric amide and the isolated species (*S*,*R*,*R*)-**L2** confirmed that the two compounds are identical. We hypothesized that the ligand oxidation, observed in the Cu-catalyzed addition of diorganozinc and organoaluminium reagents to *N*-formylimines generated in situ from α-amidosulfones, could be due to the substrate itself. The in situ formation of the imine, in fact, generates 1 equiv of zinc−sulfinate adduct, which could act as an oxidizing agent. To confirm this hypothesis, we investigated the effect that the sulfinate, added as sodium salt, has on ligand (*S*,*R*,*R*)-**L1**, under different conditions (Table 3).[30] 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, than 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 3. Effect of Sulfinate on (*S*,*R*,*R*)-L1



entry	$NaSO_2Tol$ (equiv)	Et_2Zn (equiv)	$Cu(OTf)_2$ (equiv)	**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 byproduct in the reaction or actually part of the active catalyst.

We mentioned earlier that no ligand modification was detectable 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 inevitably formed 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. The results are presented in Table 4. 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 and 2). The reaction proceeded to full conversion, overnight, and high ee values 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).

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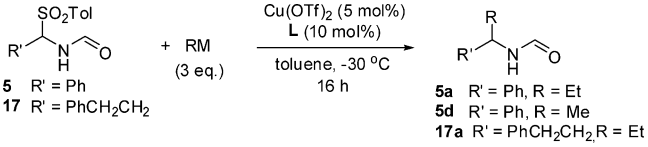
(30) Compound (*S*,*R*,*R*)-**L2** is even formed when O_2 and H_2O are rigorously excluded.

TABLE 4. 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	compd	L	RM	product	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 the 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 preliminary 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.[31] 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, first of all the solvent.[32] This observation prompted us to study the effect of the addition of HMPA in place of (*S*,*R*,*R*)-**L2** (Table 4, 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 in place of $Cu(OTf)_2$ because, from the screening of the copper salts for the Me_3Al addition (see the Supplementary Information, Table 7), it was proven to be the most effective. As shown in Table 4 (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. 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.

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Conclusions

We show 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 up to 99%. Oxidation of the chiral phosphoramidite ligand (*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, iPr_2O, DCM, and EtOAc, but not in hexane and toluene. A preliminary investigation on 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. Further mechanistic studies are ongoing to clarify the actual role played by (*S*,*R*,*R*)-**L2**. The advantage of readily available and stable starting materials as well as the easy deprotection of the obtained α-alkylamides make the new methodology a useful alternative to the existing methods for the formation of optically active α-chiral amines.

Experimental Section

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 the solution was stirred for 30 min at rt. The mixture was cooled to −50 °C and the substrate (0.50 mmol) was added. A solution of a R_2Zn (1.25 mmol) 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 (3 × 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-Phenylpropyl)formamide, 5a.**[15a] Purification by column chromatography (SiO_2; EtOAc/pentane 1:1) afforded compound **5a** in 99% isolated yield (R_f 0.4) as a colorless oil that slowly solidified, mp 56.8−58.8 °C. Chiral GC-CP Chiralsil Dex CB, 25 m × 0.25 mm × 0.25 μm; He-flow: 1 mL/min; oven: 60 °C for 10 min, 1 °C/min until 150 °C, then 10 °C/min until 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 ^1H and ^{13}C NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.36−7.22 (m, 5H), 6.02 (s, br, 1H), 4.96 (q, J = 7.8 Hz, 1H), 1.92−1.80 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H) 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 ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 12.0 Hz, 1H), 7.36−7.22 (m, 5H, H_{Ar}), 6.30 (s, br, 1H), 4.37 (q, J = 7.2 Hz, 1H), 1.92−1.80 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H) 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.

***N*-[1-(4-Chlorophenyl)propyl]formamide, 8a.**[15a] Purification by column chromatography (SiO_2; EtOAc/pentane 1:1) afforded compound **8a** in 94% isolated yield (R_f = 0.28) as a colorless oil which slowly solidified, mp 94.0−94.8 °C. Chiral GC-CP Chiralsil Dex CB, 25 m × 0.25 mm × 0.25 μm; He-flow: 1 mL/min; oven: 60 °C for 10 min, then 1 °C/min until 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 ^1H and ^{13}C NMR spectra ($CDCl_3$) show a 4:1 mixture of two rotamers (rotation of the *N*-formyl group). Major rotamer ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.31−7.25 (m, 2H), 7.19−7.15 (m, 2H), 6.54 (br d, J = 7.2 Hz, 1H), 4.86 (q, J = 7.6 Hz, 1H), 1.84−1.71 (m, 2H), 0.92−0.84 (m, 3H) 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), 7.31−7.25 (m, 2H), 7.19−7.15 (m, 2H), 7.06 (br t, J = 10.0 Hz, 1H), 4.31 (q, J = 7.6 Hz, 1H), 1.84−1.71 (m, 2H), 0.92−0.84 (m, 3H) 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. 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.

***N*-[1-(3-Methoxyphenyl)propyl]formamide, 13a.**[33] Purification by column chromatography (SiO_2; EtOAc/pentane 1:1) afforded compound **13a** in 96% isolated yield (R_f 0.30) as a colorless oil. Chiral GC-CP Chiralsil Dex CB, 25 m × 0.25 mm × 0.25 μm; He-flow: 1 mL/min; oven: 60 °C for 10 min, then 1 °C/min until 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), 7.26−7.20 (m, 1H), 6.85−6.76 (m, 3H), 6.44 (br s, 1H), 4.89 (q, J = 7.7 Hz, 1H), 3.76 (s, 3H), 1.84−1.73 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H) 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), 7.26−7.20 (m, 1H), 6.85−6.76 (m, 3H), 6.44 (br s, 1H), 4.29 (q, J = 7.6 Hz, 1H), 3.77 (s, 3H), 1.84−1.73 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H) 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-Methoxyphenyl)propyl]formamide, 14a.** Purification by column chromatography (SiO_2; EtOAc/pentane 1:1) afforded compound **14a** in 99% isolated yield (R_f 0.31) as a white solid. Mp 122.4−124.2 °C. Chiral GC-CP Chiralsil Dex CB, 25 m × 0.25 mm × 0.25 μm; He-flow: 1 mL/min; oven: 60 °C for 10 min, 1 °C/min until 150 °C, then 10 °C/min until 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), 7.26−7.21 (m, 1H), 7.71−7.11 (m, 1H), 6.93−6.87 (m, 2H), 6.73 (br s, 1H), 5.10 (q, J = 8.1 Hz, 1H), 3.84 (s, 3H), 1.87−1.78 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H) 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), 7.26−7.21 (m, 1H), 7.71−7.11 (m, 1H), 6.93−6.87 (m, 2H), 6.54 (br s, 1H), 4.45 (q, J = 8.2 Hz, 1H), 3.82 (s, 3H), 1.87−1.78 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H) 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. 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.

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 iPr$_2$O (10 mL) and the mixture was stirred for 45 min at rt. The mixture was cooled to −30 °C and substrate **5** (0.50 mmol) was added. A 1 M 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 1 M aq HCl (10 mL) and extracted with EtOAc (3 × 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-Phenylethyl)formamide, 5d.**[34] Purification by column chromatography (SiO_2; EtOAc/pentane 3:2) afforded compound **5d** in 70% isolated yield (R_f 0.37) as a colorless oil. Chiral GC-CP Chiralsil Dex CB, 25 m × 0.25 mm × 0.25 μm; He-flow: 1 mL/min; oven: 60 °C for 10 min, 1 °C/min until 150 °C, then 10 °C/min until 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), 7.37−7.23 (m, 5H), 6.32 (br s, 1H), 5.20−5.13 (m, 1H), 1.48 (d, J = 6.9 Hz, 3H) 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), 7.37−7.23 (m, 5H), 6.44 (br s, 1H), 4.69−4.61 (m, 1H), 1.53 (d, J = 6.9 Hz, 3H) 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 was stirred for 45 min at rt. The mixture was cooled to −20 °C and the substrate (0.50 mmol) was added. A 1 M solution of 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 × 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-phenylpropyl)formamide, 17a.** Purification by column chromatography (SiO_2; EtOAc/pentane 6:4) afforded compound **17a** in 81% isolated yield (R_f 0.44) as a colorless oil that slowly solidified, mp 46.8−48.1 °C. Chiral GC-CP Chiralsil Dex CB, 25 m × 0.25 mm × 0.25 μm; He-flow: 1 mL/min; oven: 60 °C for 10 min, 1 °C/min until 150 °C, then 10 °C/min until 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), 7.30−7.25 (m, 2H), 7.21−7.14 (m, 3H), 5.83 (d, J = 7.9 Hz, 1H), 4.03−3.94 (m, 1H), 2.79−2.54 (m, 2H), 1.91−1.79 (m, 1H), 1.76−1.54 (m, 2H), 1.40−1.38 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H) 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), 7.30−7.25 (m, 2H), 7.21−7.14 (m, 3H), 6.22 (t, J = 10.9 Hz, 1H), 3.20−3.11 (m, 1H), 2.79−2.54 (m, 2H), 1.91−1.79 (m, 1H), 1.76−1.54 (m, 2H), 1.40−1.38 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H) 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. 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.

***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 to 0 °C and 5 mL of a solution of H_2O_2 30% in water was added. Formation of a white precipitate was observed. The reaction mixture was warmed to rt 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, mp 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. 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.

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Supporting Information Available: Analytical and spectral characterization data for products **5b**, **5c**, **6a**, **7a**, **9a**-**12a**, **15a**, **16a**, **18a**, and **19a** and the starting materials **5**−**19**, and screening of solvents, temperatures, and Cu salts for the addition reactions to **5** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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