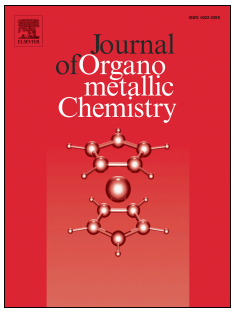

Reductive alkylation of imines via asymmetric Cu-catalyzed addition of organozirconium reagents

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Reductive Alkylation of Imines via Asymmetric Cu-Catalyzed Addition of Organozirconium Reagents

Ivana Némethová,[a1] Denisa Vargová,[a1] Brigita Mudráková,[a] Juraj Filo,[b] and Radovan Šebesta*[a]

a Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina, Ilkovičova 6, SK-84215, Bratislava, Slovakia.

b Institute of Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina, Ilkovičova 6, SK-84215, Bratislava, Slovakia.

Corresponding author tel. +421 2 60296208, e-mail: radovan.sebesta@uniba.sk

1 These authors contributed equally to the work presented and the preparation of the manuscript.

Abstract

Chiral amines are important as medicines or agrochemicals. They are often assembled by nucleophilic addition to corresponding compounds featuring C=N bond. Pre-made organometallics are typical nucleophiles in this reaction. In this work, we describe asymmetric reductive alkylation of imines with alkenes. Hydrozirconation of these alkenes generated organozirconium species in situ. The transformation is catalyzed by Cu-Segphos complex and affords chiral amines in enantioselectivities up to 93% ee.

Keywords

Imine; reductive alkylation; alkene; organozirconium reagent; Cu-catalysis

1. Introduction

Chiral amines are vital as pharmaceuticals, including levocetirizine[1], repaglinide[2], (-)-*N*-acetylcolchinol[3], ontazolast[4], crop-protection agents such as difulmetorim[5], or building blocks (Figure 1).

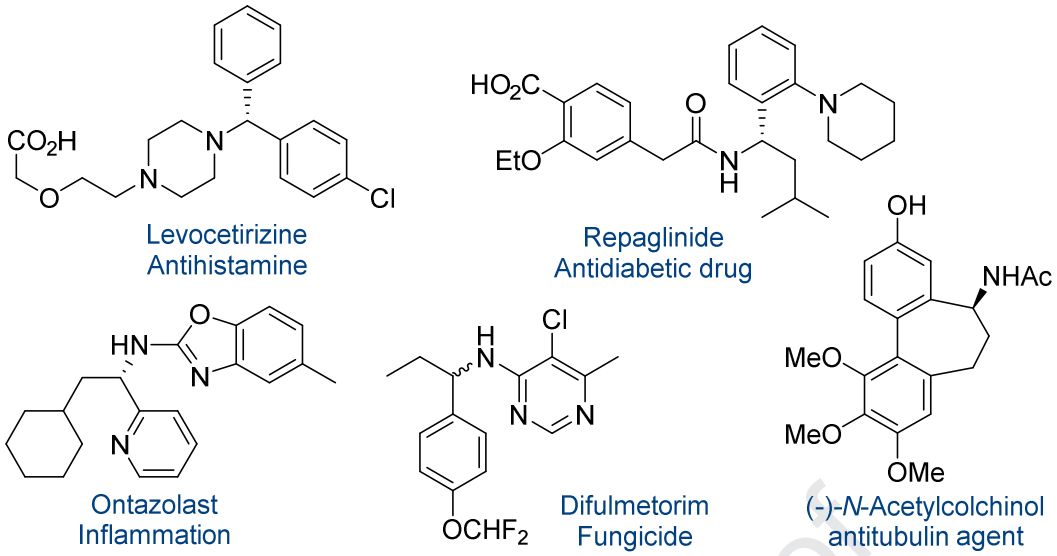


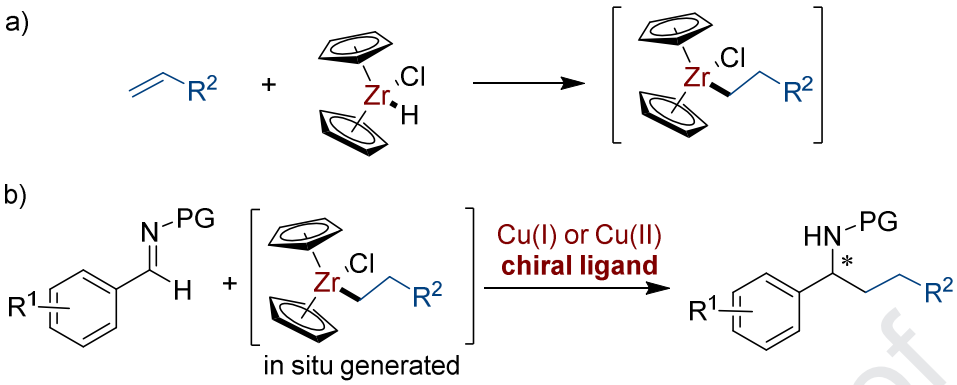
Figure 1. Industrially important bioactive chiral amines.

Common strategies for obtaining chiral amines are stereoselective nucleophilic additions to compounds featuring C=N double bond[6, 7]. The addition of carbon-based nucleophiles to imines can afford a great structural variety in possible products. A large number of stabilized, as well as non-stabilized organometallic nucleophiles, were added to imines as was comprehensively reviewed by Kobayashi[8]. Although, typical metals for catalyzing additions to imines are copper[9] or zinc, other metals such as Pd, Ni, or Co may work as well[10].

From among more recent advances, Harutyunyan developed Grignard additions to ketimines[11-13]. Organoboron compounds have traditionally been used for aryl, alkenyl, allyl or propargyl transfer[14-16], however, recent addition of bisborylalkanes to imines was also established [17]. However, these methods are somewhat limited to simpler alkyl, or aryl or highly reactive sidechains, such as allyl, or propargyl. From this point of view, the use of in situ generated organozirconium compounds seemed very beneficial as many alkenes could be used as a source of pro-nucleophile (Scheme 1). The utilization of alkenes or alkynes as pro-nucleophiles for imine additions has been only sparsely documented. Trost developed enantioselective vinylation of *N*-Boc imines with alkenylzirconium reagents using ProPhenol-type ligands[18]. Buchwald reported enantioselective hydrocupration for intramolecular synthesis of indoles[19], and intermolecular coupling of styrene to imines[20], obtaining branched products.

Organozirconium compounds are mild organometallic reagents, which have higher functional group tolerance than more reactive organometallic nucleophiles and do not require cryogenic conditions. An additional advantage of organozirconium reagents is that they can be obtained via hydrozirconation of corresponding alkenes or alkynes, thus sidestepping handling of pre-made organometallic reagents. In situ generated organozirconium reagents are useful nucleophiles in asymmetric conjugate additions and allylic substitutions[21]. To the best of our knowledge, there are no reports on reductive alkylation of imines using in situ generated organozirconium reagents (Scheme 1).

In this context, we decided to study the utilization of alkyl zirconium reagents in enantioselective addition to imines under copper catalysis.

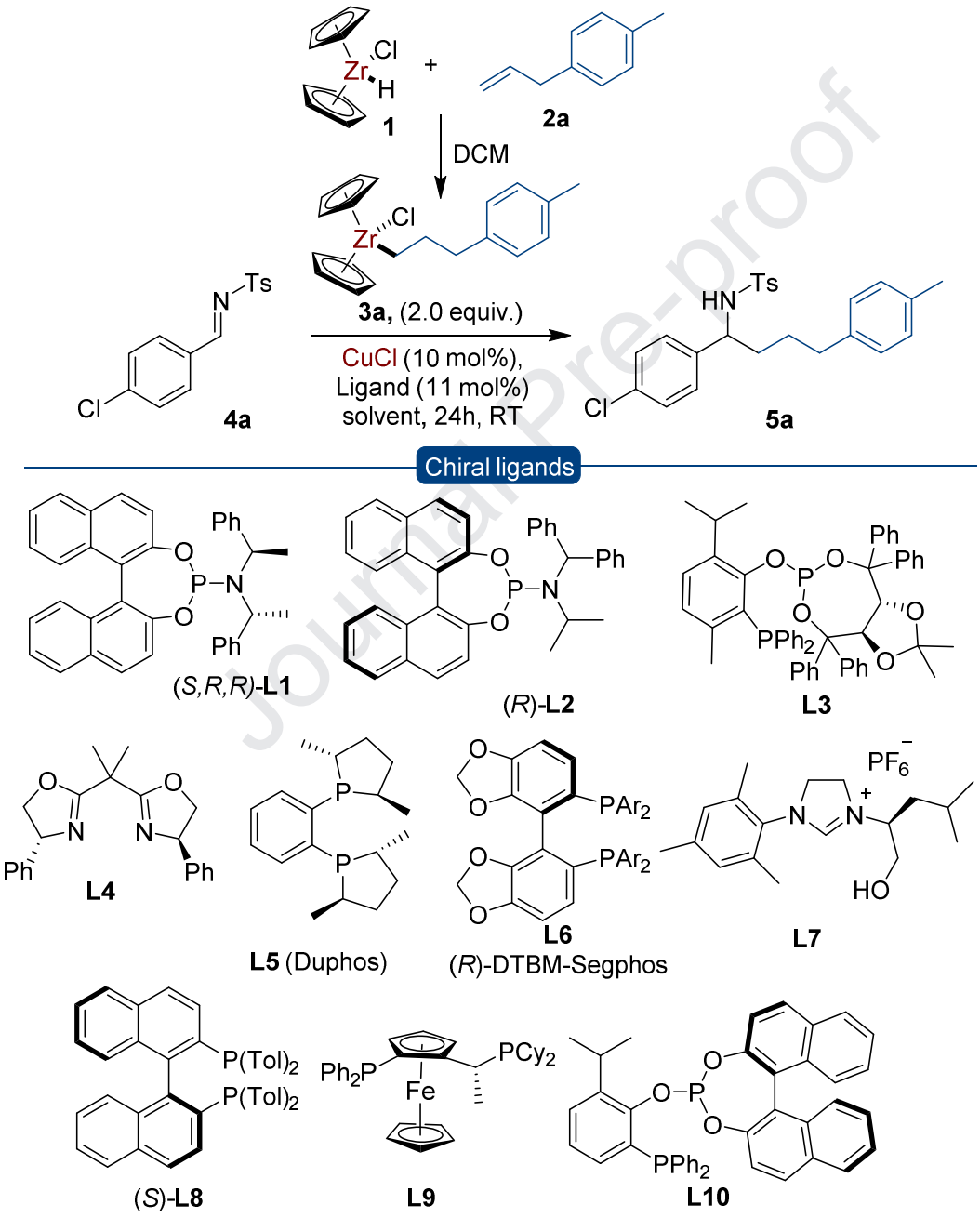


Scheme 1.

Results and Discussion

To optimize reaction conditions, we have selected an aldimine derived from 4-chlorobezaldehyde having Ts-protecting group **4a** as a starting substrate. 1-Allyl-4-methylbenzene (**2a**) was used as pro-nucleophile (Scheme 2). In a typical reaction setup, the corresponding organozirconium reagent prepared in a separate flask by mixing Schwartz reagent and the corresponding alkene, was added into a mixture of Cu/ligand complex. Into this mixture an imine was added. Firstly, we have verified how fast is an uncatalyzed background reaction. This experiment showed that the reaction of imine **4a** and organozirconium **3a** did not run in the absence of a copper catalyst. The expected product **5a** was not observed even after 24 h at room temperature, but the decomposition of starting imine **4a** has been observed by NMR. Consequently, we used monodentate phosphoramidites, as these ligands were effective in other Cu-catalyzed reactions of organozirconium reagents, such as conjugate additions[22, 23], and allylic substitutions[24, 25]. We employed CuCl as copper source and as the starting imine **4a** was fluffy solid, we added it to the reaction either straight as a solid or as a solution in DCM (Table 1, Entries 1,2). The reaction catalyzed by Cu/phosphoramidite (*S,R,R*)-**L1** indeed worked. We obtained the desired product (*S*)-**5a** in 34% yield with enantiomeric excess of 17% ee if **4a** was added as a solid in one portion. The yield of amine **5a** dropped to 17% (19% ee) when the aldimine **4a** was added as a DCM solution. This drop of yield could be explained by higher dilution of the reaction mixture. If ligand (*R*)-**L2** was used, we observed a dramatic increase in enantioselectivity favoring the formation of (*R*)-enantiomer in 42% ee (entry 3). The reaction, however, did not provide the full conversion of the starting material. The desired amine (*R*)-**5a** was isolated in only 33% yield. Changing the order of addition, and slow addition of the alkyl zirconium reagent both decreased the yield and enantioselectivity (entries 6 and 7). Somewhat unexpected reaction outcome was obtained with diphosphane ligand **L3**, which afforded amine (*S*)-**5a** in 39% yield and enantiomer purity of 43% ee. The class of Schmalz ligands was broadly employed in metal-catalyzed reactions, such as vinylation, allylic alkylations, cycloadditions or hydrocyanations[26-30]. We have tested several ligands from this family having either bulky achiral part or chiral binaphthol

back-bone. Unfortunately, none of the tested ligands gave better results, than **L3**. Surprisingly, if weakly coordinating **L4** was used we obtained good results in terms of yield (46%) and enantioselectivity (54% ee, (*S*)-**5a**). Interestingly, diphosphane (*R*)-DTBM-Segphos **L6** gave promising enantiomeric excess 73% ee of (*R*)-**5a** (entry 11). Using Hoveyda's NHC ligand **L7** (entry 12), a full consumption of the starting material was observed, but unfortunately the enantiomeric purity of amine **5a** decreased to 24% ee affording again the (*R*)-enantiomer. (S)-Tol-BINAP **L8** gave the product (*S*)-**5a** in 22% yield, but only 12% ee (entry 12). Josiphos ligand **L9** as well as Schmaltz type ligand with a chiral binaphthol unit **L10** were ineffective in this reaction as they gave only 7% and 3% yield, respectively (entries 13 and 14).



Scheme 2. Screening of chiral ligands in the addition of **3a** to imine **4a**.

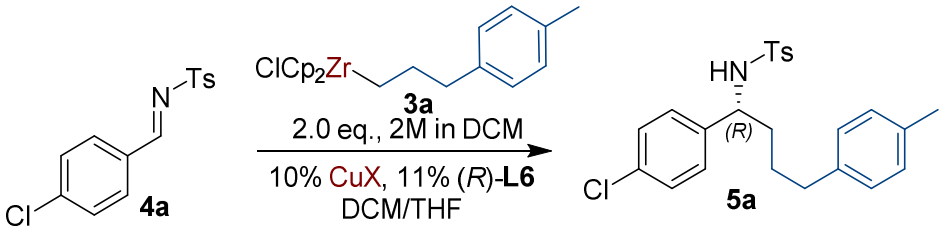
Table 1. Initial results of the addition of organozirconium **3a** to imine **4a**.

Entry[a)]	Ligand	Solvent	Yield **5a**[c)]	ee **5a** (%)
1	(*S,R,R*)-**L1**	Et_2O [b)]	34	17 (*S*)
2	(*S,R,R*)-**L1**	Et_2O [c)]	17	19 (*S*)
3	(*R,R,R*)-**L1**	Et_2O	45	19 (*S*)
4	(*R*)-**L2**	Et_2O [b,d)]	55	45 (*R*)
5	(*R*)-**L2**	THF [b)]	67	47(*R*)
6	(*R*)-**L2**	THF [e)]	31	11 (*R*)
7	(*R*)-**L2**	THF [f)]	19	50 (*R*)
8	**L3**	THF [b)]	39	43 (*S*)
9	**L4**	THF [b)]	46	54 (*S*)
10	**L5**	THF [b)]	14	50 (*R*)
11	(*R*)-**L6**	THF [b)]	**12**	**73** (*R*)
12	**L7**[g)]	THF [b)]	65[h)]	24 (*R*)
13	(*S*)-**L8**	THF [b)]	22	12 (*S*)
14	**L9**	THF [b)]	7	2 (*S*)
15	**L10**	THF [b)]	3	20 (*S*)

a) Chiral ligand (11 mol%, 0.022 mmol) and CuCl (10 mol%, 0.02 mmol) were stirred for 40 min in THF (0.8 mL). Schwartz reagent **1** (2.0 equiv., 0.4 mmol, 103 mg) was suspended in DCM (0.4 mL), followed by the addition of alkene **2a** (2.5 equiv., 0.5 mmol), stirred until yellow transparent. Combined reaction mixture was stirred for 24h. b) Imine **4a** was added as powder last; c) Imine added as a solution last; d) 0.4 mmol; e) reagent **3a** added last; f) reagent **3a** added last over 85 min; g) BuLi was used to generate carbene in situ; h) Full conversion on TLC.

Next, we screened various copper sources (Table 2). Interestingly, CuI did not give any product (entry 2). Even more surprising was the result that even copper(II)-salts were able to catalyze the addition. The reaction with $CuCl_2.2H_2O$ and DTBM-Segphos ligand **L6** afforded the corresponding product (*R*)-**5a** in 29 % yield and with 90% ee (entry 4). The use of anhydrous $CuCl_2$ gave worse results (Entry 5). $Cu(OAc)_2$ and $[Cu(MeCN)_4]BF_4$ performed poorly (Entries 6,7). Finally, the most efficient copper source for this reaction was $[Cu(MeCN)_4]PF_6$, which afforded amine **5a** in 45 % with high enantiomeric purity (87% ee). We were hoping to increase the yield of this promising result by using the preformed complex of Segphos-type ligands with $[Cu(MeCN)_4]PF_6$. Using complex (*R*)-DTBM-Segphos.$Cu(MeCN)PF_6$.PhMe, we observed a small improvement in the enantioselectivity – 93% ee, but the yield dropped to less than 20%. Using (*R*)-Segphos.$Cu(MeCN)PF_6$.2PhMe we did not obtain any product.

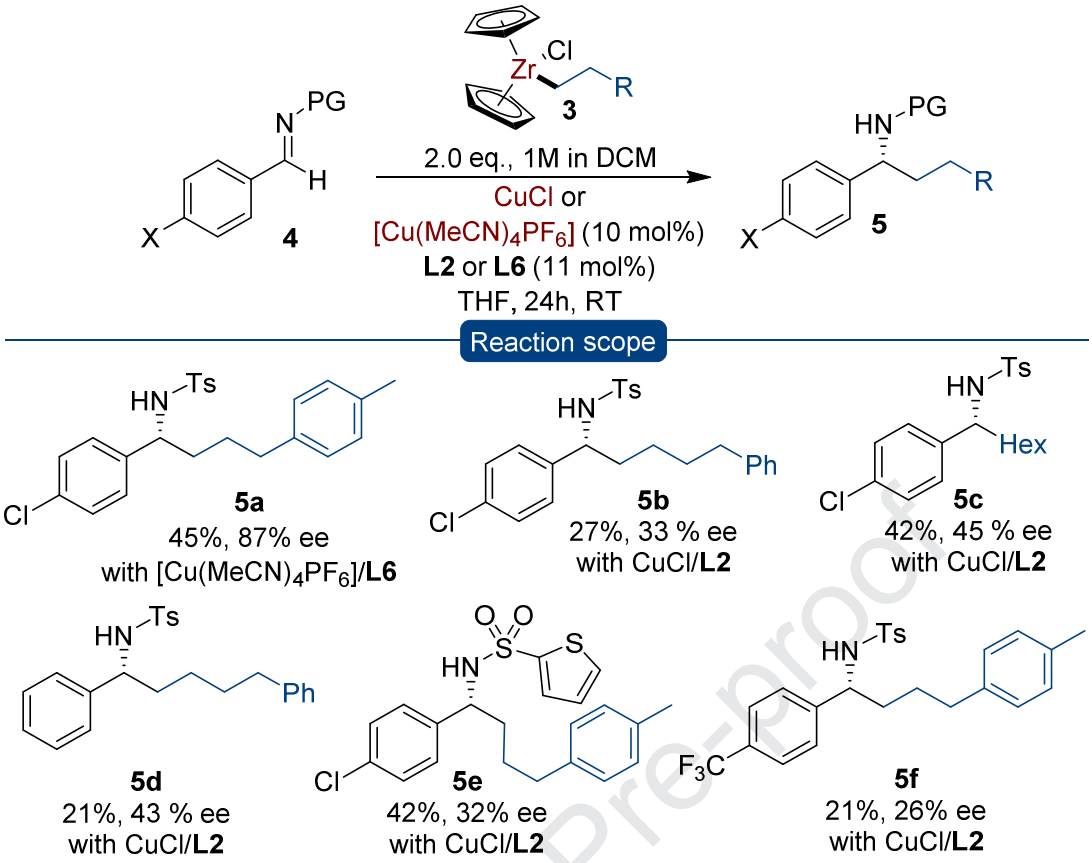
Table 2. Screening of copper sources in the alkylation of imine **4** with organozirconium **3**.



Entry	Cu source	Yield of **5a** (%)	ee **5a** (%)
1	CuCl	12	73
2	CuI	0	-
3	$CuBr.SMe_2$	29	n.d.
4	$CuCl_2.2H_2O$	29	90
5	$CuCl_2$	15	50
6	$Cu(OAc)_2$	0	n.d.
7	$[Cu(MeCN)_4]BF_4$	3	n.d.
8	$[Cu(MeCN)_4]PF_6$	45	87
9	(*R*)-DTBM-Segphos.$Cu(MeCN)PF_6$.PhMe	<20	93
10	(*R*)-Segphos.$Cu(MeCN)PF_6$.2PhMe	0	-

A brief additive screening was performed. Lewis acids TMSOTf and $BF_3.OEt_2$ as well as highly polar additives DMPU and DMEU we tested (see supplementary information for more details, Table S1, S2), but with no significant improvement of the yield, or enantioselectivity.

We have briefly evaluated the scope of the reaction using either (*R*)-**L2** or (*R*)-**L6** (Scheme 3). *p*-Chloro-substituted amine (*R*)-**5b** was obtained only in 27% yield with enantiopurity of 33 % ee. Aliphatic (*R*)-**5c** was obtained in 42% yield and 45 % ee. For the non-chlorinated product (*R*)-**5d** 21% yield and 43% ee was obtained. Different protecting groups were tried as well. Using TMS, nosyl, -SO_2NMe_2 or 5-methylpyrid-2-yl no products were obtained. Thiophenesulphonyl group provided the product (*R*)-**5e** in 42% yield and 32% ee. Amine **5f** with CF_3 group was obtained in 21% yield and 26% enantiomer purity.



Scheme 3. Product scope of the asymmetric 1,2-addition of alkylzirconium reagents to aldimines.

The absolute configuration of the stereogenic center was assigned as (*R*) by comparison of the optical rotation of a similar compound from the literature[31]. For (*S*)-N-(1,3-diphenylpropyl)-4-methylbenzenesulfonamide was measured $[\alpha]^{23}_{589}$ –37.8 (*c* 0.1, DCM) (sample with 99% ee). Our sample of (*R*)-**5d** had $[\alpha]^{20}_{589}$ + 16.3 (*c* 0.35, $CHCl_3$) for 43% ee.

To understand the reaction mechanism in greater detail, we have monitored the course of the reaction using ^{1}H NMR (Figure 2a). In the reaction mixture, we observed a by-product 1-methyl-4-propylbenzene (**6**) formed from the reduction of the alkene, which could explain the lower yields of amine products. However, the product formation continued nevertheless, over 24 h. For this experiment we used the conditions with ligand (*R*)-**L2**, in order to see more of the product in spectra. The reaction in the NMR tube proceeded until 35% conversion of imine **4a** to product **5a**. Lower conversion can be attributed to the absence of stirring in the NMR tube. Reaction profile depicted on the Figure 2a shows that the reaction proceeds throughout the whole time, albeit with a low rate. The slow reaction is likely caused by inherently lower nucleophilicity of the zirconium reagent **3a** in comparison to more reactive organometallics. In order to avoid undesired reduction of the starting alkene, we purged the mixture with argon during hydrozirconation, to get rid of any possible hydrogen formation that might have formed from the Schwartz reagent reacting with some residual moisture. Even after doing so, we still observed the reduced product **6** in the reaction mixture, albeit in somewhat lower concentration. This observation has led us to think that the reduced product **6** might be initially formed by other secondary reduction. Analysis of the NMR mixture confirmed that the reduced product is initially formed at around 50% conversion and is increasing only slightly in concentration over the 24h (Figure 2b). The initial concentration of 4-allyltoluene (**2a**) starts around

50%, since the hydrozirconation was stirred for 30 min prior to the addition to the NMR tube, by which time the reduced product formed.

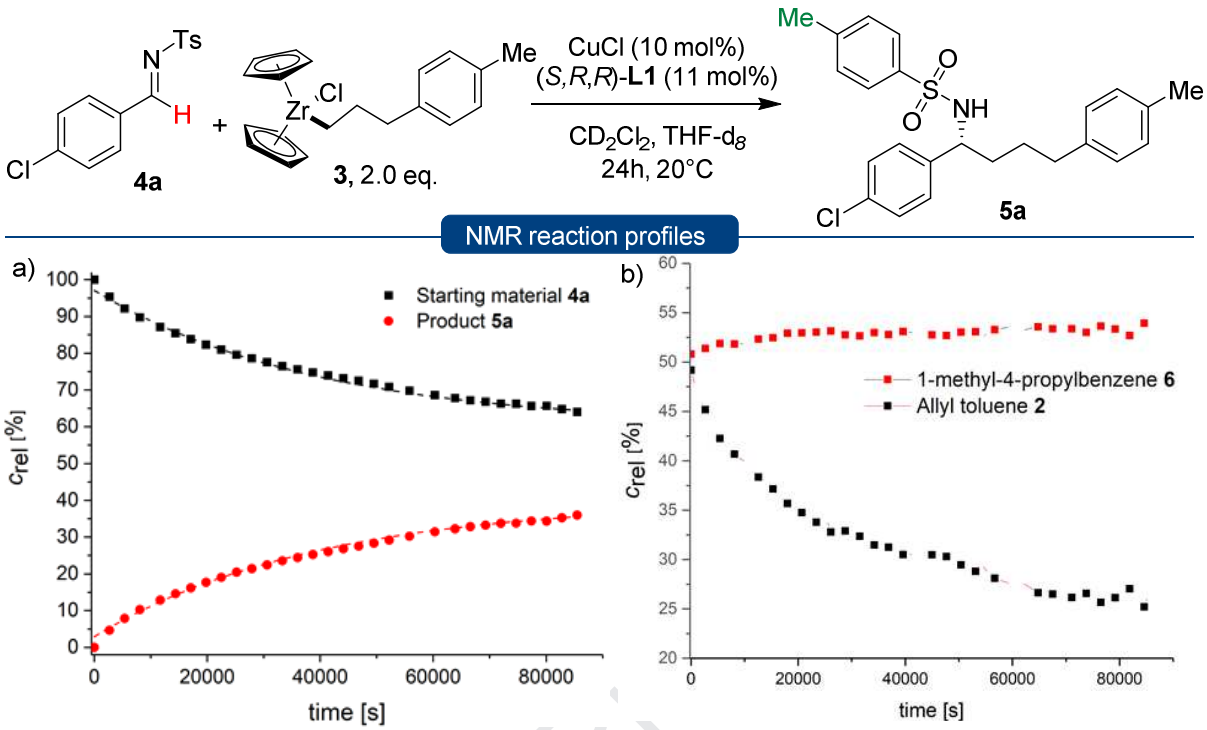
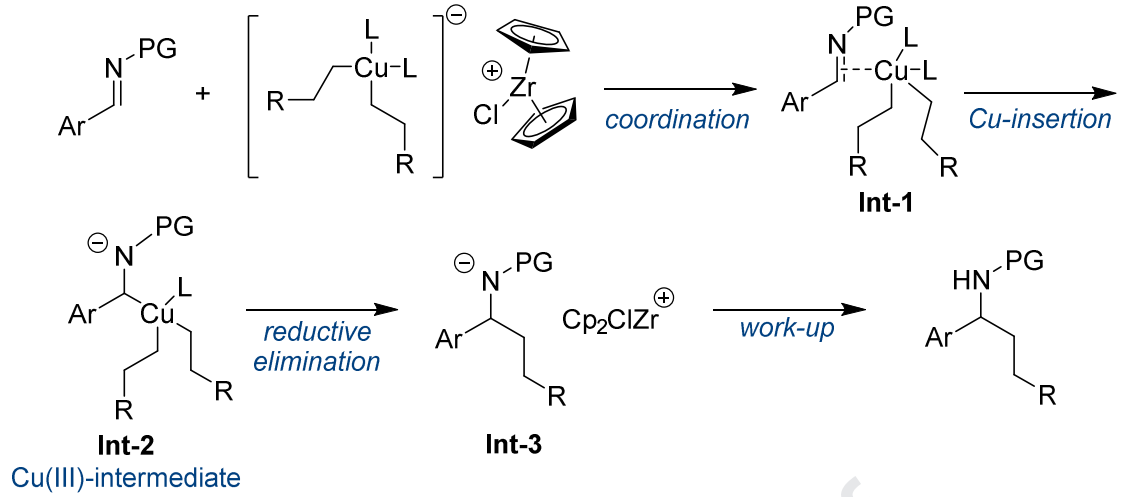


Figure 2. Reaction progress followed by ^{1}H NMR. Spectra were recorded every 15 minutes over 24 h. a) Relative concentration of the product was determined through integration of the Zr-salt of **5a** compared and starting imine **4b**; b) Relative concentration of 1-methyl-4-propylbenzene **6** and allyl toluene **2** determined through integration of the signals of the terminal protons on the double bond, and -CH_2- of 1-methyl-4-propylbenzene (**6**)**.** The formation of product **5a** from **4a** was taken into consideration.

Buchwald published a study[32] where complexes of imines and zirconium species were trapped by alkenes via intermediary zirconaaziridine species. Therefore, we decided to investigate the possibility of a similar mechanism in our case, however, presence of such species could not be ascertained in the reaction mixture by NMR. Therefore, we presume a mechanism analogous to 1,4-additions might be operational also for 1,2-addition to imines (Scheme 4)[33]. Organozirconium compounds often form dimer and this possibility need to be consider, but we could not confirm whether there were only one or two molecules of alkyl zirconium species involved. We presume that there would be a large steric hindrance for two molecules of alkylzirconium reagent in the transition state. After the transmetallation step, coordination to the imine should follow. Reductive elimination of the Cu(III)-intermediate **Int-2** leads to Zr- salt **Int-3**. After aqueous work-up the product is obtained.



Scheme 4: Tentative mechanisms of 1,2-addition of zirconium species to imines.

^{31}P NMR spectra of copper complexes of (*R*)-**L6** and zirconium reagents were measured (Figure 3, spectrum 4). Comparison with spectra of pre-formed complex (Figure 3, spectrum 3), new species were formed. If the alkylzirconium reagent was combined with $[Cu(MeCN)_4]PF_6$ no significant shift in the PF_6^- signal was observed (Figure 3, spectrum 2). Finally, to rule out the possibility of a monoligated copper, we measured (*R*)-**L6** with 0.5 equiv of $[Cu(MeCN)_4]PF_6$ (Figure 3, spectrum 1). In this case a large amount of free ligand was observed, a small amount of the complex, but no monocoordinated ligand. These data suggest that the transmetallation from zirconium to copper is efficient and is demonstrated by the new species observed in the spectrum 4. There is a possibility to form dimers, or other high-order oligomers, which would explain why there are multiple new signals.

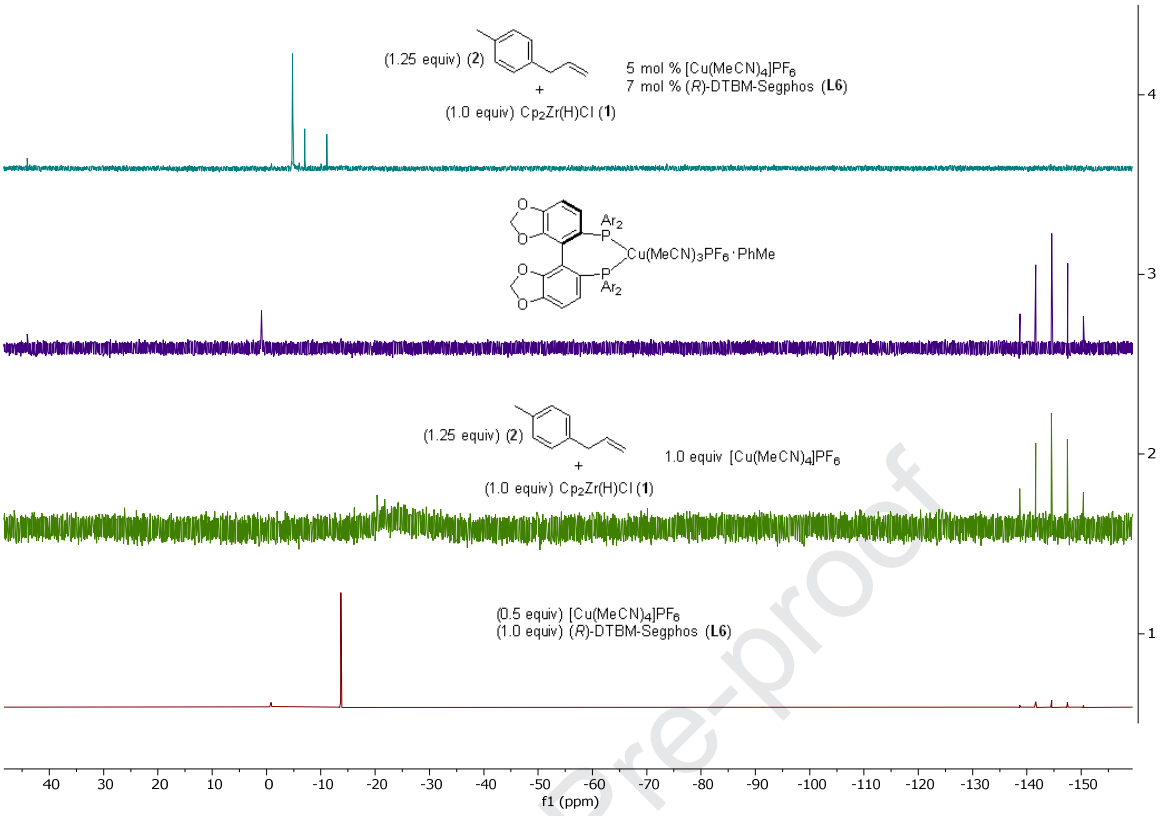


Figure 3. ^{31}P spectra of Cu-Segphos complexes.

Conclusion

In this work, we studied the asymmetric Cu-catalyzed addition of organozirconium species to aldimines. This so far unprecedented methodology would provide new possibilities for synthesis of chiral secondary alcohols. The best results were achieved by using catalytic system composed of $[Cu(MeCN)_4]PF_6$ and (*R*)-**L6**. Corresponding chiral products were obtained in enantiomeric purities up to 93% however in low yield. The course of reaction was studied via ^{1}H NMR with the emphasis to the reaction mechanism.

Experimental Section

General procedure for asymmetric addition of organozirconium species

Chiral ligand (11 mol%, 0.022 mmol) and CuX (10 mol%, 0.02 mmol) were weighed into heat-dried Schlenk flask flushed with Ar. Anhydrous THF (0.8 mL) was added and the mixture was stirred for 40 min under Ar atmosphere at RT. In the meantime, Schwartz reagent **1** (2.0 equiv., 0.4 mmol, 103 mg) was weighed into heat-dried flask flushed with Ar. Anhydrous DCM (0.4 mL) was added to the reaction mixture, followed by the addition of starting alkene (2.5 equiv., 0.5 mmol). The resulting slurry was stirred until it became yellow and transparent (approx. 20 min). The solution of $Cp_2Zr(R)Cl$ was transferred to the solution of Cu-catalyst. The combined reaction mixture was stirred for 10 min

at room temperature before aldimine was added in one portion. The combined reaction mixture was then stirred for 24h at RT. The reaction was quenched using aqueous NH_4Cl (1M, 1 mL), extracted by DCM (3x10 mL) and washed with aq. $NaHCO_3$ (5%, 10 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on SiO_2 (hexane/EtOAc).

Characterization data

(*R*)-*N*-(1-(4-chlorophenyl)-4-(p-tolyl)butyl)-4-methylbenzenesulfonamide (5a)

White solid, yield: 67% (50 mg), **m.p.** 121 – 125 °C, on SiO_2 (hexane/EtOAc gradient 8:1 to 3:1).
IR: 3236 (N-H), 2918 (C-H), 1314 (S=O), 1158 (S=O) cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ= 7.48 (d, *J* = 8.3 Hz, 2H), 7.11 – 7.06 (m, 4H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.95 (br.s, 1H, NH), 4.26 (q, *J* = 7.2 Hz, 1H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.36 (s, 3H), 2.30 (s, 3H), 1.74 (dddd, *J* = 12.5, 10.3, 7.2, 5.2 Hz, 1H), 1.67 – 1.61 (m, 1H), 1.57 – 1.50 (m, 1H), 1.43 – 1.36 (m, 1H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 143.2, 139.3, 138.3, 137.5, 135.3, 133.1, 129.2, 129.0, 128.5, 128.2, 127.9, 127.0, 57.5, 36.8, 34.7, 27.5, 21.4, 20.9 ppm. **HRMS** (HESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}ClNO_2S$: 428.1450, found: 428.1455. **HPLC:** Chiralpak IB, hexane/*i*-PrOH = 90:10, 1 mL/min, 222 nm, t_R(major) = 12.28 min, t_R(minor) = 20.84 min. **$[\alpha]^{20}_{589}$** + 3.4 (*c* 1.0, $CHCl_3$) for 45% ee.

(*R*)-*N*-(1-(4-chlorophenyl)-5-phenylpentyl)-4-methylbenzenesulfonamide (5b)

White solid, yield: 27% (21 mg), **m.p.** 95 – 99 °C, purified on SiO_2 (hexane/EtOAc gradient 8:1 to 3:1).
IR: 3268 (N-H), 2928 (C-H), 2857 (CH_2), 1320 (S=O), 1155 (S=O) cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.2 Hz), 7.24 (d, *J* = 7.6 Hz), 7.19 – 7.06 (m, 4H), 6.92 (d, *J* = 8.4 Hz), 5.01 (d, *J* = 7.1 Hz, 1H, NH), 4.22 (q, *J* = 7.3 Hz), 2.51 – 2.45 (m, 2H), 2.37 (s, 3H), 1.78 – 1.71 (m, 1H), 1.68 – 1.60 (m, 1H), 1.52 (p, *J* = 7.7 Hz, 2H), 1.31 – 1.22 (m, 1H), 1.18 – 1.09 (m, 1H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 143.2, 142.1, 139.4, 137.5, 133.1, 129.3, 128.5, 128.3, 127.9, 127.0, 125.7, 57.6, 37.3, 35.5, 30.8, 25.3, 21.4 ppm.
HRMS (HESI): *m/z* $[M]^-$ calcd for $C_{24}H_{26}ClNO_2S$: 426.1300, found: 426.1292. **HPLC:** Chiralpak IB, hexane/*i*-PrOH = 93:7, 1 mL/min, 222 nm, t_R(major) = 15.30 min, t_R(minor) = 19.90 min. **$[\alpha]^{20}_{589}$** +163.0 (*c* 0.4, $CHCl_3$) for 33% ee.

(*R*)-*N*-(1-(4-chlorophenyl)heptyl)-4-methylbenzenesulfonamide (5c)

White solid, yield: 42% (32 mg), **m.p.** 87 – 92 °C, on SiO_2 (hexane/EtOAc gradient 8:1 to 3:1).
IR: 3254 (N-H), 2929 (C-H), 2863 (CH_2), 1314 (S=O), 1164 (S=O) cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.3 Hz, 2H), 7.14 – 7.09 (m, 4H), 6.96 – 6.93 (m, 2H), 4.82 (d, *J* = 7.0 Hz, 1H, NH), 4.24 (q, *J* = 7.2 Hz, 1H), 2.37 (s, 3H), 1.70 (ddd, *J* = 12.4, 8.8, 5.3 Hz, 1H), 1.65 – 1.57 (m, 1H), 1.24 – 1.10 (m, 7H), 1.10 – 1.01 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 143.2, 139.5, 137.5, 133.0, 129.3, 128.4, 127.9, 127.0, 57.6, 37.5, 31.5, 28.7, 25.7, 22.5, 21.4, 14.0 ppm. **HRMS** (HESI): *m/z* $[M]^-$ calcd for $C_{20}H_{26}ClNO_2S$: 378.1300, found: 378.1291. **HPLC:** Chiralpak IB, hexane/*i*-PrOH = 93:7, 1 mL/min, 222 nm, t_R(major) = 9.63 min, t_R(minor) = 14.63 min. **$[\alpha]^{20}_{589}$** +16.8 (*c* 1.0, $CHCl_3$) for 45% ee.

(*R*)-*N*-(1,5-diphenylpentyl)-4-methylbenzenesulfonamide (5d)

Deliquescent white solid, yield: 21% (17 mg), purified on SiO_2 (hexane/EtOAc gradient 8:1 to 3:1). **IR:** 3272 (N-H), 2926 (C-H), 2856 (CH_2), 1320 (S=O), 1154 (S=O) cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.55 – 7.51 (m, 2H), 7.26 – 7.23 (m, 2H), 7.19 – 7-14 (m, 4H), 7.12 – 7.07 (m, 4H), 7.01 – 6.97 (m, 2H), 4.85 (d, *J* = 7.3 Hz, 1H, NH), 4.25 (q, *J* = 7.3 Hz, 1H), 2.51 – 2.47 (m, 2H), 2.35 (s, 3H), 1.79 (dddd, *J* = 12.8, 10.2, 7.1, 5.5 Hz, 1H), 1.74 – 1.66 (m, 1H), 1.55 – 1.49 (m, 2H), 1.33 – 1.26 (m, 1H), 1.20 – 1.11 (m, 1H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 142.9, 142.2, 140.9, 137.6, 129.3, 128.4, 128.3, 128.2, 127.3, 127.0, 126.4, 125.7, 58.2, 37.4, 35.6, 30.9, 25.5, 21.4 ppm. **HRMS** (HESI): *m/z* $[M]^-$ calcd for $C_{24}H_{27}NO_2S$: 392.1690, found: 392.1679. **HPLC:** Chiralpak IB, hexane/*i*-PrOH = 93:7, 1 mL/min, 222 nm, t_R(major) = 11.25 min, t_R(minor) = 18.47 min. **$[\alpha]^{20}_{589}$** +16.3 (*c* 0.35, $CHCl_3$) for 43% ee.

(*R*)-*N*-(1-(4-chlorophenyl)-4-(p-tolyl)butyl)thiophene-2-sulfonamide (5e)

White solid, 42% yield, 32% ee, **m.p.** 84.2 – 85.5 °C, purified on SiO_2 (hexane/EtOAc gradient 8:1 to 3:1). **^{1}H NMR** (600 MHz, $CDCl_3$): δ= 7.45 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.31 (dd, *J* = 3.7, 1.3 Hz, 1H), 7.17 – 7.13 (m, 2H), 7.06 (d, *J* = 7.7 Hz, 2H), 6.96 (t, *J* = 8.8 Hz, 4H), 6.89 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.89 (d, *J* = 7.3 Hz, 1H), 4.35 (q, *J* = 7.3 Hz, 1H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.30 (s, 3H), 1.82 – 1.73 (m, 1H), 1.72 – 1.65 (m, 1H), 1.61 – 1.56 (m, 1H), 1.48 – 1.40 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ= 141.6, 139.1, 138.3, 135.4, 133.3, 132.3, 131.8, 129.1, 128.7, 128.2, 127.8, 127.1, 57.9, 36.8, 34.7, 27.5, 20.9. **HRMS (HESI):** *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}ClNO_2S_2Na$: 444.0643, found: 444.0648. **HPLC:** Chiralpak IB, hexane/*i*-PrOH = 93:7, 1 mL/min, 222 nm, t_R(major) = 16.8 min, t_R(minor) = 21.3 min. **$[\alpha]^{20}_{589}$** +21.9 (c 0.2, $CHCl_3$) for 32% ee.

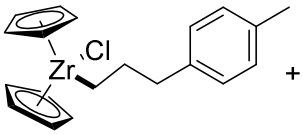
(*R*)-N-(1-(4-trifluoromethyl)henyl)-4-(*p*-tolyl)butyl)-4-methylbenzenesulfonamide (5f)

White solid, yield: 21% (20 mg), **m.p.** 142.8-145.1°C, purified on SiO_2 (hexane/EtOAc gradient 7:1 to 4:1). **IR**: 3259 (N-H), 2923 (C-H), 1319 (S=O), 1153 (S=O) cm^{-1}. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.05 (dd, *J* = 14.5, 7.6 Hz, 6H), 6.94 (d, *J* = 7.8 Hz, 2H), 4.72 (d, *J* = 7.0 Hz, 1H, NH), 4.37 (q, *J* = 7.1 Hz, 1H), 2.50 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 2.30 (s, 3H), 1.76 (ddd, *J* = 12.8, 10.5, 6.1 Hz, 1H), 1.66 (ddd, *J* = 19.3, 11.7, 5.9 Hz, 1H), 1.62 – 1.55 (m, 1H), 1.50 – 1.39 (m, 1H) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 144.7, 143.3, 138.2, 127.3, 135.4, 129.2, 129.0, 128.2, 126.9, 126.9, 125.3, 125.2, 125.2, 125.2, 125.0, 57.7, 36.7, 34.6, 27.4, 21.3, 21.0 ppm. **^{19}F NMR** (564 MHz, $CDCl_3$) δ -62.7 (s) ppm. **HRMS (HESI):** m/z [M+H]+ calcd for $C_{25}H_{27}F_3NO_2S$: 462.1715, found: 462.1712. **HPLC:** Chiralpak IB, hexane/*i*-PrOH = 90:10, 1 mL/min, 222 nm, t_R(major) = 10.22 min, t_R(minor) = 13.44 min. **$[\alpha]^{20}_{589}$** + 1.2 (c 0.25, $CHCl_3$) for 26% ee.

Procedure for NMR experiments

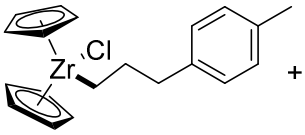
For all NMR experiments an amberized, valved NMR tube was used (Norell S-5-600-VT-7). Before setting up an experiment, the tube was connected to a Schlenk line, evacuated and backfilled with Ar 3 times. After addition of solid material, the procedure was repeated. The addition of solvent was performed under constant Ar flow from the Schlenk line.

^{31}P measurements:



+ 5% $[Cu(MeCN)_4]PF_6$
7% (*R*)-DTBM-Segphos

$[Cu(MeCN)_4]PF_6$ (2.5 mg, 0.007 mmol) and (*R*)-DTBM-Segphos **L6** (11.0 mg, 0.009 mmol) were added to a heat dried flask, and stirred in anhydrous CD_2Cl_2 (0.4 mL) for 30 min. Simultaneously, 4-allyltoluene (26 µL, 0.170 mmol) and Schwartz reagent **1** (35 mg, 0.136 mmol) were stirred in anhydrous CD_2Cl_2 (0.4 mL). The solutions were combined in the NMR tube, and ^{31}P was measured immediately.



+ 1.0 equiv $[Cu(MeCN)_4]PF_6$

$[Cu(MeCN)_4]PF_6$ (20 mg, 0.050 mmol), 1-allyl-4-methylbenzene (10 µL, 0.067 mmol) and Schwartz reagent **1** (13 mg, 0.050 mmol) were combined directly in the NMR tube, dissolved in CD_2Cl_2 (0.6 mL) and measured in 20 minutes.

$[Cu(MeCN)_4]PF_6$ (0.5 equiv) and (*R*)-DTBM-Segphos **L6** (1.0 equiv)

$[Cu(MeCN)_4]PF_6$ (3.0 mg, 0.008 mmol) and (*R*)-DTBM-Segphos **L6** (20 mg, 0.016 mmol) were combined directly in the NMR tube, dissolved in CD_2Cl_2 (0.6 mL) and measured in 20 min.

Kinetic measurement:

(*S,R,R*)-**L1** (7.0 mg, 0.013 mmol, 11 mol%) and CuCl (1.2 mg, 0.012 mmol, 10 mol%) were weighed into heat-dried Schlenk flask flushed with Ar. THF-d_8 from a sealed vial (0.6 mL) was added and the mixture was stirred for 40 min under Ar atmosphere at RT. In the meantime, Schwartz reagent **1** (2.0 equiv., 69 mg, 0.27 mmol) was weighed into heat-dried flask flushed with Ar. Anhydrous CD_2Cl_2 (0.3 mL) was added to the reaction mixture, followed by the addition of 1-allyl-4-methylbenzene (**2a**, 2.5 equiv., 50 µL, 0.34 mmol). The resulting slurry was stirred until it became yellow and transparent (approx. 20 min). The solution of Cu-catalyst solution was transferred to the NMR tube, followed by the solution of $Cp_2Zr(R)Cl$ and aldimine (1.0 equiv., 40 mg, 0.135 mmol). ^1H NMR spectra were recorded every 15 min over 24 h.

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Reductive Alkylation of Imines via Asymmetric Cu-Catalyzed Addition of Organozirconium Reagents

I. Némethová, D. Vargová, B. Mudráková, J. Filo, R. Šebesta

Highlights:

- Imines can be reductively alkylated with alkenes
- The reaction proceed via in situ generated organozirconium reagents obtained by hydrozirconation of alkenes
- The transformation is catalyzed by Cu-Segphos or phosphoramidite complexes
- Kinetic ^{1}H NMR experiments revealed reaction profile
- Catalytically active complexes were studied by ^{31}P NMR

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: