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Reaction prospecting by ^{31}P NMR: enantioselective rhodium-DuPhos catalysed addition of $ZnMe_2$ to diphenylphosphinoylimines

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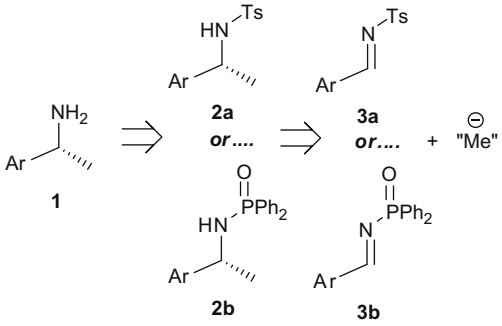
ABSTRACT

Chiral shift ^{31}P NMR spectroscopy allows the identification of ligand leads in asymmetric catalyst systems for $ZnMe_2$ addition to ArCH=NP(O)Ph_2. Subsequent GC-based optimisation shows $[RhCl(CH_2{=}CH_2)_2]_2$ and (*R,R*)-MeDuPhos to be the optimal pre-catalyst combination (product in 78–93% ee). Transmetallation of [(MeDuPhos)Rh{N(P(O)Ph_2–CHMeAr}] with $ZnMe_2$ appears to be the rate limiting step of the catalytic cycle as competing coordination by the imine starting material leads to $Ph_2P(O)NHCH_2Ar$ via MVP hydrogen-transfer. This limitation can largely be overcome by the slow addition of the imine.

1. Introduction

Convenience and technical simplicity are defining goals in contemporary organic methodology. Recently, we experienced a need for chiral 2-arylethylamines **1** (Scheme 1) for use in ligand synthesis[1] and sought to attain a straightforward method for their production from precursor aldimines **3** via protected **2**. Our criteria for such a preparation were: (i) that the *N*-protecting group must engender crystallinity in the products, but be easily removed (ii) that any chiral ligand and metal additives used in preparing **2** be readily commercially available (iii) that the reaction proceed rapidly and (iv) that any screening procedures leading to the enantioselective catalyst for production of **2** should be readily applicable to high throughput screening and not complicated by the presence of impurities. Recently several excellent processes for the preparation of precursors to **1** have appeared in the literature,[2,3] but these often raise issues when compared against harsh criteria (i)–(iv) above. Hayashi[3b] has described active and selective diene-ligated rhodium catalysts. However in this case, the use of aldimine **3a** (PG = Ts) is required. The removal of such tosyl protecting groups sometimes can be problematic. Charette[3c] has described $Cu(OTf)_2$/DuPhos-monooxide approaches using **3b** [PG = P(O)Ph_2] in up to 97% ee but the reaction is relatively slow (48 h). In our hands, alkylations employing **3b** were also prone to producing significant amounts (~10%) of fluorescent co-eluting by-products in initial trials that invalidated or slowed down chiral HPLC high throughput screenings when using **3b**. We thought that we might be able to utilize the power of ^{31}P NMR spectroscopy to overcome these issues in catalyst discovery.



Scheme 1. Typical approaches to 2-arylethylamines.

2. Results and discussion

2.1. Synthesis of aldimines 3b and catalyst discovery by ^{31}P NMR spectroscopy

In our hands the starting aryl imines **3b** were best prepared using the detailed $Ph_2P(O)NH_2/TiCl_4$/ArCHO procedure provided by Scheidt.[4] We were only able to improve on this procedure in two ways. Firstly, the isolated yields of the somewhat hydrolytically labile imines **3b** are improved by prompt chromatography in $EtOAc/CH_2Cl_2$ compared to just EtOAc, as recommended, due to solubility issues with **3b**. Secondly, the relatively commercially expensive $Ph_2P(O)NH_2$ was prepared from inexpensive $Ph_2P(O)Cl$ and aqueous ammonia avoiding the need for liquid NH_3 use.[5] Racemic **2ba** (Ar = Ph) was easily prepared by the reaction of **3ba** with MeMgBr. Preliminary investigations indicated that group 8 metal salts in the presence of phosphines led to active systems for the

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addition of $AlMe_3$ or $ZnMe_2$ in refluxing THF in under 3 h. To avoid fluorescent by-product issues when screening crude catalytic mixtures of **2ba** we have developed an alternative procedure for the catalyst assay using ^{31}P NMR spectroscopy. Conveniently, in the presence of camphorsulfonic acid (CSA), two resolved diastereomeric ^{31}P NMR signals can be attained on in situ formed **2ba**·CSA (Ar = Ph) using material directly attained from the reaction mixture. Optimal separations were attained with ca. 10 mg samples of crude **2ba** in $CDCl_3$ (0.6 ml) with CSA (4 equiv) added as a solid. Phosphorus spectra were collected under standard conditions.[6] The two diastereomeric ^{31}P signals were reproducibly separated by 0.2 ppm. Typical spectra are shown in Figure 1. Control experiments indicated that this ^{31}P NMR approach is accurate enough (error range ±2–6%, average ±4% ee) to allow the discovery of selective metal–ligand combinations (Fig. 2). Rapid (5 min/sample) matrices of the type shown in Figure 3 could be built up from samples collected on an autosampler equipped NMR spectrometer.

From the range tested (>60 combinations,[7] not all shown in Fig. 3), it was clear that the use of methyl-DuPhos $\mathbf{L_A}$ and a rhodium(I) source, in the presence of $ZnMe_2$, afforded an optimal catalyst for **2ba** production (typically at 86–93% ee). Deviation from this choice led to much poorer behavior. For example, the use of the convenient, commercially available precursor [Rh(COD)($\mathbf{L_A}$)]BF_4 ($Rh_{(1)}$) with $AlMe_3$ provided **2ba** in only 32% ee. The use of the air-stable analogue of trimethylaluminium DABAL-Me_3[8] unfortunately also led to very poor conversions and selectivities.

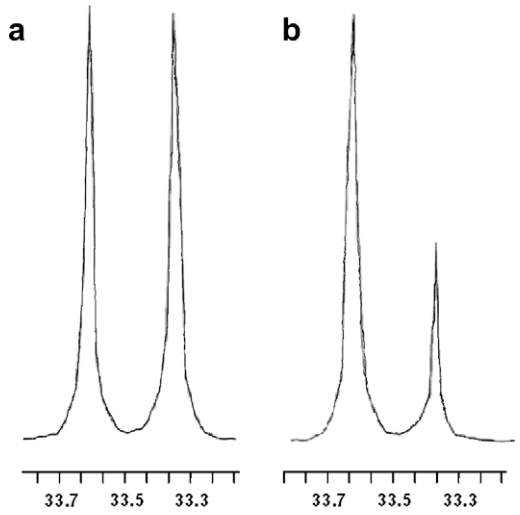


Figure 1. ^{31}P NMR assay of **2ba** (Ar = Ph) 0.05 M in $CDCl_3$ in the presence of camphorsulfonic acid (4.0 equiv).[6] Sample (a) is from racemic **2ba**; sample (b) from a reaction using [RhCl(CH_2=CH_2)$_2$]$_2$/$\mathbf{L_G}$ showing 47 ± 4% ee (*R*)-**2ba**, based on the integrals of the signals at 33.6 (major) and 33.4 (minor) ppm respectively (determined as 49% ee by chiral GC).

2.2. Catalyst system optimisation

Two issues remained to be resolved with the discovered Rh(I)–MeDuPhos system. Firstly, as anticipated, problems were encountered with the co-elution of a minor by-product in the HPLC assays of the reaction mixture. Secondly, reactions catalysed by the isolated complex [Rh(COD)($\mathbf{L_A}$)]BF_4 occasionally led to non-reproducible runs where the enantioselectivity fell to unacceptable levels (down to 77%). We turned our attention to the chemoselectivity issue first. The final optimisation of the Rh(I)–MeDuPhos system was carried out by chiral GC analysis (error ± 1% ee) to avoid any potential issues with HPLC (co-eluting impurities) or ^{31}P NMR (less accu-

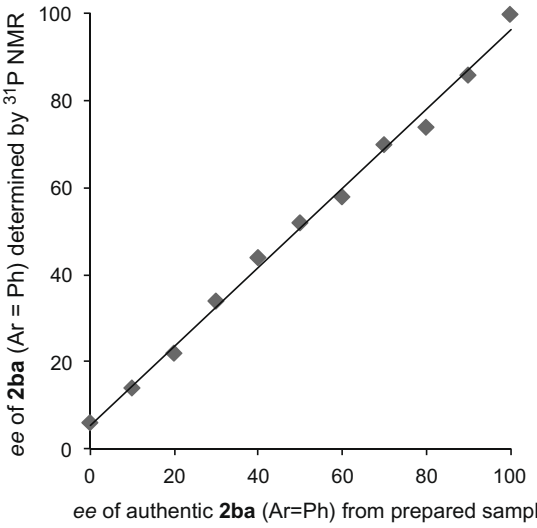


Figure 2. Comparison of ee values (%) determined by ^{31}P NMR spectroscopy[6] on **2ba**·CSA (Ar = Ph) against independently prepared authentic scalemic samples (0–100% ee in 10% steps).

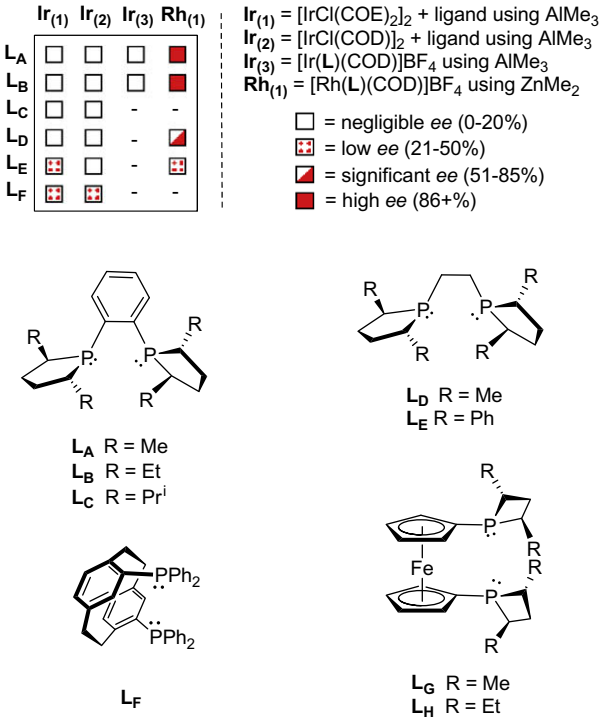
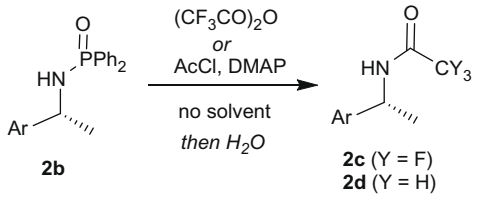


Figure 3. Selected discovery data for active catalyst combinations using ^{31}P NMR assay[6] of **2ba** (Ar = Ph) from reactions of imine **3ba** with various methyl sources ($AlMe_3$, $ZnMe_2$) in the presence of a range of metal complexes with (or without) added chiral ligands. Reaction conditions: refluxing THF, 3 h, 5.8 mol % metal–ligand. Ligand $\mathbf{L_G}$ gave 49% ee while $\mathbf{L_H}$ led to inactive systems.



Scheme 2. Derivatisation of the phosphoramides **2b** by in situ *trans*-acetylation.

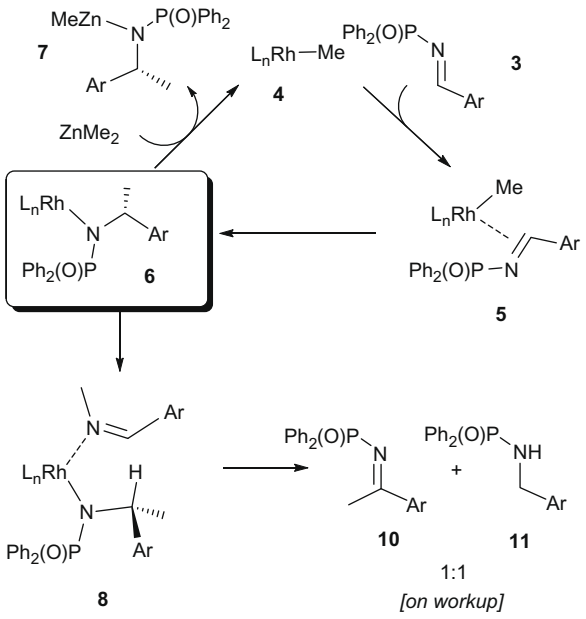
racy) assay. Direct exchange of the $P(O)Ph_2$ group to suitable acetates without the need to isolate the free amine **1** was developed (Scheme 2). The addition of water promotes the reaction, presumably by hydrolysis of the acylated intermediates. While efficient, this derivatisation was not as quick as the ^{31}P NMR ee measurement process described earlier (overnight sample preparation and >20 min run vs 10 min sample preparation + 5 min run).

The absolute stereochemistry of the product **2ba** (Ar = Ph) could confirmed by its independent synthesis from authentic (*R*)-**1** (Ar = Ph) using TFAA. This confirmed that (*R,R*)-MeDuPhos $\mathbf{L_A}$ causes the addition to the *re*-face of the imine **2ba**. The other imines are assumed to undergo the same sense of asymmetric addition. The use of the 4-tolyl imine **3bb** allowed us to confirm the formation of 4-TolCH_2NHP(O)Ph_2 **11bb** as the minor (reduction) impurity (4–5%) in the methylation product **2bb**. Due to the similarity of both their chromatographic properties and crystallinity, the identity of 4-TolCH_2NHP(O)Ph_2 was confirmed by its independent synthesis. Such reductive behaviour appears to not have been noted before in methylation reactions of diphenylphosphinoyl or tosyl protected imines. As no β-hydrogens are available in the supposed Rh–Me intermediates, we believe that this product arises out of MVP hydrogen transfer reactions at rhodium (Scheme 3).

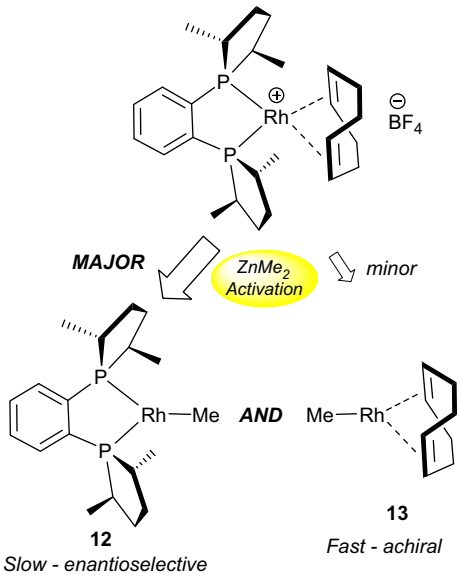
Thus, an initial rhodium methyl species coordinates to the imine leading to **5** which after enantioselective methyl transfer affords key unsaturated intermediate **6**. If transmetallation with $ZnMe_2$ is rapid then the cycle closes leading to **2** after protolytic workup. However if transmetallation is slow, then **6** can coordinate a second equivalent of **3** leading to **8**, which is predisposed to MVP hydrogen transfer. Although the catalytic cycle still closes, a 1:1 mixture of **10**:**11** is generated on workup. Consistent with this picture, the presence of both **11** and **10** (and/or its acetophenone hydrolysis product) could be detected in the proton NMR spectra of crude samples of **2bb** (Ar = 4-Tol). The spectra of both were identical to authentic independently prepared samples of **10**–**11**. As expected, **11** also became the sole product if $ZnEt_2$ was used due to efficient β-elimination at rhodium. The key involvement of **6** in determining methylation versus reduction was probed by the following reactions. Refluxing equimolar mixtures of **2** and **3** in the presence of $ZnMe_2$ alone did not give any **11**. Similarly, the deliberate formation of **7** (by the addition of $ZnMe_2$ to **2**) followed by the addition of an equivalent of **3** and $ZnMe_2$ activated [Rh(COD)($\mathbf{L_A}$)]BF_4 (5.8 mol %) did not lead to increased levels of **11**, even after extended reflux. This implies that there is no equilibrium cross-over between the two reaction pathways and the chemoselectivity of the reaction depends only on the kinetic fate of **6** as a function of reaction conditions. As the physical separation of **2** and **11** is hindered by their similar properties we sought reaction conditions to maximise the efficiency of the upper methylation cycle of Scheme 3. Lowering the reaction temperature to 25 °C or changing the solvent to 2-methyltetrahydrofuran, DME or 1,4-dioxane had no positive effect. Changing the reaction's concentration in the range 0.05–0.15 M had no beneficial effect, nor did increasing the number of equivalents of $ZnMe_2$ used from 2 to 3. The most effective strategy we could identify was the slow addition of imine **3** (over 2.6 h). Clearly this helps us to minimise the concentration of **8** maximising the reaction's chemoselectivity.

While the use of the commercial hydrogenation catalyst [Rh(COD)($\mathbf{L_A}$)]BF_4 had its advantages (purity, good 'shelf life', ease of use), the use of this catalyst gave non-reproducible results and wide ee fluctuations often occurred. Re-subjecting the isolated product **2ba** to the reaction conditions led to no racemisation. We proposed that the non-reproducibility is due to the generation of achiral [MeRh(COD)] during the genesis of the active catalyst (Scheme 4).

It is known that the relative catalytic activity of rhodium-based systems in C–C coupling is: $MeRh^{I}$(diene) >> $MeRh^{I}$ > $MeRh^{I}$



Scheme 3. Competing transfer hydrogenation in methylation of **3b**.

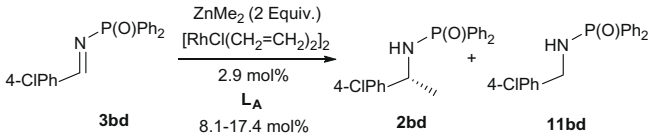


Scheme 4. Competing activation paths for [Rh(COD)($\mathbf{L_A}$)]BF_4.

(diphosphine).[9] Rhodium diphosphine complexes show ligand retardation rather than acceleration effects.[10] Under the conditions of Scheme 4, the generation of any **13** (and to a lesser extent any other achiral 'naked' Rh^{I} species) results in a serious erosion of the selective reaction engendered by **12**. Support for this idea comes from studies using a [RhCl(CH_2=CH_2)$_2$]$_2$ pre-catalyst in the presence of increasing amounts of (*R,R*)-Me-DuPhos $\mathbf{L_A}$ and imine **3bd** (Ar = 4-ClPh) Table 1.

At Rh:$\mathbf{L_A}$ ratios of 1:1, poor reproducibility in the ee value (66–82%) derived for product **2bd** was noted. Up to Rh:$\mathbf{L_A}$ ratios of 1:1.8, the ee of **2bd** increased smoothly to 86% (run 3) before falling again at higher ligand concentrations (runs 4–5). We attribute this poor performance to the formation of significant populations of inactive [Rh($\mathbf{L_A}$)$_2$]$^+$ in the reaction mixture. Consistent with the picture of Scheme 4 the species [RhCl(COD)]$_2$ was found to be an active catalyst for the addition of $ZnMe_2$ to **3ba** leading to racemic **3ba**. Attempts to maximise the profitable cleavage to **12** by using

Table 1
Rh:$\mathbf{L_A}$ effects in 1,2-addition of $ZnMe_2$ to imine **3bd**[a]

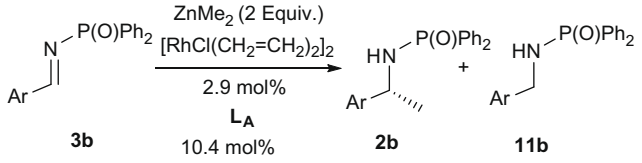


Run	Rh:$\mathbf{L_A}$	Conv.[a] (%)	**2bd**:**11bd**[b]	ee (**2bd**)[b] (%)
1	1:1	100	90:10	66–82 (*R*)
2	1:1.4	100	92:8	82 (*R*)
3	1:1.8	100	95:5	86 (*R*)
4	1:2.2	86	94:6	80 (*R*)
5	1:3.0	11	72:28	78 (*R*)

[a] Ratio of **3bd**:Rh (5.8 mol %):$ZnMe_2$ 0.6:0.035:1.2 mmol; 10 ml THF, reflux, 3 h. Conversion based on ^{1}H NMR spectroscopy.
[b] Chemoselectivity determined by ^{1}H NMR on crude sample; ee by GC (CP-ChiraSil-Dex CB on trifluoroacetate derivative).

various dienes and counter anions in the [Rh($\mathbf{L_A}$)(diene)]X pre-catalyst (diene = COD, nbd; X = BF_4, OTf) were not successful so we continued to use a strategy involving 2.9 mol % $[RhCl(CH_2{=}CH_2)_2]_2$ in the presence of excess $\mathbf{L_A}$ (10.4 mol %). The results for a range of substrates are given in Table 2.

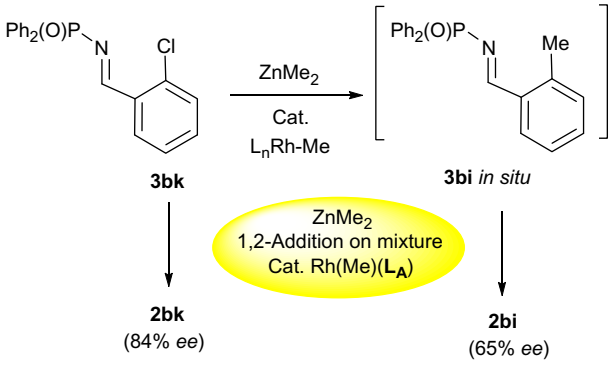
Table 2
1,2-Addition of $ZnMe_2$ to a range of imines **3**[a]



Run	Ar (**3b**)	Yield[b] (%)	**2b**:**11b**[c]	ee (**2b**)[c] (%)
1	Ph (**3ba**)	63	96:4	93 (>99)[d]
2	4-MePh (**3bb**)	59	97:3	92
3	4-FPh (**3bc**)	49	94:6	84
4	4-ClPh (**3bd**)	60	93:7	86
5	4-BrPh (**3be**)	65	93:7	75
6	4-CF_3Ph (**3bf**)	70	95:5	78
7	3-MePh (**3bg**)	60	95:5	89
8	3-ClPh (**3bh**)	44	89:11	78
9	2-MePh (**3bi**)	34	91:9	79
10	2-Naphthyl (**3bj**)	73	96:4	84

[a] Ratio of **3b**:Rh (5.8 mol %):$\mathbf{L_A}$:$ZnMe_2$ 0.6:0.035:0.07:1.2 mmol; 10 ml THF, slow addition of **3b** (2.6 h), then reflux (3 h).
[b] Isolated combined yield of **2b** and **11b**.
[c] Chemoselectivity determined by ^{1}H NMR on crude sample; ee by GC (columns of Table 3 on trifluoroacetate or acetate derivative).
[d] After recrystallisation from CH_2Cl_2–hexane.

A range of aromatic diphenylphosphinoylimines gave (*R*):(*S*) selectivities in the 10–20:1 range although in all cases, some minor competing reduction was also seen. The enantioselectivity is clearly determined by both steric (compare runs 2 and 9) and electronic (runs 7 and 8) effects in the substrate imine. The ketimine **10bb** (Ar = 4-Tol, Scheme 3) was inactive in the attempted methylation using this system. The use of the 2-chloroimine **3bk** led to an approximate 1:1 mixture of the 2-Cl and 2-Me functionalised amides **2bk** (84% ee) and **2bi** (65% ee) (Scheme 5). Given that the enantioselectivities are different, it is likely that methylation takes place *prior* to 1,2-methyl addition. Although pure **3bi** undergoes



Scheme 5. In situ methylation of 2-chloroimine **3bk**.

methylation at 79% ee, we have observed strong solvent and additive effects in this chemistry, and the reduction of the ee to 65% in the presence of a mixture of **3bi**/**3bk** was expected.

3. Conclusion

The use of ^{31}P NMR enabled us to realise our goal of identifying a useful system for the preparation of 2-arylethyl amines **1** through the addition of methyl organometallics to imines **3b**. Complications were observed due to competing chemoselectivity (reduction) issues and the apparent complex dependency of the enantiofacial selectivity as a function the substituent pattern within the aryl group. Fortunately, the phosphamides **2b** are all crystalline compounds and enantioselective enrichment to >99% ee can be affected via simple recrystallisation, at least in the case of compound **2ba** (Ar = Ph).

4. Experimental

4.1. General

All experiments were carried out under an argon atmosphere using standard Schlenk techniques. Solvents were dried prior to use: THF and diethyl ether were distilled from sodium-benzophenone ketyl and dichloromethane from calcium hydride. Proton, ^{13}C and ^{31}P NMR spectra were recorded on Bruker DPX400, Bruker AV400 and Bruker AV(III)400 spectrometers using Me_4Si or residual $CHCl_3$ as an internal reference. Infrared spectra were recorded on a Bruker Tensor 27 machine. Mass spectra were recorded using electrospray (ES) or electron impact (EI) techniques using a Bruker ApexIV FT-ICR machine. Optical rotations were measured using a Bellingham Stanley ADP440 digital polarimeter at ambient temperature in units of 10^{-1} deg cm^2 g^{-1} (*c* in g/100 cm^3). Enantioselectivities were determined by chiral GC. GC analyses were performed on a Varian 430 gas chromatograph using chiral columns under the conditions given (Table 3). Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 $F_{254+366}$ precoated plates (0.25 mm) silica. The plates were visualised by the use of a combination of ultraviolet light (254 and 366 nm) and/or aqueous potassium permanganate with heating. Liquid chromatography was by forced flow (flash chromatography) with the solvent systems indicated using Silica Gel 60 (220–240 mesh) supplied by Fluka. The starting imines and product amides were compared against genuine samples prepared by literature procedures except where noted as new compounds herein.

4.2. Diphenylphosphinic amide

This compound is commercially available (Aldrich) but is relatively expensive. It is best prepared by treatment of $Ph_2P(O)Cl$

Table 3
GC conditions for measurement of the enantioselectivities

Comp.	Ar	PG	Column	Program	Ret. times (min)
2ca	Ph	$COCF_3$	CB[a]	100 °C (isothermal)	(*R*) 17.7 (*S*) 18.2
2db	4-MePh	Ac	CB	165 °C (isothermal)	(*S*) 9.0 (*R*) 9.3
2cc	4-FPh	$COCF_3$	CB	100 °C (isothermal)	(*R*) 22.6 (*S*) 23.6
2cd	4-ClPh	$COCF_3$	CB	120 °C (isothermal)	(*R*) 22.0 (*S*) 22.7
2ce	4-BrPh	$COCF_3$	CB	115–125 °C at 0.2 °C/min +15 min at 125 °C	(*R*) 43.1 (*S*) 43.8
2cf	4-CF_3Ph	$COCF_3$	CB	100 °C (isothermal)	(*R*) 35.1 (*S*) 35.9
2cg	3-MePh	$COCF_3$	2,6-γ[b]	70 °C (isothermal)	(*S*) 134.0 (*R*) 134.1
2ch	3-ClPh	$COCF_3$	CB	115 °C (isothermal)	(*R*) 25.6 (*S*) 27.7
2ci	2-MePh	$COCF_3$	CB	100 °C (isothermal)	(*S*) 22.5 (*R*) 23.0
2dj	2-Naph	Ac	CB	160 °C (isothermal)	(*S*) 47.5 (*R*) 49.6
2ck	2-ClPh	$COCF_3$	CB	120 °C (isothermal)	(*R*) 12.1 (*S*) 13.3

[a] Column: CP-ChiraSil-Dex CB: 0.25 mm × 0.25 μm × 25 m.
[b] Column: *Octakis*(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin 0.25 μm id (60% in OV 1701 w/w).

(5.0 cm^3, 26.2 mmol) in THF (70 cm^3) with saturated aqueous ammonia (3.6 cm^3 of ca. 35% w/w solution, 65.5 mmol, Stench!). The resulting suspension was filtered, and the filtrate was washed with water and extracted with dichloromethane. The solution was evaporated to dryness and the product was allowed to dry under vacuum (100 °C, 1 h) to give $Ph_2P(O)(NH_2)$ (5.57 g, 98%). An optional recrystallisation step in hot toluene afforded the product (4.32 g, 76%) as a white powder with literature properties.[5]

4.3. Preparation of imines 3b

Titanium tetrachloride (0.5 equiv, 5.0 mmol) in CH_2Cl_2 (4 cm^3) was added dropwise to a stirred solution of the aldehyde (1 equiv, 10.0 mmol), diphenylphosphinic amide (1 equiv, 10.0 mmol) and triethylamine (3.5 equiv, 35.0 mmol) in CH_2Cl_2 (50 cm^3) at 0 °C. The solution was stirred at 0 °C for 1 h and room temperature for 1 h. The suspension was filtered through a silica pad, washed with 1:1 CH_2Cl_2/EtOAc. The filtrate was concentrated to a cream solid and purified by prompt flash chromatography (1:1 CH_2Cl_2/EtOAc).

4.4. Enantioselective preparation of phosphoramides 2b

A flame-dried Schlenk tube was charged with $[RhCl(C_2H_4)_2]_2$ (6.8 mg, 5.8 mol % Rh), (*R,R*)-MeDuPhos (**L_A**) (19.1 mg, 10.4 mol %) and THF (6 cm^3). The solution was stirred at room temperature for 30 min before $ZnMe_2$ (2.0 M in toluene, 0.6 cm^3, 1.2 mmol) was added. The imine (0.6 mmol) in THF (4 cm^3) was added slowly by syringe pump (2.6 h). The reaction mixture was stirred at reflux for 3 h, then cooled and quenched with saturated NH_4Cl solution (20 cm^3), extracted with CH_2Cl_2 (3 × 20 cm^3). The organics were dried (Na_2SO_4) and concentrated *in vacuo* to an oil, which was purified using flash chromatography (100% EtOAc).

4.5. Enantiomeric excess determination by ^{31}P NMR spectroscopy

A sample of crude **2b** attained from the quench of an aliquot of the reaction (typically ca. 10.0 mg) was dissolved in $CDCl_3$ and placed in a 5 mm NMR tube. Solid (1*S*)-10-camphorsulfonic acid (4.0 equiv) was added and the tube capped and shaken to produce a homogeneous solution. The ^{31}P NMR were acquired under standard conditions and the relative enantiomeric composition determined by integration of the signals at +33.4 and +33.6 ppm.

4.6. (*R*)-*N*-(1-(3-Chlorophenyl)ethyl)-P,P-diphenylphosphinic amide 2bh

Prepared from **3bh**. R_f 0.19 (EtOAc); mp 168–170 °C; $[\alpha]_D$ = +15.5 (*c* 1.06, MeOH, for 78% ee material); IR ($CHCl_3$) ν_{max}/cm^{-1} 3377, 2986, 1439, 1189, 1124, 1108, 963; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93–7.87 (m, 2H), 7.82–7.77 (m, 2H), 7.53–7.42 (m, 4H), 7.39–7.34 (m, 2H), 7.24–7.14 (m, 4H), 4.42–4.32 (m, 1H), 3.22 (dd, 1H, *J* = 9.6, 5.6 Hz), 1.55 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.1, 134.3, 132.3 (d, *J* = 9.6 Hz), 132.0, 131.8 (d, *J* = 9.5 Hz), 131.9 (d, *J* = 2.8 Hz), 129.8, 128.5 (t, *J* = 12.9 Hz), 127.2, 126.1, 124.3, 50.6, 25.8 (d, *J* = 3.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 22.7; HRMS (ESI positive) calcd for $C_{20}H_{19}ClNOP$, [M+H] 356.0966, found 356.0974.

4.7. (*R*)-*P,P*-Diphenyl-*N*-(1-*o*-tolylethyl)phosphinic amide 2bi

Prepared from **3bi**. R_f 0.13 (EtOAc); mp 201–204 °C; $[\alpha]_D$ = +7.1 (*c* 1.02, MeOH, for 79% ee material); IR ($CHCl_3$) ν_{max}/cm^{-1} 3382, 2984, 1439, 1183, 1125, 1086, 958; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93–7.87 (m, 2H), 7.76–7.71 (m, 2H), 7.51–7.40 (m, 6H), 7.33–7.28 (m, 1H), 7.25 (t, *J* = 6.8 Hz, 1H), 7.14 (td, *J* = 7.4, 1.2 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.65–4.55 (m, 1H), 3.28 (dd, *J* = 8.8, 5.6 Hz, 1H), 2.00 (s, 3H), 1.50 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 143.7 (d, *J* = 7.0 Hz), 133.3 (d, *J* = 150 Hz), 132.4 (d, *J* = 9.7 Hz), 131.8 (d, *J* = 9.4 Hz), 131.8 (d, *J* = 2.4 Hz), 131.7 (d, *J* = 2.7 Hz), 130.3, 128.4 (d, *J* = 12.5 Hz), 128.2 (d, *J* = 12.7 Hz), 126.8, 126.5, 124.7, 47.1, 26.0 (d, *J* = 3.0 Hz), 18.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 22.7; HRMS (ESI positive) calcd for $C_{21}H_{22}NOP$, [M+H] 336.1512, found 336.1499.

4.8. *N*-(1-(2-Chlorophenyl)ethyl)-*P,P*-diphenylphosphinic amide 2bk

Prepared from **3bk**. R_f 0.17 (EtOAc); mp 209–211 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3379, 2984, 1602, 1439, 1186, 1124, 1107, 958; ^{1}H

NMR (400 MHz, $CDCl_3$) δ_H 7.91–7.86 (m, 2H), 7.79–7.73 (m, 2H), 7.52–7.40 (m, 4H), 7.38–7.30 (m, 2H), 7.28–7.23 (m, 2H), 7.16 (td, J = 7.6, 2.0 Hz, 2H), 4.79–4.69 (m, 1H), 3.49 (dd, J = 9.6, 6.0 Hz, 1H), 1.57 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.3 (d, J = 5.6 Hz), 132.9 (d, J = 127 Hz), 132.3 (d, J = 9.6 Hz), 131.9, 131.8 (d, J = 9.4 Hz), 131.7 (d, J = 2.8 Hz), 131.1, 129.8, 128.4 (d, J = 12.4 Hz), 128.2 (d, J = 12.5 Hz), 128.1, 127.4, 127.1, 49.1, 25.0 (d, J = 3.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ_P 22.8; HRMS (ESI positive) calcd for $C_{20}H_{18}ClNOP$, [M+Na] 378.0785, found 378.0781.

4.9. Protecting group exchange—conversion of 2b into trifluoroacyl or acyl derivatives 2c/d

A 10 cm^3 vial equipped with a magnetic stirrer was charged with the pure protected secondary amine **2b** (30 mg) and trifluoroacetic anhydride (50 equiv) or acetyl chloride (50 equiv) with DMAP (7 mol %). The suspension was stirred for 30 min before the cautious addition of two drops of water. The resulting solution was stirred overnight and the reaction mixture was transferred in a larger container before quenching it cautiously with a saturated $NaHCO_3$ solution (30 cm^3). The mixture was extracted with CH_2Cl_2 (3×20 cm^3), dried (Na_2SO_4) and concentrated. The residue was purified by filtration over a pad of silica (CH_2Cl_2) or by flash chromatography (pet. ether/EtOAc 1:1). Samples of **2c/d**, assessed pure by ^{1}H NMR spectroscopy, were used directly for ee determination by GC. Assays were carried out on an autosampler equipped Varian 430 using the conditions and columns described in Table 3.

4.10. (*R*)-2,2,2-Trifluoro-*N*-(1-(4-fluorophenyl)ethyl)acetamide 2cc

Prepared from **2bc**. R_f 0.53 (CH_2Cl_2); mp 55–57 °C; $[\alpha]_D$ = +75.1 (*c* 1.23, MeOH, for 84% ee material); IR ($CHCl_3$) ν_{max}/cm^{-1} 3429, 1723, 1607, 1513, 1170, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31–7.26 (m, 2H), 7.07–7.03 (m, 2H), 6.48 (br s, 1H), 5.12 (quintet, J = 7.2 Hz, 1H), 1.58 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 162.4 (d, J = 245 Hz), 156.3 (d, J = 37.1 Hz), 136.7 (d, J = 10.6 Hz), 127.9 (d, J = 8.2 Hz), 115.9 (d, J = 21.5 Hz), 115.7 (d, J = 286 Hz), 49.1, 21.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −75.9, −113.8; HRMS (ESI negative) calcd for $C_{10}H_9F_4NO$, [M−H] 234.0548, found 234.0543.

4.11. (*R*)-*N*-(1-(4-Chlorophenyl)ethyl)-2,2,2-trifluoroacetamide 2cd

Prepared from **2bd**. R_f 0.67 (CH_2Cl_2); mp 106–107 °C; $[\alpha]_D$ = +44.8 (*c* 1.10, MeOH, for 86% ee material); IR ($CHCl_3$) ν_{max}/cm^{-1} 3429, 1725, 1530, 1495, 1170, 828; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36–7.33 (m, 2H), 7.27–7.24 (m, 2H), 6.47 (br s, 1H), 5.11 (quintet, J = 7.2 Hz, 1H), 1.57 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.4 (q, J = 37.1 Hz), 139.5, 134.1, 129.2, 127.7, 114.4, 49.3, 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −75.9; HRMS (ESI negative) calcd for $C_{10}H_9ClF_3NO$, [M−H] 250.0252, found 250.0242.

4.12. (*R*)-2,2,2-Trifluoro-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)acetamide 2cf

Prepared from **2bf**. R_f 0.66 (CH_2Cl_2); mp 78–80 °C; $[\alpha]_D$ = +106.7 (*c* 1.16, MeOH, for 78% ee material); IR ($CHCl_3$) ν_{max}/cm^{-1} 3429, 1726, 1531, 1327, 1171, 1132, 1070, 841; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.64 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.48 (br s, 1H), 5.19 (quintet, J = 7.2 Hz, 1H), 1.61 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.7, 156.3, 145.0, 130.6, 130.3, 126.5, 126.1, 126.1, 126.0, 126.0, 122.6, 117.2, 114.3, 111.5, 49.5, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −62.7, −75.8; HRMS (ESI negative) calcd for $C_{11}H_9F_6NO$, [M−H] 284.0516, found 284.0515.

4.13. (*R*)-2,2,2-Trifluoro-*N*-(1-*m*-tolylethyl)acetamide 2cg

Prepared from **2bg**. R_f 0.85 (CH_2Cl_2); mp 65–66 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3429, 1722, 1529, 1171; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28–7.25 (td, J = 7.2, 1.2 Hz, 1H), 7.14–7.10 (m, 3H), 6.52 (br s, 1H), 5.10 (quintet, J = 6.8 Hz, 1H), 2.36 (s, 3H), 1.57 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.2 (q, J = 36.6 Hz), 140.8, 138.8, 128.9, 128.9, 127.0, 123.1, 115.8 (q, J = 287 Hz), 49.9, 21.4, 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −75.9; HRMS (ESI negative) calcd for $C_{11}H_{12}F_3NO$, [M−H] 230.0798, found 230.0810.

4.14. (*R*)-*N*-(1-(3-Chlorophenyl)ethyl)-2,2,2-trifluoroacetamide 2ch

Prepared from **2bh**. R_f 0.67 (CH_2Cl_2); mp 52–54 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3428, 2984, 1724, 1530, 1169, 879; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33–7.28 (m, 3H), 7.21–7.19 (m, 1H), 6.59 (br s, 1H), 5.10 (quintet, J = 7.2 Hz, 1H), 1.57 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.5 (q, J = 37.1 Hz), 143.0, 134.9, 130.4, 128.4, 126.4, 124.5, 115.8 (q, J = 286 Hz), 49.4, 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −75.8; HRMS (ESI negative) calcd for $C_{10}H_9ClF_3NO$, [M−H] 250.0252, found 250.0252.

4.15. (*R*)-2,2,2-Trifluoro-*N*-(1-*o*-tolylethyl)acetamide 2ci

Prepared from **2bi**. R_f 0.55 (CH_2Cl_2); mp 65–67 °C; $[\alpha]_D$ = +39.0 (*c* 1.15, MeOH, for 79% ee material); IR ($CHCl_3$) ν_{max}/cm^{-1} 3428, 3012, 1723, 1528, 1171; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31–7.19 (m, 4H), 6.37 (br s, 1H), 5.34 (quintet, J = 7.2 Hz, 1H), 2.37 (s, 3H), 1.58 (d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1 (q, J = 36.8 Hz), 138.8, 136.0, 131.1, 128.1, 126.6, 124.6, 115.8 (q, J = 286.3 Hz), 46.3, 20.5, 19.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −75.8; HRMS (ESI negative) calcd for $C_{11}H_{12}F_3NO$, [M−H] 230.0798, found 230.0801.

4.16. *N*-(1-(2-Chlorophenyl)ethyl)-2,2,2-trifluoroacetamide 2ck

Prepared from racemic **2bk**. R_f 0.75 (CH_2Cl_2); mp 101–103 °C; IR ($CHCl_3$) ν_{max}/cm^{-1} 3432, 1726, 1530, 1171, 1041; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42–7.39 (m, 1H), 7.34–7.31 (m, 1H), 7.30–7.25 (m, 2H), 6.78 (br s, 1H), 5.42 (quintet, J = 7.2 Hz, 1H), 1.61 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.1 (q, J = 37.1 Hz), 138.0, 133.0, 130.5, 129.3, 127.4, 127.4, 115.8 (q, J = 286 Hz), 48.2, 20.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −75.9; HRMS (ESI negative) calcd for $C_{10}H_9ClF_3NO$, [M−H] 250.0252, found 250.0255.

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