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Chiral Phosphine-Aminophosphine Ligands for Copper-Catalyzed Asymmetric Hydrogenation

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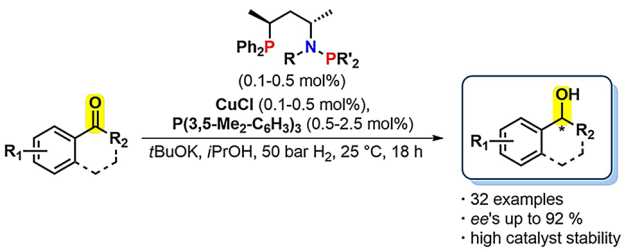
Abstract

New chiral bidentate phosphine-aminophosphine ligands based on a pentane-2,4-diyl backbone, with the general formula $Ph_2PCH(CH_3)CH_2CH(CH_3)N(R^1)PR^2_2$ (R^1 = Me, Et, *n*Pr, *n*Bu, *i*Pr; R^2 = Ph, Cy), have been developed and applied in the copper-catalyzed asymmetric hydrogenation of simple ketones. The addition of achiral monodentate phosphines as co-ligands significantly enhanced both catalytic turnover and enantioselectivity. It was observed that the steric properties of the ligands predominantly influence catalytic activity and enantioinduction, whereas their electronic characteristics play a secondary role. Comprehensive screening of reaction conditions, including variation of the metal source and careful selection of both chiral and achiral ligands with appropriately tuned stereochemistry, enabled the hydrogenation to proceed with low catalyst loadings (0.5 mol%) while maintaining high yields and enantioselectivities (up to 92% *ee*) across a broad substrate scope. Based on experimental findings and relevant literature precedents, a mechanistic proposal is presented to explain the observed reactivity trends.

Graphical Abstract

Graphical Abstract



Keywords Copper catalysis · Asymmetric hydrogenation · Prochiral ketone · Phosphine-aminophosphine · Stereoelectronic properties

Abbreviations

ee	Enantiomeric excess, enantioselectivity
BDPP	2,4-Bis(diphenylphosphino)pentane
PN,P	Phosphine-aminophosphine
BoPhoz	1-[2-Diarylphosphinoferrocenyl](N-alkyl)(N-diarylphosphino)ethylamine)
THF	Tetrahydrofuran
COD	(Z,Z)-cycloocta-1,5-diene
TOF	Turnover frequency
TON	Turnover number

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1 Introduction

The transition-metal catalyzed asymmetric hydrogenation of prochiral ketones undoubtedly represents one of the most practical chemical transformations leading to optically active secondary alcohols as valuable building blocks for a number of biologically active compounds such as medicines, fragrances and agrochemicals [1–4]. The field is dominated by the complexes of noble metals, such as Ru, Os, Rh, Ir, Pd, Pt, as highly efficient catalytic systems [5]. However, the noble metals that are currently most common amongst homogeneous hydrogenation catalysts suffer from high toxicity and environmental impact in addition to their scarcity and ensuing high cost. Motivated by these facts, in recent years, remarkable progress has been devoted to replace noble metal catalysts with earth-abundant, less expensive, and less toxic first row transition metals [6–8], like iron [9], cobalt [10], nickel[11] and manganese [12]. Besides these options, copper as a catalyst metal also offers an economically and ecologically benign solution to the difficulties associated with the use of noble metal catalysts [13]. In fact, amongst transition metals, copper is a base metal that has one of the lowest supply risks, even lower than that of iron. [8] Despite the early success in the development of copper based homogeneous C=O hydrogenation catalysts [14–17], only limited examples are available for the utilization of this transition metal in the asymmetric hydrogenation of prochiral ketones compared to other non-noble metals.

The pioneering work of Shimizu opened new horizons in the development of chiral copper-based catalysts [18]. Simple Cu(I)-precursors in combination with the pentane-2,4-diyl based ditertiary phosphine, BDPP (2,4-bis(diphenylphosphino)pentane) and achiral monophosphines proved to be highly efficient in the hydrogenation of alkyl-aryl ketones providing high activity and *ee*'s up to 90%. Later, the same group reported on the successful application of chiral copper catalysts in the asymmetric hydrogenation of heteroaromatic ketones and in the chemo- and enantioselective reduction of α,β-unsaturated carbonyl compounds [19]. Beller and coworkers used different binaphthyl-based monophosphines as stereoselectors in the hydrogenation of ketonic substrates (*ee*'s up to 89%) [20]. The utilization of the C_1-symmetry phosphine-aminophosphine type BoPhoz (1-[2-diarylphosphinoferrocenyl](N-alkyl)(N-diarylphosphino)ethylamine) ligands in asymmetric copper-catalyzed hydrogenation by Johnson et al. significantly improved the enantioselectivity and *ee*'s up to 98% could be obtained for substrates with more pronounced steric demand [21]. In recent years, copper-based chiral catalysts provided outstanding selectivities in the hydrogenation/dynamic kinetic resolution of 2-substitued tetralone-derivatives [22], in the chemo- and enantioselective C=O hydrogenation of exocyclic α,β-unsaturated pentanones [23] and in the reduction of unsymmetrical *ortho*-Br substituted benzophenones [24].

The above examples clearly demonstrate the competitiveness and synthetic utility of copper-catalyzed asymmetric hydrogenation. However, the expansion of this specific research area continues to be slow, which may be attributed to the lack of dedicated chiral ligands and limited understanding of the structure–activity relationships within these catalytic systems.

Previous literature reports have shown that copper-catalyzed asymmetric hydrogenation could be realized with high activity using pentane-2,4-diyl based diphosphine, BDPP, [18, 19] and with excellent enantioselectivity by employing C_1-symmetry hybrid phosphine-aminophosphine type ligands. [21] To combine the benefits of these parent stereoselectors, we envisioned applying chiral pentane-2,4-diyl based phosphine-aminophosphine (PN,P) ligands in the copper-catalyzed asymmetric hydrogenation of prochiral ketones.

Recently, we synthesized several novel PN,P ligands for the rhodium-catalyzed asymmetric hydrogenation of prochiral alkenes [25]. A notable advantage of these ligands is the highly modular nature of their synthesis that facilitates the systematic investigation of the stereoelectronic properties and their influence on catalytic activity and enantioselectivity. Guided by this philosophy in ligand design, we report on the synthesis of novel pentane-2,4-diyl based phosphine-aminophosphine ligands and their catalytic application in asymmetric copper-catalyzed hydrogenation.

2 Results and Discussions

2.1 Ligand Synthesis

In the present study, we expanded the scope of our phosphine-aminophosphine ligands (**L1-3**, **L6**) [25] using the same highly modular, three-step synthetic procedure (Fig. 1). Initially, chiral cyclic sulfate **1** was treated with primary amines, resulting in the formation of the corresponding sulfated amines (**2**). Subsequent reaction of compounds **2** with lithium diphenylphosphide afforded the desired (*S*,*S*)-phosphine-amines **3** in high yields. The novel P,NP ligands **L4** and **L5** were then synthesized by treating these phosphine-amines with 1.5 equivalents of diphenylchlorophosphine in the presence of a base. In the final step, no tedious workup procedures were required, as passing the reaction mixture through a pad of activated alumina afforded the products in generally high yield and in pure form.

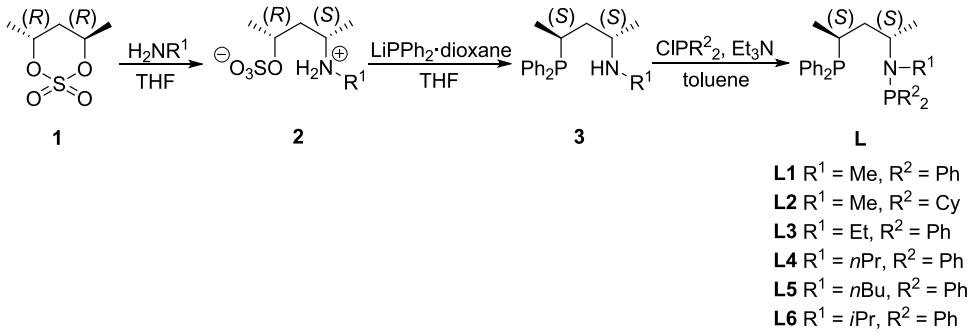
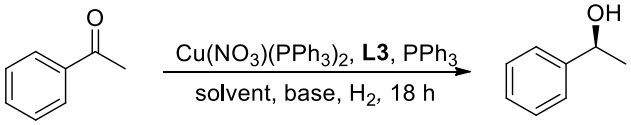


Fig. 1 Synthesis of (*S*,*S*)-pentane-2,4-diyl based phosphine-aminophosphine ligands

Table 1 Asymmetric hydrogenation of acetophenone: screening the reaction conditions[a]



S1 P1

Entry	Pressure [bar]	Temp. [°C]	Solvent	Base	B/C	Conv. [%]	Ee [%]
1[b]	50	25	*i*PrOH	*t*BuOK	10	57	44
2	50	25	*i*PrOH	*t*BuOK	10	>99	67
3	50	40	*i*PrOH	*t*BuOK	10	>99	63
4	30	25	*i*PrOH	*t*BuOK	10	98	66
5	50	25	*n*BuOH	*t*BuOK	10	>99	64
6	50	25	*t*BuOH	*t*BuOK	10	83	66
7	50	25	EtOH	*t*BuOK	10	55	61
8	50	25	MeOH	*t*BuOK	10	0	-
9	50	25	toluene	*t*BuOK	10	0	-
10	50	25	dioxane	*t*BuOK	10	7	31
11	50	25	*i*PrOH	*t*BuOLi	10	11	65
12	50	25	*i*PrOH	KOH	10	28	57
13	50	25	*i*PrOH	*t*BuOK	5	23	63
14	50	25	*i*PrOH	*t*BuOK	20	>99	66

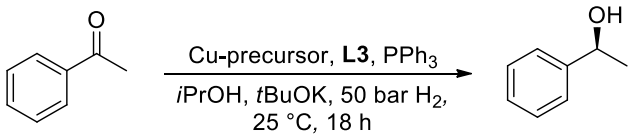
[a]Reaction conditions: ligand **L3**: 0.006 mmol, $Cu(NO_3)(PPh_3)_2$: 0.006 mmol, PPh_3: 0.018 mmol, acetophenone: 0.6 mmol, solvent: 1 mL, reaction time 18 h. Conversion and enantioselectivity were determined by chiral GC. The prevailing product enantiomer is (*S*)-1-phenylethanol in each case. [b]The reaction was carried out without PPh_3

2.2 Catalytic Studies

With ligands **L1-L6** in hand, we set out to optimize the reaction conditions for the copper-catalyzed asymmetric hydrogenation of acetophenone, used here as a benchmark substrate. Following established literature protocols, [18, 19] the catalyst was generated in situ by reacting the copper precursor $Cu(NO_3)(PPh_3)_2$ with one molar equivalent of chiral ligand **L3** in isopropanol. Initial catalytic experiments were conducted in the same solvent under 50 bar H_2 pressure at 25 °C. The addition of three equivalents of PPh_3 as a co-ligand significantly enhanced both the catalytic activity and the enantioselectivity of the reaction (Table 1, entries 1 and 2). A similarly remarkable mixed-ligand effect has also been observed in previous studies. [18, 21, 22] Raising the reaction temperature or lowering the hydrogen pressure led to a slight decrease in selectivity and activity, respectively (entries 3 and 4). The reaction was also evaluated in various alcohols and aprotic solvents (entries 5–10); however, isopropanol emerged as the solvent of choice, offering the best balance of activity and enantioselectivity. The highest conversion and enantiomeric excess were achieved using the initially applied base, *t*BuOK, at a base-to-catalyst molar ratio of 10 (entries 11–14).

In the next set of experiments, we performed the hydrogenation of acetophenone in the presence of different copper precursors by using different amounts of PPh_3 co-ligand (Table 2). Generally, higher conversions and enantioselectivities could be obtained at a PPh_3/Cu molar ratio of 5. Although the enantioselectivities do not change significantly by the variation of the copper precursor, copper(I)-chloride provided slightly higher enantioselectivity (entry 7). The following catalytic tests were conducted by using simple CuCl as the copper source.

Table 2 Screening of copper precursors and the PPh_3/Cu molar ratio

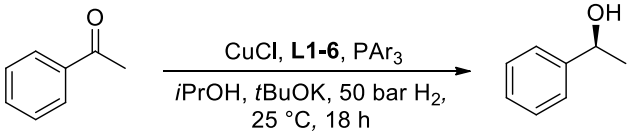


S1 P1

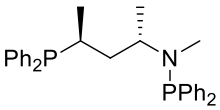
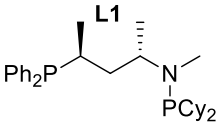
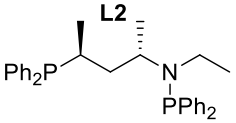
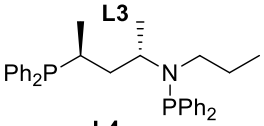
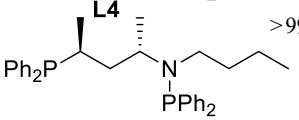
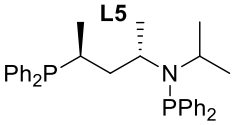
Entry	Cu precursor	PPh_3/Cu ratio	Conversion[%]	Ee [%]
1	$CuNO_3(PPh_3)_2$	3	>99	67
2	$Cu(OAc)_2$	3	61	64
3		5	98	65
4	$[Cu(COD)Cl]_2$	3	83	65
5		5	>99	66
6	CuCl	3	>99	65
7		5	>99	69

Reaction conditions: ligand **L3**: 0.006 mmol, Cu-precursor: 0.006 mmol, *t*BuOK: 0.06 mmol, acetophenone: 0.6 mmol, *i*PrOH: 1 mL, H_2 pressure: 50 bar, temperature: 25 °C, reaction time: 18 h. Conversion and enantioselectivity were determined by chiral GC. The prevailing product enantiomer is (*S*)-1-phenylethanol in each case

Table 3 Screening of chiral PN,P ligands **L1-L6** in the asymmetric hydrogenation of acetophenone



S1 P1

Entry	Chiral ligand	Reaction with PPh_3		Reaction with $P(3,5\text{-Xyl})_3$	
		Conversion [%]	*Ee* [%]	Conversion [%]	*Ee* [%]
1		>99	53	>99	73
2	L1 	44	24	16	0
3	L2 	>99	69	>99	82
4	L3 	>99	69	>99	86
5	L4 	>99	67	>99	84
6	L5 	>99	0	>99	12

L6

Reaction conditions: chiral ligand: 0.012 mmol, CuCl: 0.012 mmol, *t*BuOK: 0.12 mmol, PPh_3 or $P(3,5\text{-Xyl})_3$: 0.06 mmol, acetophenone: 1.2 mmol, *i*PrOH: 1 mL, H_2 pressure: 50 bar, temperature: 25 °C, reaction time: 18 h. Conversion and enantioselectivity were determined by chiral GC. The prevailing product enantiomer is (*S*)-1-phenylethanol in each case

We next examined the effect of the chiral ligand on the reaction selectivity. Ligands **L1-L6** were screened using CuCl as the copper precursor in the presence of five equivalents of an achiral phosphine (Table 3). Literature reports [18, 21] have demonstrated that employing *tris*(3,5-dimethylphenyl)phosphine ($P(3,5\text{-}Me_2\text{-}C_6H_3)_3$) instead of PPh_3 can significantly enhance the enantioselectivity of hydrogenation reactions. Therefore, we carried out the

catalytic reaction with $P(3,5\text{-}Me_2\text{-}C_6H_3)_3$ in addition to PPh_3. Indeed, replacing PPh_3 with $P(3,5\text{-}Me_2\text{-}C_6H_3)_3$ led to a notable increase in the optical yield in almost every case. Furthermore, variation of the N-alkyl substituent had a substantial impact on enantioselectivity. Increasing the length of the alkyl chain attached to the nitrogen atom generally improved selectivity. The highest *ee* was obtained with ligand **L4**, which bears an N–*n*-propyl substituent. Interestingly, introducing a bulkier N-isopropyl group, compared to its linear analogue, completely suppressed enantioselectivity while maintaining full conversion. Similarly, with ligand **L2**, which contains sterically demanding cyclohexyl substituents on phosphorus, the *ee* was markedly reduced. These observations suggest that the steric properties of the chiral ligands play a decisive role in determining selectivity.

To substantiate this assumption, we aimed to estimate the electronic differences among the phosphorus donors as a function of the N-substituent. A convenient method to assess the σ-donor strength of phosphorus functionalities is to measure the magnitude of the $^1J(^{77}Se\text{-}^{31}P)$ coupling constant in the ^{77}Se isotopomer of the corresponding phosphine selenide [26]. This value is roughly inversely proportional to the basicity of the phosphine. Accordingly, we synthesized the diselenides of ligands **L1-L6** using elemental selenium. The corresponding $^1J(^{77}Se\text{-}^{31}P)$ coupling constants are summarized in Table 4. Variation of the N-substituent resulted in only marginal changes in the $^1J(^{31}P\text{–}^{77}Se)$ coupling constants ($\Delta J \leq 4.3$ Hz), indicating no significant electronic differences amongst ligands **L1**, **L3-L6**. Based on these findings, the steric properties of the chiral ligands appear to dominate in determining the reaction selectivity. As expected, ligand **L2**, containing a PCy_2 moiety, exhibits a more electron-donating aminophosphine unit compared to its phenyl-substituted analogue **L1**. In this case electronic effects may also play a significant role in decreased activity and selectivity.

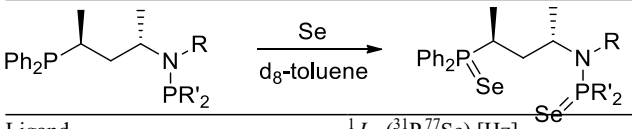
Next, various monophosphines were screened as ancillary ligands in combination with **L4** as the chiral stereocontrolling agent (Table 5). Interestingly, only catalysts containing triarylphosphine type ancillary ligands exhibited both high activities and enantioselectivities (entries 1–17 vs. entries 18 and 19). The absence of monophosphine resulted in reduced activity and selectivity at an **L4**/Cu molar ratio of 1; however, increasing the **L4**-to-copper ratio to 2 or 3 afforded full conversion and higher enantioselectivity (entry 20). Variation of the *para*-substituent (entries 1, 4, and 13–16) within the triarylphosphine series did not lead to any substantial change in enantioselectivity compared to PPh_3: across the range from the electron-donating *p*-OMe ($^1J(^{31}P\text{-}^{77}Se) = 745.9$ Hz, Table S1) to the electron-withdrawing *p*-CF_3 substituent ($^1J(^{31}P\text{-}^{77}Se) = 785.3$ Hz, Table S1), the largest difference in *ee* was only about 7%.

In contrast, the presence of 2-substituted or 3,5-disubstituted aryl rings led to pronounced changes in both catalytic activity and selectivity. Increasing the number of 3,5-dimethylphenyl groups (entries 1 and 5–7) resulted in a steady enhancement of enantioselectivity ($\Delta ee = 17\%$), reaching up to 86% *ee* with $P(3,5\text{-}(CH_3)_2\text{-}C_6H_3)_3$. Notably, the use of $P(3,5\text{-}(CF_3)_2\text{-}C_6H_3)_3$, featuring a strongly electron-deficient phosphorus donor, led to an inversion of stereoselectivity, affording the major product with the (*R*) configuration, albeit with significantly lower overall conversion. Although steric factors seem to dominate the catalytic process, it is assumed that electronic effects may prevail when the electronic disparity is sufficiently high (for $P(3,5\text{-}(CF_3)_2\text{-}C_6H_3)_3$ $^1J(^{31}P\text{-}^{77}Se) = 816.0$ Hz, for $P(3,5\text{-}(CH_3)_2\text{-}C_6H_3)_3$, $^1J(^{31}P\text{-}^{77}Se) = 751.2$ Hz, Table S1).

The introduction of *o*-substituents drastically reduced both the activity and selectivity of the catalysts. This effect is likely attributable to the reduced coordinating ability of these ligands toward the copper center under equilibrium conditions due to their large cone angle. Indeed, increasing the $P(2,4\text{-}Me_2\text{-}C_6H_3)_3$/Cu molar ratio from 5 to 10, and thus shifting the equilibrium, significantly improved selectivity (from 40 to 70% *ee*, Table 5, entry 10). These observations – consistent with the conclusions drawn for the chiral ligands – underscore the pivotal role of steric effects in governing both activity and selectivity in the copper-catalyzed hydrogenation reaction.

In the next series of experiments, the catalyst was evaluated at various substrate-to-catalyst (S/C) molar ratios. The enhancement of the S/C ratio resulted in a slight reduction

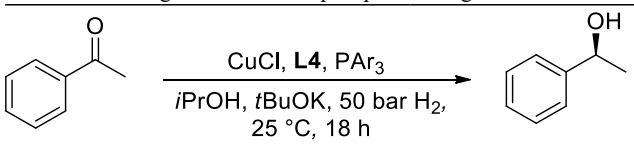
Table 4 $^1J(^{31}P,^{77}Se)$ coupling constants of the diselenides of **L1-L6**



Ligand	$^1J_{PN}(^{31}P,^{77}Se)$ [Hz]	$^1J_{PC}(^{31}P,^{77}Se)$ [Hz]
L1	772.9	756.8
L2	747.5	755.4
L3	771.4	757.5
L4	771.8	760.0
L5	773.5	758.4
L6	769.2	757.6

$^{31}P\{^1H\}$ NMR spectra were recorded in d_8-toluene at 25 °C

Table 5 Screening of achiral monophosphine co-ligands[a]



S1 P1

Entry	$PR^1R^2R^3$			Conv. [%]	Ee [%]
	R^1	R^2	R^3		
1	Ph	Ph	Ph	>99	69
2	2-Me-C_6H_4	2-Me-C_6H_4	2-Me-C_6H_4	60	56
3	3-Me-C_6H_4	3-Me-C_6H_4	3-Me-C_6H_4	>99	75
4	4-Me-C_6H_4	4-Me-C_6H_4	4-Me-C_6H_4	>99	63
5	Ph	Ph	3,5-Me_2-C_6H_3	>99	70
6	Ph	3,5-Me_2-C_6H_3	3,5-Me_2-C_6H_3	>99	76
7	3,5-Me_2-C_6H_3	3,5-Me_2-C_6H_3	3,5-Me_2-C_6H_3	>99	86
8	Ph	Ph	2,4-Me_2-C_6H_3	96	30
9	Ph	2,4-Me_2-C_6H_3	2,4-Me_2-C_6H_3	58	56
10	2,4-Me_2-C_6H_3	2,4-Me_2-C_6H_3	2,4-Me_2-C_6H_3	57 (97)[b]	40 (70)[b]
11	Ph	Ph	4-MeO-C_6H_4	>99	59
12	Ph	4-MeO-C_6H_4	4-MeO-C_6H_4	>99	62
13	4-MeO-C_6H_4	4-MeO-C_6H_4	4-MeO-C_6H_4	>99	64
14	4-CF_3-C_6H_4	4-CF_3-C_6H_4	4-CF_3-C_6H_4	>99	62
15	4-F-C_6H_4	4-F-C_6H_4	4-F-C_6H_4	>99	65
16	4-CF_3-C_6H_4	4-CF_3-C_6H_4	4-MeO-C_6H_4	>99	63
17	3,5-$(CF_3)_2$-C_6H_3	3,5-$(CF_3)_2$-C_6H_3	3,5-$(CF_3)_2$-C_6H_3	22 (>99)[c]	51[d] (57)[c,d]
18	Cy	Cy	Cy	35	59
19	Ph	Ph	Me	>99	25
20	–	–	–	57[e] (>99[f],>99 [g])[e]	44[e] (67[f], 68 [g])[e]

[a]Reaction conditions: chiral ligand **L4**: 0.012 mmol, CuCl: 0.012 mmol, *t*BuOK: 0.12 mmol, monophosphine: 0.06 mmol, acetophenone: 1.2 mmol, *i*PrOH: 1 mL, H_2 pressure: 50 bar, temperature: 25 °C, reaction time: 18 h. Conversion and enantioselectivity were determined by chiral GC. The prevailing product enantiomer is (*S*)-1-phenylethanol in each case. [b]Monophosphine: 0.12 mmol. [c]*t*BuOH was used as solvent. [d]The prevailing product enantiomer is (*R*)-1-phenylethanol. [e]No monophosphine was used as ancillary ligand. [f]Chiral ligand **L4**: 0.024 mmol. [g]Chiral ligand **L4**: 0.036 mmol

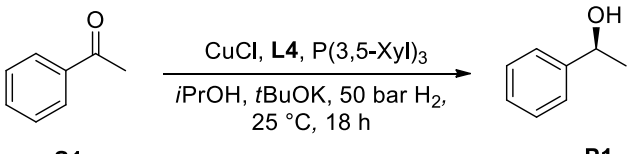
in enantioselectivity. At an S/C ratio of 500, 77% conversion was achieved, corresponding to a turnover frequency (TOF) of 21 h^{-1}. Notably, the catalyst remained active and selective even at an S/C ratio of 1000. Although a reaction time of 48 h was required to achieve full conversion, this result clearly demonstrates the high stability of the catalytic system, which is capable of operating with a turnover number of 1000. These values are comparable to those reported for copper-catalyzed asymmetric hydrogenation using the ditertiary phosphine BDPP.18 On the basis of these results, copper-catalyzed hydrogenation emerges as a promising approach amongst non-noble metal catalyzed homogeneous reduction processes. (Table 6)

To demonstrate the general applicability of our catalytic protocol, we evaluated the hydrogenation of a broad range of substrates. Accordingly, chiral ligand **L4** in combination with P(3,5-Me_2-C_6H_3)$_3$ was employed to modify the copper center at a substrate-to-catalyst molar ratio of 200. In general, high enantioselectivities (>80% *ee*) and yields (>90%) were achieved in the hydrogenation of *p*-substituted acetophenones, regardless of the electronic nature of the substituent. In contrast, substrates bearing *o*-Me (**S2**) or *o*-MeO (**S5**) substituents were hydrogenated with low yields, whereas the reduction of *o*-bromoacetophenone (**S8**) readily afforded the corresponding chiral alcohol in high isolated yield. Again, this observation further supports the conclusion that steric effects play a dominant role in the catalytic process.

Interestingly, the reduction of substrate **S14**, bearing two strongly electron-withdrawing CF_3 substituents, afforded only 10% yield and 63% *ee*. Modification of the substrates' R' group influenced both catalytic activity and enantioselectivity. Increasing the length of the linear alkyl R' substituent (**S17**-**S19**) led to decreased yields, while the enantiomeric excess remained nearly unchanged. In contrast to this, variations in the structure of the branched R' group primarily affected the enantioselectivity of the reaction (**S20**-**S22**).

Hydrogenation of substrate **S20** furnished the corresponding chiral alcohol in 95% yield and 90% *ee*. The C=O reduction of tetralone (**S23**) proceeded with considerably lower yields and enantioselectivities compared to simple alkyl-aryl ketones. The catalyst was also effective in the

Table 6 Asymmetric hydrogenation of acetophenone at different substrate/catalyst molar ratios[a]



S1 P1

Entry	S/C	Conversion [%]	Ee [%]
1	100	>99	86
2	200	>99	82
3	250	97	82
4	500	77	82
5[b]	1000	>99	79

[a]Reaction conditions: chiral ligand **L4**: 0.012 mmol, CuCl: 0.012 mmol, *t*BuOK: 0.12 mmol, monophosphine P(3,5-Me_2-C_6H_3)$_3$: 0.06 mmol, acetophenone: 1.2–12 mmol, *i*PrOH: 1 mL, H_2 pressure: 50 bar, temperature: 25 °C, reaction time: 18 h. Conversion and enantioselectivity were determined by chiral GC. The prevailing product enantiomer is (*S*)-1-phenylethanol in each case. [b]Reaction time: 48 h

hydrogenation of heterocyclic ketones (**S24** and **S25**), providing the corresponding alcohols with high selectivity (up to 92% *ee*) and activity. Several acetophenone derivatives (**S26**-**S29**) bearing nitrile, ester or amide groups were also subjected to hydrogenation in order to evaluate the influence of the polar substituents on the activity and the chemoselectivity of the reaction.

In all cases, selective hydrogenation of the ketonic C=O moiety was observed, however, a noticeable decrease in catalytic activity was detected. This behavior can plausibly be ascribed to the coordination of the nitrogen or oxygen donor atoms of the substrate to the copper center, analogous to the effect observed for **S5**. Consequently, the reactions were conducted at lower S/C ratios and/or with prolonged reaction times to achieve satisfactory conversion. Since the hydrogenation was performed in *i*PrOH, transesterification occurred during the conversion of **S28**, leading to formation of an isopropyl ester. The hydrogenation of **S30** proceeded chemoselectively, affording the corresponding allylic alcohol (4-phenylbut-3-en-2-ol), albeit in somewhat reduced isolated yield. Finally, the catalyst was shown to be active in the hydrogenation of dialkyl ketones (**S31**, **S32**) with lower selectivity. (Fig. 2).

Based on our catalytic results and previous literature reports, a plausible mechanism for copper-catalyzed asymmetric hydrogenation can be proposed (Fig. 3). It is generally accepted that phosphine-ligated copper hydrides tend to form oligomeric complexes (e.g. dimers, trimers, pentamers)[27] which are considered less reactive than monomeric L_mCuH species in the hydride-transfer step [28, 29]. In our system, however, the enhanced catalytic activity and enantioselectivity observed upon addition of an achiral monodentate ancillary ligand can most consistently be rationalized by the participation of oligomeric assemblies. The oligomeric framework enables the formation of mixed-ligand (heteroligated) structures, in which both chiral bidentate and achiral monodentate ligands are incorporated within the same entity, in contrast to homoligated systems that contain only the same type of (chiral or achiral) ligands. Indeed, a recent work by Kozlowski and co-workers demonstrated that dimeric hydride-transfer transition-state structures lie lower in energy than their mononuclear analogues [22]. Moreover, their study revealed that heteroligated dimeric transition states are significantly more stable than homoligated ones, resulting in a pronounced rate acceleration of the hydride-transfer step.

Accordingly, the increased enantioselectivity and activity upon addition of the achiral ancillary ligand (Table 1, entries 1 and 2) supports the involvement of the low energy heteroligated transition states instead of monomeric systems (Fig. 3). Furthermore, the observed switch in enantioselectivity upon employing the electron-deficient ligand P(3,5-$(CF_3)_2$-C_6H_3)$_3$, compared to its more electron-donating analogue P(3,5-$(CH_3)_2$-C_6H_3)$_3$ (Table 5, entries 17 and 7, respectively), can also be attributed to distinct heteroligated transition states. Since the catalyst modified exclusively with the chiral bidentate ligand **L4**, in the absence of an ancillary ligand, provides the (*S*)-enantiomer (Table 5, entry 20) as the major product, the addition of P(3,5-$(CF_3)_2$-C_6H_3)$_3$ must redirect the hydride-transfer step through a heteroligated transition state that favors (*R*)-selectivity. In contrast, when P(3,5-$(CH_3)_2$-C_6H_3)$_3$ is used, both homo- and heteroligated systems deliver the same major enantiomer. As noted earlier, the marked difference in selectivity between these two 3,5-disubstituted phosphines likely arises from their pronounced electronic disparity (see Table S1 in the Supporting Information).

Obviously, other factors may also contribute to the observed reactivity and selectivity, such as the formation of multiple oligomeric systems with different composition and stoichiometry depending on the ligands used, or the stereoelectronic influence of the ligands on the activity and selectivity of the heteroligated assemblies. Additionally, the presence of less stable yet catalytically highly

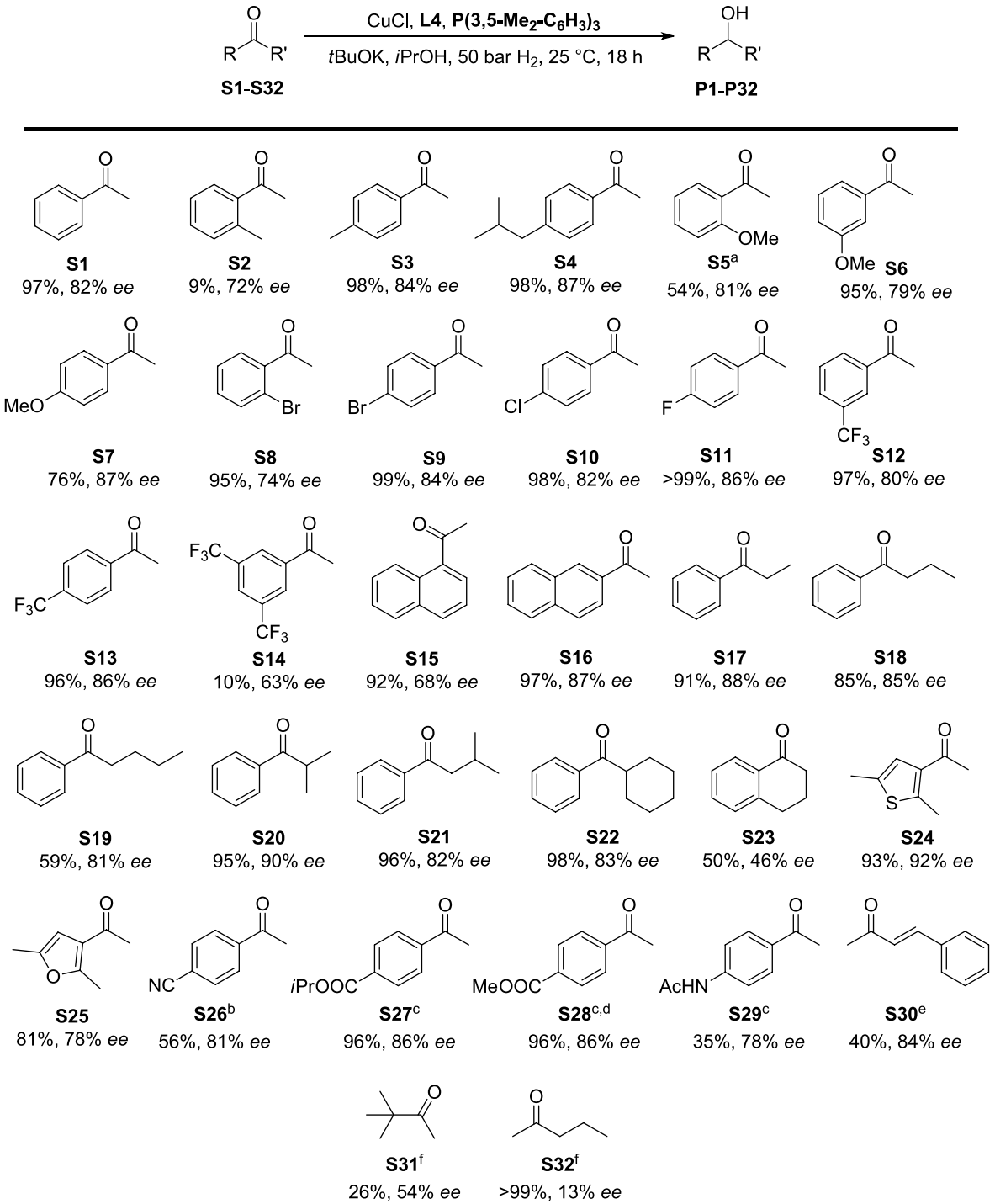


Fig. 2 Screening of substrates. Reaction conditions: chiral ligand **L4**: 0.012 mmol, CuCl: 0.012 mmol, *t*BuOK: 0.12 mmol, P(3,5-$Me_2C_6H_3)_3$: 0.06 mmol, substrate: 2.4 mmol, *i*PrOH: 1 mL, H_2 pressure: 50 bar, temperature: 25 °C, reaction time: 18 h. Isolated yields after column chromatography. Enantioselectivity was determined by chiral GC or HPLC. The prevailing product enantiomer is (*S*) in each case. [a]Substrate: 1.2 mmol, reaction time: 24 h. [b]Substrate: 1.2 mmol, reaction time: 72 h. [c]Substrate: 0.6 mmol. [d]The product alcohol is the isopropyl ester. [e]A conversion of 47% and a chemoselectivity of > 99% for 4-phenylbut-3-en-2-ol were determined by NMR. Isolated yield and *ee* are given for 4-phenylbut-3-en-2-ol. [f]GC yield instead of isolated yield due to the volatility of the product

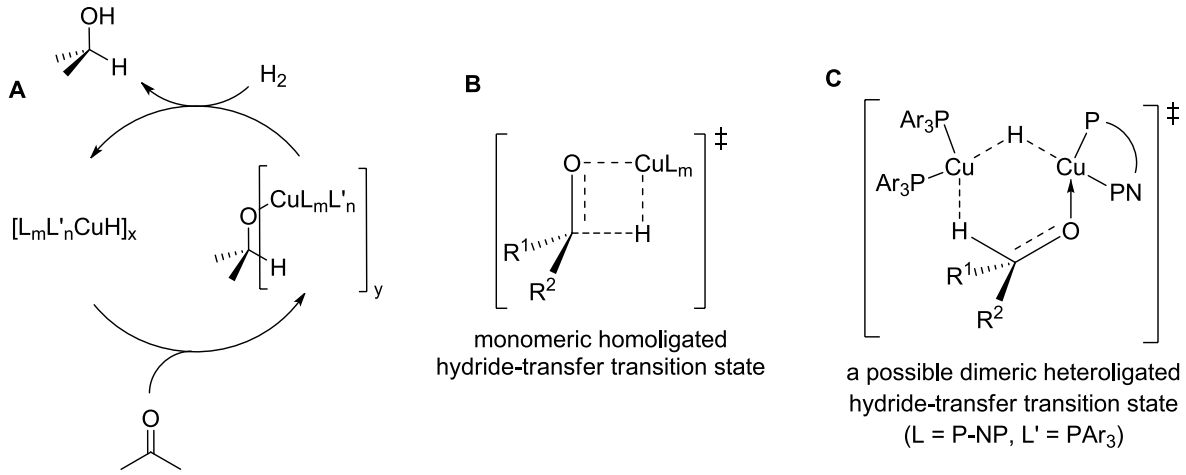


Fig. 3 Proposed mechanism for copper-catalyzed hydrogenation involving oligomeric species (**A**), a monomeric homoligated (**B**) and a dimeric heteroligated transition state of the hydride transfer (**C**) based on the original proposal by Koslowski et al.[22]

active mixed-ligand mononuclear species ($L_mL'_nCuH$) containing both a chiral bidentate and an achiral monodentate ligand cannot fully be ruled out. However, as highlighted by Caulton et al., the hydride bridge in a dimeric $[Cu_2(\mu\text{-}H)_2]$ core is stronger than a potential third P–Cu interaction in the corresponding mononuclear system [30]. The formation of such mononuclear species is therefore highly unlikely under the reaction conditions. Nevertheless, the proposed mechanistic scheme provides a coherent explanation for the observed reactivity trends and may establish a solid basis for future mechanistic studies in the copper-catalyzed asymmetric hydrogenation of simple ketones.

3 Conclusions

In summary, a family of chiral pentane-2,4-diyl-based phosphine-aminophosphine ligands, in combination with achiral monodentate phosphines, was applied in the copper-catalyzed asymmetric hydrogenation of ketonic substrates. The highly modular synthetic approach employed for the chiral ligands allowed for straightforward structural fine-tuning. The catalytic activity and enantioselectivity were strongly influenced by the steric properties of the ligands, whereas electronic effects played a secondary role. Variation of the N-substituent in the chiral ligands, along with the appropriate selection of the monodentate ancillary ligand, resulted in high activity and enantioselectivity (up to 92% *ee*). Based on the experimental results and previous literature findings, a mechanistic model was proposed in which dimeric heteroligated transition states are involved in the hydrogen transfer. The ligand-design strategy that led to the development of the pentane-2,4-diyl-based phosphine-aminophosphines proved to be successful in copper-catalyzed asymmetric hydrogenation, delivering novel chiral ligands with a highly modular framework suitable for further structural fine-tuning. We anticipate that the findings reported herein will contribute to the design of new copper-based hydrogenation catalysts and promote further advancements in this area of research.

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Author Contributions Z.S.: experimental work, data curation; Z.C.: experimental work, editing, investigation, supervision, data curation; M.K.: formal analysis, editing, investigation; J.B.: review and editing; G.F.: writing original draft, conceptualization, supervision, investigation.

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Data Availability All data supporting the findings of this study are available within the paper and its Supplementary Information.

Material Availability All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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