Synthesis, Properties and Applications of BICAP: a New Family of Carbazole-Based Diphosphine Ligands

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Received: December 23, 2003; Accepted: March 30, 2004

Dedicated to Joe P. Richmond on the occasion of his 60th birthday.

Abstract: A new family of bidentate phosphine ligands based on the biscarbazole backbone has been synthesized and applied in the ruthenium- and rhodium-catalyzed asymmetric hydrogenations of methyl acetoacetate and dimethyl itaconate. The nitrogen atoms in these BICAP ligands allow facile introduction of substituents providing structurally similar, but electronically different ligands, which were used to fine-tune these reactions to 98% and 55% ee, respectively.

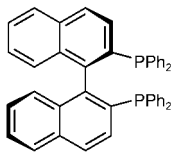
Keywords: asymmetric catalysis; atropisomerism; enantioselectivity; hydrogenation; P ligands

Introduction

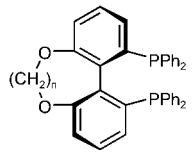
Since the introduction of BINAP **1** by Noyori,[1] the field of asymmetric homogenous catalysis has been enriched with a multitude of different C_2-symmetric biaryl ligands.[2] The large structural variety of these ligands is mainly responsible for the high level of sophistication this area has reached nowadays.[3] The optimization, however, of the many transition metal-catalyzed asymmetric transformations is still often a matter of trial and error because small changes in the geometric, steric, and electronic properties of the ligands can have dramatic effects on the outcome of the reactions.

To circumvent the often laborious syntheses of ligand analogues for fine-tuning catalysis, the availability of a biaryl scaffold in which diversity can be easily introduced in the last synthesis step would be desirable. Several approaches in this direction have been published over the years. An obvious approach is variation of the phosphine substituents on a known biaryl backbone.[4] Another striking example are the Tunaphos ligands **2**, developed by Zhang and co-workers.[5] This set of biaryl-type bidentate ligands, in which the bite angle can be altered by connection of the atropisomeric parts *via* a bridging tether with variable length, proved to be useful for a systematic study of transition metal-catalyzed asymmetric reactions.

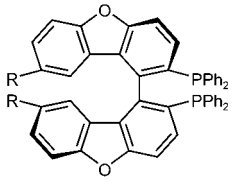
Our studies towards a more widely applicable skeleton led to the development of the BIFAP diphosphine ligand **3** in 1999.[6] An advantage of using the dibenzofuran moiety is the high regioselectivity in the sulfonation of BIFAP to give the water-soluble analogue BIFAPS **4** in 98%, due to the *para*-directing furan oxygen. A similar selectivity in electrophilic substitutions may be expected when the backbone is constructed from two carbazole moieties. The BICAP ligands **5** thus obtained can be further functionalized using the carbazole nitrogen. We envisaged that the parent BICAP **5a** is a versatile synthon to synthesize a new set of ligands in a facile way, with the same steric environment but with a different electronic behaviour. In this way asymmetric cata-



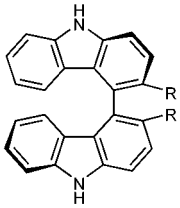
(*R*)-BINAP **1**



(*R*)-C*n*-TunaPhos **2**, n = 1 - 6



R = H: (*R*)-BIFAP **3**
R = SO_3K: (*R*)-BIFAPS **4**



R = PPh_2: (*R*)-BICAP **5a**
R = OH: (*R*)-BICOL **6**

 DOI: 10.1002/adsc.200303241 © 2004 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

lytic reactions can be optimized by using different ligands which all originate from a single backbone.

Results and Discussion

Synthesis of Diphosphine Ligands

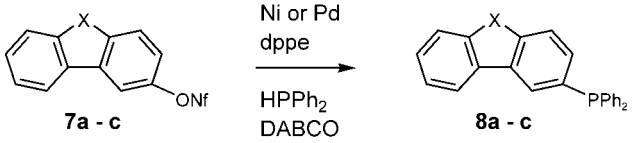
The diphosphine BICAP **5a** was prepared from the diol BICOL **6**. We recently published the synthesis and resolution of this latter configurationally stable diol, which can be performed on a multigram scale.[7] Our first attempts to convert BICOL **6** into BICAP **5a** proceeded *via* the corresponding dinonaflate in order to apply a transition metal-catalyzed cross-coupling reaction for the introduction of the diphenylphosphine moieties.[8a]

The cross-coupling reactions were tested in model nonaflates **7a–c**, which were synthesized from commercially available 2-hydroxydibenzofuran and readily prepared 3-hydroxycarbazole.[9] The most promising results for the synthesis of phosphines **8a–c** were obtained using the combination of $Ni(dppe)Cl_2$[8b] or $Pd(OAc)_2$/dppe with $HPPh_2$ as nucleophile and DABCO as base (Table 1). The dibenzofuran-derived phosphine **8a** could be isolated in high yield by applying both methods (entries 1 and 2). The synthesis of the carbazole-derived phosphine proved to be more problematic (entry 3). The use of a different phosphine source, such as $HPPh_2 \cdot BH_3$[8c] or the combination of $ClPPh_2$ and metallic zinc,[8d] gave no improvement. Protection of the carbazole nitrogen as a tosylate proved to be important for the yield of the reactions (entries 4 and 5).

We then went on to extend the positive results of the monomeric substrates to the dimeric cases. Much to our satisfaction, treatment of BIFOL-derived dinonaflate **10** with diphenylphosphine in the presence of $Pd(OAc)_2$/dppe and DABCO yielded BIFAP in one step in a 35% yield (Scheme 1). This procedure simplified the synthesis of BIFAP dramatically compared to our earlier work.[6]

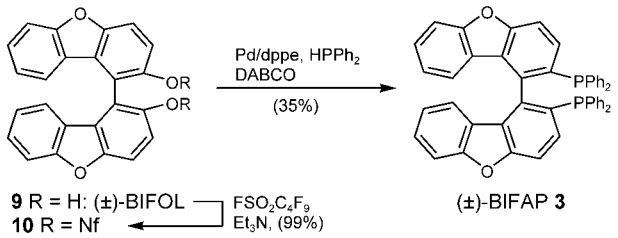
Diastereomerically pure **11**, obtained in the resolution of BICOL,[7] was used for the synthesis of dinonaflate **12** (Scheme 2). This *N*-tosyl protected precursor for the phosphination reactions was obtained after a three-

Table 1. Cross-coupling reactions using $HPPh_2$.

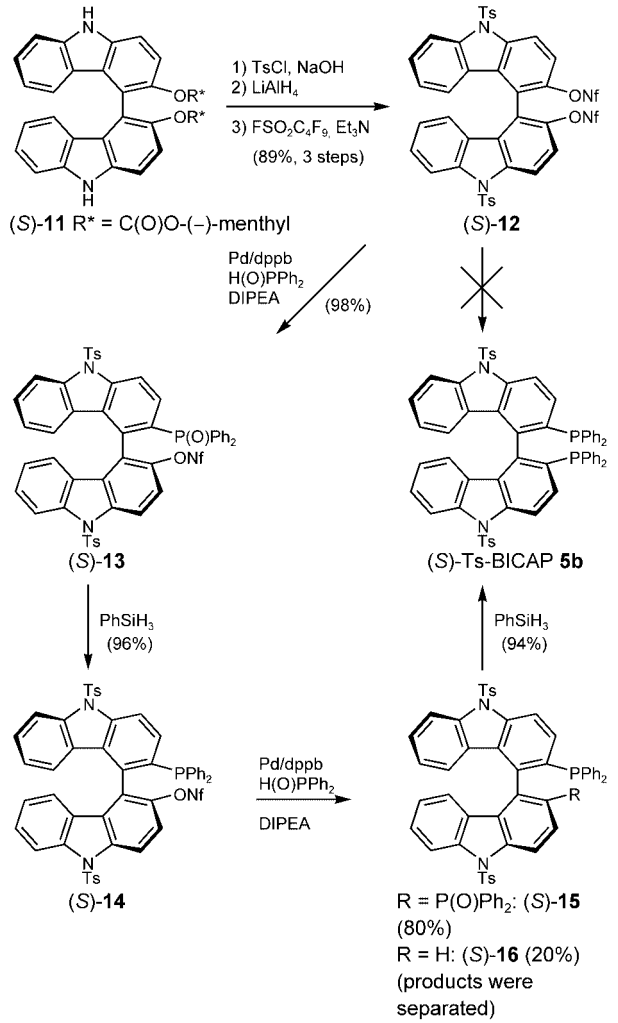


Entry	Precursor	Catalyst precursor[a]	Yield **8** [%][b]
1	**7a** (X = O)	$Ni(dppe)Cl_2$	94
2	**7a** (X = O)	$Pd(OAc)_2$/dppe	96
3	**7b** (X = N-Nf)	$Ni(dppe)Cl_2$	52[c]
4	**7c** (X = N-Ts)	$Ni(dppe)Cl_2$	78[d]
5	**7c** (X = N-Ts)	$Pd(OAc)_2$/dppe	93

[a] For details, see Experimental Section.
[b] All products isolated as phosphine oxide after treatment with H_2O_2.
[c] Substantial amounts of NH-carbazole were obtained.
[d] The reduced (3*H*)-carbazole was also isolated in 22% yield.



Scheme 1. Synthesis of BIFAP using $HPPh_2$.



Scheme 2. Synthesis of Ts-BICAP.

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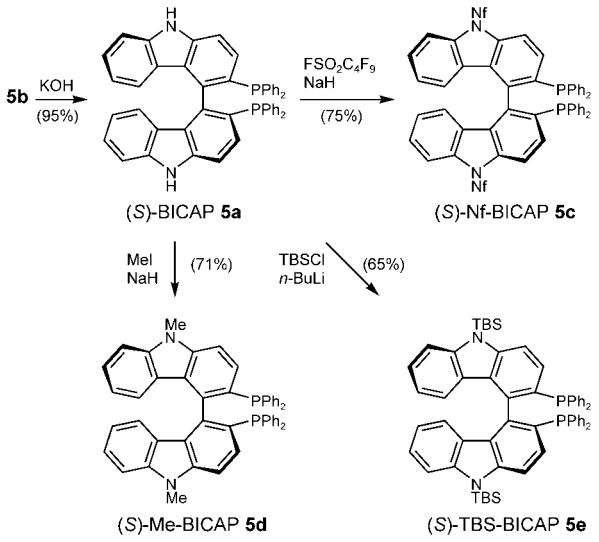
step sequence involving *N*-tosylation of **11**, reductive removal of the chiral menthol auxiliary using $LiAlH_4$, followed by sulfonylation of the bisphenol using $F\text{-}SO_2C_4F_9$ and Et_3N. In contrast to BIFAP **3**, all attempts to synthesize Ts-BICAP **5b** in one step from **12** by the use of a palladium- or nickel-catalyzed cross-coupling with $HPPh_2$ failed.

For the synthesis of BICAP we then relied on a stepwise procedure involving the successive introduction of two diphenylphosphine oxide moieties with a reduction step in between.[10] The first diphenylphosphine oxide group could be successfully introduced in **12** by the use of $Pd(OAc)_2$ and dppb to produce **13** followed by reduction to the phosphine by stirring the substrate in phenylsilane at a temperature of 114 °C in an excellent overall yield of 94% (Scheme 2). At higher temperatures considerable over-reduction to **16** was observed. The introduction of the second phosphine was carried out using the same sequence to give (*S*)-Ts-BICAP **5b**. The formation of by-product **16** in the second cross-coupling could not be avoided completely.

To allow diversification of the BICAP backbone the tosyl groups were removed from **5b** by treatment with KOH in MeOH.[11] The resulting parent BICAP **5a** ($[\alpha]_D^{20}$: −147 (*c* 0.49), mp 328–329 °C) proved to be an ideal precursor for the direct synthesis of a series of analogues by alkylation of the nitrogen atoms with several different electrophiles (Scheme 3). Treating BICAP with NaH and methyl iodide, for example, yielded the electron-rich Me-BICAP **5d** in 71% yield. Treating **5a** with NaH and F-Nf, on the other hand, yielded the electron-deficient Nf-BICAP **5c** (75% yield). Finally, TBS-Cl in combination with NaH provided TBS-BICAP **5e** in a yield of 65%. In this way a series of ligands was obtained which are sterically alike, but feature different electronic properties of the phosphine groups.



Scheme 3. Creation of the BICAP family.

Characterization and Properties of the BICAP Ligands

The electronic differences of the BICAP ligands seemed to be reflected in the ^{31}P NMR data (Table 2). The signal ranged from −14.0 ppm for the most electron-poor Nf-BICAP **5c** to −17.9 ppm for the most electron-rich Me-BICAP **5d**.

The electron-deficient (*S*)-Nf-BICAP showed remarkably complex NMR spectra, indicating slow dynamic processes on the NMR timescale. Increasing the temperature during the measurements clearly sharpened the signals, although even at 150 °C the signals were still not as sharp as the signals obtained in the NMR spectra of the other BICAP members. As the phenomenon was only observed with Nf-BICAP **5c**, model substrate **17** (Figure 1) was synthesized from (±)-BICOL in order to investigate the behaviour in more detail.

The ^1H NMR spectrum of a symmetric bicarbazole skeleton normally shows six signals, which belong to the six pairs of equivalent protons. The ^1H NMR of tetratriflate **17** showed the same splitting pattern as observed for Nf-BICAP. Every signal seemed to be split into four; one large signal, two smaller signals of the same intensity and one even smaller signal. The ratio is fixed at roughly 1:0.4:0.4:0.1 (Figure 1a, proton 1). When the ^1H NMR spectrum was measured at higher temperatures (Figure 1b–e), coalescence was reached (T=70 °C). Further heating sharpened the signals to the "normal" six doublets and triplets (T=100 °C).

The origin of this fluxional behaviour had to be in the sulfonamide part of the molecules. The X-ray crystal structure of **17** (Figure 2) showed that the bonds at the nitrogen atom are in the same plane as the planar carbazole moiety. This planarity ruled out an inversion of pyramidal nitrogen and so a hindered rotation about the N–S bond is suggested as the cause of the multiplicity of the NMR spectra.[12] The strongly electron-withdrawing character of the fluorinated groups apparently increases the double-bond character of the N–S bond causing a higher rotational barrier. The hindered rotation of the sulfonamide is most likely enhanced by the two *ortho*-hydrogens of the carbazole. The bulky CF_3

Table 2. ^{31}P NMR data of the BICAP family.

Ligand	δ[a] (ppm)
(*S*)-Nf-BICAP **5c**	−14.0[b]
(*S*)-Ts-BICAP **5b**	−15.8
(*S*)-TBS-BICAP **5e**	−17.5
(*S*)-BICAP **5a**	−17.7
(*S*)-Me-BICAP **5d**	−17.9

[a] Measured in $CDCl_3$.
[b] Major signal.

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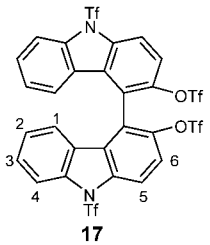

17

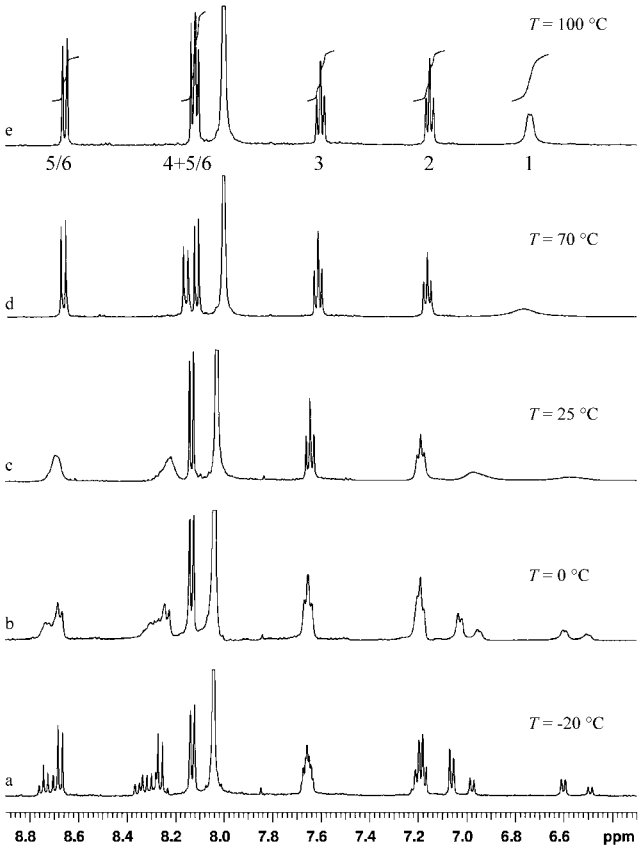

Figure 1. ^{1}H NMR spectra of **17** at different temperatures (in DMF-d_7).

group will position above or below the carbazole plane. Due to steric hindrance, the C_2-symmetric backbone divides the two possible orientations of the CF_3 group into a favoured *exo* position (the tail is pointing away from the other carbazole moiety) and an unfavoured *endo* position (the CF_3 group points towards the other carbazole moiety). The observed four isomers in the NMR spectra are thus:

- The most abundant species has the two CF_3 groups pointing in the *exo*-direction just like the situation found in the solid state (Figure 2). This implies C_2 symmetry resulting in a single signal for H1.
- The least abundant isomer has both CF_3 groups in an *endo* position, which again implies C_2 symmetry.
- In the third isomer one CF_3 is *exo* and the other *endo*. This implies loss of symmetry and as a result for H1 two signals of equal intensity are found.

To ascertain the structure of the ligands and in order to compare the structural features of BICAP with BIFAP **3** and BINAP **1**, the crystal structures of both (*S*)-Me-BICAP **5d** and ((*S*)-Me-BICAP)$PdCl_2$ **18** were determined by X-ray diffraction (Figures 3 and 4, respectively). Close examination led to the conclusion that BIFAP and Me-BICAP have similar geometries reflecting the central C–C bonds (1.512 Å and 1.511 Å, respectively) and the P–P distances (3.891 Å and 4.139 Å, respectively). Slightly different are the dihedral angles between the two planar moieties in the biaryls: 81.4° for the angle of the dibenzofuran units in BIFAP and 88.5° for the angle between the two carbazole parts. In both ligands the two phenyl rings at each phosphorus atom are non-equivalent as usual.

Because the crystal structures of the BINAP[13] and BIFAP[6] palladium dichloride complexes are known, they can be compared to **18**. In all three complexes the palladium atom adopts a distorted square-planar coor-

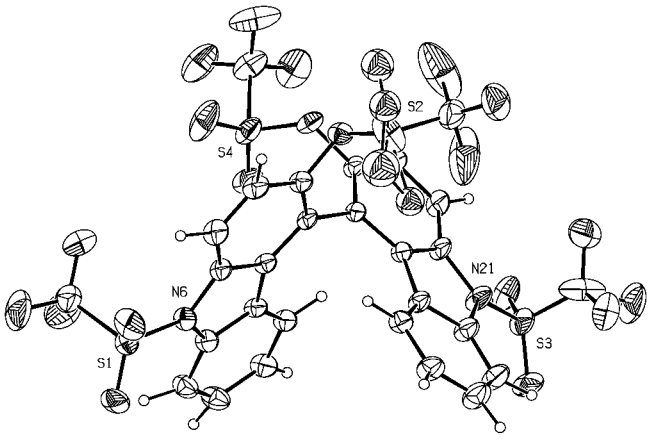

Figure 2. ORTEP drawing of the crystal structure of **17**.

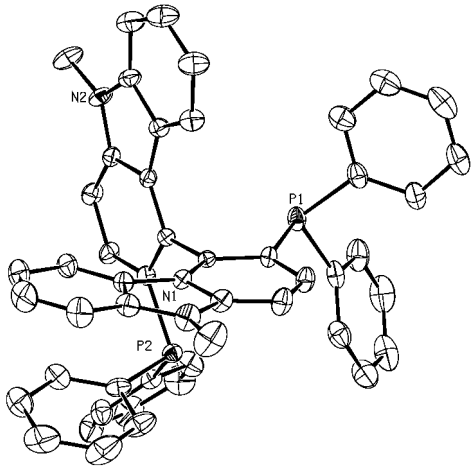

Figure 3. ORTEP drawing of the crystal structure of (*S*)-Me-BICAP **5d**.

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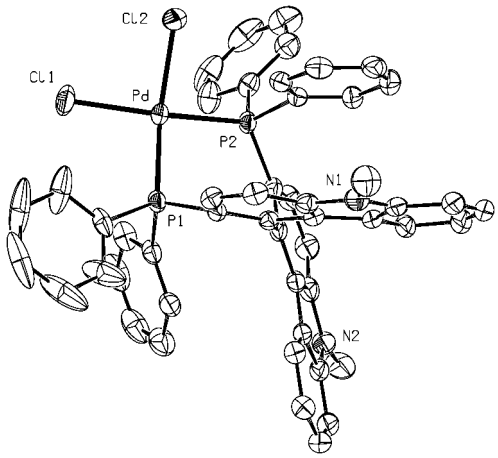


Figure 4. ORTEP drawing of the crystal structure of [(*S*)-Me-BICAP]$PdCl_2$ **18**.

dination, with central C–C bond lengths of the two connecting carbon atoms of 1.484 Å (**18**), 1.48 Å [(BINAP)$PdCl_2$] and 1.499 Å [(BIFAP)$PdCl_2$]. The P1–Pd–P2 bite angle in complex **18** (92.205°) is similar to those of (BINAP)$PdCl_2$ (92.69°) and (BIFAP)$PdCl_2$ (94.39°). The last observation from the crystal structures is that the free Me-BICAP ligand has to squeeze more than the free BIFAP ligand in order to chelate to the palladium. The torsion angles decreases from 88.5° in Me-BICAP to 71.6° in **18**, compared to a change from 81.4 in BIFAP to 73.4 in (BIFAP)$PdCl_2$.

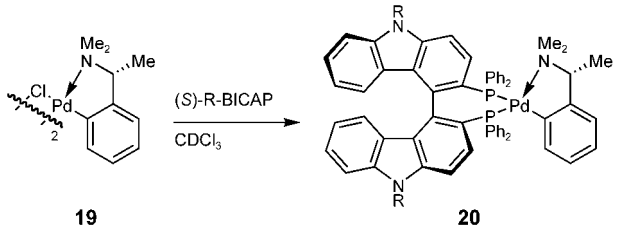
Before testing the ligands in asymmetric hydrogenations, the enantiopurity of the ligands was checked by examination of the ^{31}P NMR spectra of the diastereomeric complexes **20**, obtained after the reaction between the enantiopure palladium dimer **19** and the ligands[14] (Scheme 4). All spectra showed only two sets of doublets, indicating that the enantiopurity of the backbone is retained in the reaction sequence from BICOL to BICAP.

Asymmetric Hydrogenations with the BICAP Family

The performance of the new BICAP family was first investigated in the asymmetric hydrogenation of methyl acetoacetate **21** (Table 3).[15] This ruthenium-catalyzed reaction was carried out in a stainless steel autoclave, using methanol as the solvent at a hydrogen pressure of 100 bar. The behaviour of the BICAP family proved to be comparable with those of BINAP and BIFAP[6] (entries 5 and 6). The conversions and the stereochemical outcome of the hydrogenations proved to be excellent and the absolute configuration of products **22** was the same for all reactions. We observed a small but significant drop in the enantiomeric excess when using the more electron-rich H-BICAP and Me-BICAP (entries 3 and 4).

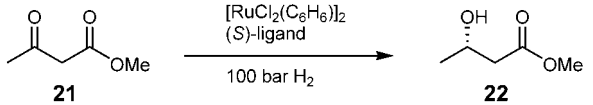
To study the behaviour of the BICAP ligands in more detail we searched for an asymmetric hydrogenation in which the product was expected to be obtained with high conversions, but with lower ees. Dimethyl itaconate (**23**) was found to be a suitable substrate for this purpose.[16] The rhodium-catalyzed hydrogenations of this olefin provided succinate **24** in quantitative yields when applying any of the BICAP members, but the enantioselectivities differed dramatically (Table 4). When the most electron-deficient Nf-BICAP was used, there was hardly any asymmetric induction (entry 1). The ee increased for the more electron-rich Ts-BICAP, TBS-BICAP and H-BICAP (entries 2–4) and the highest ee was obtained with the most electron-rich Me-BICAP (entry 5). The 55% ee of this last reaction is close to the result found for BINAP (entry 6).

Thus, for the hydrogenation of methyl acetoacetate (**21**) a more electron-deficient BICAP-catalyst is desirable, while the more electron-rich BICAP-catalysts perform better in the hydrogenation of dimethyl itaconate (**23**). The changes in stereocontrol are most likely caused by variations in the coordination strengths of the different BICAP/metal complexes to the substrate, influencing the outcome of the reactions.



Scheme 4. Checking the enantiopurity of the BICAP ligands.

Table 3. Asymmetric hydrogenation of methyl acetoacetate.



21 22

Entry[a]	Ligand	Conversion[b] [%]	ee[c] [%]
1	(*S*)-Nf-BICAP	100	98
2	(*S*)-Ts-BICAP	100	98
3	(*S*)-H-BICAP	100	96
4	(*S*)-Me-BICAP	100	94
5	(*S*)-BINAP	100	99
6	(S)-BIFAP	100	99

[a] Ratio substrate : Ru : ligand = 100 : 0.1 : 0.11.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC of the benzoyl ester.

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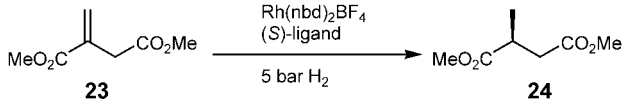
Table 4. Asymmetric hydrogenation of dimethyl itaconate.



23 24

Entry[a]	Ligand	Conversion[b] [%]	ee[c] [%]
1	(*S*)-Nf-BICAP	100	2
2	(*S*)-Ts-BICAP	100	14
3	(*S*)-TBS-BICAP	100	31
4	(*S*)-H-BICAP	100	44
5	(*S*)-Me-BICAP	100	55
6	(*S*)-BINAP	100	67

[a] Ratio substrate : Rh : ligand = 100 : 1 : 1.1.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral GC.

Conclusions

Enantiopure BICOL can be transformed into a new family of C_2-symmetric bicarbazole-based diphosphine ligands abbreviated as BICAP. The nitrogen of these ligands serves as an ideal handle for the introduction of diversity. Thus, BICAP proves to be an excellent scaffold for the synthesis of a variety of biaryl ligands, which are sterically alike, but differ in their electronic properties with respect to the electron density on phosphorus. This provides an opportunity for the fine-tuning of catalytic asymmetric reactions as has been shown for the asymmetric hydrogenations of methyl acetoacetate and an itaconic acid derivative.

Experimental Section

General Information

Unless otherwise noted, materials were purchased from commercial suppliers and used without purification. Diphenylphosphine was freshly distilled before use. Toluene, DMF, DMSO, MeOH, dichloromethane and acetonitrile were freshly distilled from calcium hydride. Tetrahydrofuran was freshly distilled from sodium with benzophenone as indicator. Triethylamine and DIPEA were stored over potassium hydroxide pellets and used as such. All air- and moisture-sensitive reactions were carried out under an inert atmosphere of dry argon. Column chromatography was performed using Aldrich silica gel (70–230 mesh, 60 Å). Infrared spectra were recorded on a Bruker IFS 28 spectrophotometer. ^{1}H NMR and ^{13}C NMR (APT) spectra were determined in $CDCl_3$ (unless states otherwise) on a Bruker ARX 400 (400 and 100.6 MHz, respectively) or a Varian Inova-500 (500 and 125 MHz, respectively). Spectra are reported in units of ppm on the δ scale, relative to chloroform (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). ^{31}P NMR spectra were recorded in $CDCl_3$ (unless states otherwise) on a Bruker 300 AMX (121.5 MHz) or a Varian Inova-500 (202.4 MHz). Chemical shifts are given in ppm downfield from external 85% H_3PO_4. Mass spectra were measured using a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. Melting points are uncorrected.

1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic Acid Dibenzofuran-2-yl Ester (7a)

To a solution of 2-hydroxydibenzofuran (2.50 g, 13.6 mmol) in acetonitrile (70 mL) were added triethylamine (3.0 mL, 21.8 mmol) and $FSO_2C_4F_9$ (3.66 mL, 20.4 mmol) and the reaction mixture was stirred for 18 h at room temperature. The mixture was diluted with EtOAc (150 mL) and the organic phase was washed with aqueous 0.5 M $NaHSO_3$ (2 × 100 mL) and brine (1 × 75 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE : EtOAc = 5 : 1) afforded **7a** as a white solid; yield: 6.28 g (13.5 mmol, 99%); mp 73–74 °C; ^{1}H NMR (400 MHz): δ = 7.96 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 2.6 Hz, 1H), 7.60 (m, 2H), 7.53 (td, J = 7.2, 1.3 Hz, 1H), 7.35–7.41 (m, 2H); ^{13}C NMR (100.6 MHz, due to C-F coupling the fluorinated carbons were not visible): δ = 157.3, 154.7, 145.2, 128.5, 125.6, 123.3, 123.2, 121.1, 120.0, 113.7, 112.8, 112.0. IR: ν = 1472, 1445, 1428, 1201, 1143, 1034, 912 cm^{-1}. HRMS (FAB +): calcd. for $C_{16}F_9H_8O_4S$ ($M + H^+$): 467.0000; found: 466.9991.

1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic Acid 9-(Nonafluorobutane-1-sulfonyl)-9*H*-carbazol-3-yl Ester (7b)

To a solution of 3-hydroxycarbazole (0.70 g, 3.82 mmol) in acetonitrile (38 mL) were added triethylamine (1.60 mL, 11.5 mmol) and $FSO_2C_4F_9$ (2.74 mL, 15.3 mmol) and the reaction mixture was stirred for 18 h at room temperature. By adding Et_2O (150 mL) the formed precipitate was dissolved and the organic phase was washed with aqueous 0.5 M $NaHSO_3$ (2 × 75 mL) and brine (1 × 75 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE : EtOAc = 5 : 1) afforded **7b** as a white solid; yield: 2.86 g (3.78 mmol, 99%); mp 91–92 °C; ^{1}H NMR (400 MHz): δ = 8.19 (d, J = 9.2 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 7.1 Hz, 1H), 7.91 (d, J = 2.5 Hz, 1H), 7.61 (td, J = 7.4, 1.3 Hz, 1H), 7.53 (td, J = 7.7, 0.8 Hz, 1H), 7.42 (dd, J = 9.2, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, due to C-F coupling the fluorinated carbons were not visible): δ = 147.1, 138.9, 136.9, 129.4, 128.0, 125.9, 125.0, 120.8, 120.7, 116.5, 115.2, 113.4; IR: ν = 2815, 1479, 1422, 1353, 1201, 1144, 916, 871, 813 cm^{-1}. HRMS (FAB +): calcd. for $C_{20}F_{18}H_8NO_5S_2$ ($M + H^+$): 747.9556; found: 747.9551.

1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic Acid 9-(Toluene-4-sulfonyl)-9*H*-carbazol-3-yl Ester (7c)

A solution of 3-hydroxycarbazole (0.25 g, 1.36 mmol) and triethylamine (0.21 mL, 1.50 mmol) in acetonitrile (13.6 mL) was stirred for 10 min. at room temperature before adding $FSO_2C_4F_9$ (0.39 mL, 2.18 mmol). The mixture was stirred for another 45 min. The reaction was quenched by addition of wa-

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ter (50 mL) and EtOAc (50 mL) and the organic phase was washed with aqueous 0.5 M $NaHSO_3$ (1×35 mL) and brine (1×40 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 2.5:1) afforded the mono-nonaflate as a white solid; yield: 0.58 g (1.24 mmol, 92%); mp 116–117 °C; ^{1}H NMR (400 MHz): $\delta = 8.20$ (br. s, 1H), 8.07 (d, $J = 7.6$ Hz, 1H), 7.96 (d, $J = 2.4$ Hz, 1H), 7.43–7.51 (m, 3H), 7.27–7.34 (m, 2H); ^{13}C NMR (100.6 MHz, acetone-d_6, due to C-F coupling the fluorinated carbons were not visible): $\delta = 144.6$, 140.6, 142.7, 128.5, 125.2, 124.0, 122.3, 121.1, 120.1, 114.7, 113.5, 113.0; IR: $\nu = 3421$, 1428, 1235, 1202, 1144, 1124, 1033, 908 cm^{-1}; HRMS (FAB+): calcd. for $C_{16}F_9H_9NO_3S$ ($M+H^+$): 466.0159; found: 466.0135.

To a solution of the mono-nonaflate (2.75 g, 5.91 mmol) in CH_2Cl_2 (30 mL) were added LiHMDS (7.8 mL of a 1 M solution in THF) and TsCl (1.69 g, 8.87 mmol). After stirring the mixture for 48 h at room temperature, the reaction was quenched by addition of water (150 mL) and CH_2Cl_2 (100 mL) and the organic phase was washed with aqueous 0.5 M $NaHSO_3$ (1×35 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 12:1) afforded **7c** as a white solid; yield: 3.40 g (5.50 mmol, 93%); mp 111–112 °C; ^{1}H NMR (400 MHz): $\delta = 8.39$ (d, $J = 9.1$ Hz, 1H), 8.33 (d, $J = 8.4$ Hz, 1H), 7.91 (d, $J = 7.7$ Hz, 1H), 7.80 (d, $J = 2.5$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.56 (td, $J = 7.4$, 1.2 Hz, 1H), 7.37–7.43 (m, 2H), 7.15 (d, $J = 8.2$ Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100.6 MHz, due to C-F coupling the fluorinated carbons were not visible): $\delta = 146.0$, 145.5, 139.1, 134.6, 129.9, 128.7, 127.6, 126.5, 125.0, 124.2, 120.5, 120.1, 116.3, 115.2, 112.9, 21.5. IR: $\nu = 3105$, 1476, 1426, 1377, 1202, 1144, 909, 813 cm^{-1}. HRMS (FAB+): calcd. for $C_{23}F_9H_{15}NO_5S_2$ ($M+H^+$): 620.0248; found: 620.0219.

General Procedures for the Cross-Coupling Reactions on Nonaflates using $HPPh_2$

Method A: Precisely according the literature procedure,[8b] except that the last two portions of phosphine (2×0.4 equivs.) were added after 5 and 15 min. The reaction mixtures were stirred at 110 °C until all the starting materials were consumed (monitored by TLC). When completed the mixture was diluted with toluene, whereafter the volatiles were removed under vacuum. The mixture was filtered over hyflo (eluted with toluene) and concentrated again. The crude products were dissolved in THF and aqueous H_2O_2 (35%) was added. After stirring for 30 min the mixture was diluted with EtOAc and washed with water ($2 \times$). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purifications were performed by column chromatography.

Method B: Nonaflate (1.0 equiv.), $Pd(OAc)_2$ (0.02 equivs.), dppe (0.022 equivs.) and DABCO (2 equivs.) were weighed into a Schlenk tube and after three argon/vacuum cycles DMF (0.2 mL) was added and the solution was stirred for 1 h at room temperature upon which the colour changed from yellow to orange. After addition of $HPPh_2$ (1.2 equivs.) the solution was heated to 120 °C until all starting materials were consumed (monitored by TLC). The work-up was the same as in method A.

2-(Diphenylphosphinoyl)-dibenzofuran (8a)

Compound **7a** (0.15 g, 0.32 mmol) was reacted for 6 h according to method A. Purification by column chromatography (PE:EtOAc = 4:1) afforded **8a** as a white solid; yield: 0.11 g (0.30 mmol, 94%); mp 159–160 °C; ^{1}H NMR (400 MHz): $\delta =$ 8.40 (d, $J = 12.1$ Hz, 1H), 7.90 (d, $J = 7.7$ Hz, 1H), 7.54–7.73 (m, 9H), 7.46–7.50 (m, 5H), 7.34 (t, $J = 7.5$ Hz, 1H); ^{31}P NMR (121.5 MHz): $\delta = 30.8$; IR: $\nu = 3054$, 1469, 1437, 1189, 1117 cm^{-1}; HRMS (FAB+): calcd. for $C_{24}H_{18}O_2P$ ($M+H^+$): 369.1044; found: 369.1049.

3-(Diphenylphosphinoyl)-9-(nonafluorobutane-1-sulfonyl)-9*H*-carbazole (8b)

Compound **7b** (0.15 g, 0.20 mmol) was reacted for 5 h according to method A. Purification by column chromatography (PE:EtOAc = 1:1→1:3) afforded **8b** as a white solid; yield: 67 mg (0.10 mmol, 52%); mp 153 °C; ^{1}H NMR (400 MHz): $\delta = 8.53$ (d, $J = 11.5$ Hz, 1H), 8.17 (dd, $J = 8.6$, 1.5 Hz, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 7.98 (d, $J = 7.4$ Hz, 1H), 7.44–7.75 (m, 13H); ^{31}P NMR (121.5 MHz): $\delta = 28.6$; IR: $\nu = 3417$, 1713, 1410, 1353, 1195, 1143, 1120, 1033; HRMS (FAB+): calcd. for $C_{28}H_{18}F_9NO_3PS$ ($M+H^+$): 650.0601; found: 650.0602.

3-(Diphenylphosphinoyl)-9-(toluene-4-sulfonyl)-9*H*-carbazole (8c)

Compound **7c** (0.15 g, 0.24 mmol) was reacted for 5 h according to method B. Purification by column chromatography (PE:EtOAc = 1:2) afforded **8c** as a white solid; yield: 117 mg (0.22 mmol, 93%); mp 106–108 °C; ^{1}H NMR (400 MHz): $\delta =$ 8.39 (d, $J = 7.8$ Hz, 1H), 8.32 (d, $J = 11.8$ Hz, 1H), 8.31 (d, $J =$ 8.4 Hz, 1H), 7.64–7.72 (m, 7H), 7.45–7.57 (m, 8H), 7.34 (t, $J = 7.5$ Hz, 1H), 7.11 (d, $J = 8.2$ Hz, 2H), 2.27 (s, 3H); ^{31}P NMR (121.5 MHz): $\delta = 31.0$; IR: $\nu = 1716$, 1437, 1373, 1176, 1120, 1006, 974 cm^{-1}; HRMS (FAB+): calcd. for $C_{31}H_{25}NO_3PS$ ($M+H^+$): 522.1293; found: 522.1300.

(±)-1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic Acid 2′-(Nonafluorobutane-1-sulfonyloxy)-[1,1′]bi[dibenzofuranyl]-2-yl Ester (10)

To a solution of (±)-BIFOL (0.50 g, 1.36 mmol) in acetonitrile (14 mL) were added triethylamine (0.57 mL, 4.09 mmol) and $FSO_2C_4F_9$ (0.98 mL, 5.44 mmol) and the reaction mixture was stirred at 60 °C for 2 h. The mixture was diluted with EtOAc (60 mL) and the organic phase was washed with aqueous 0.5 M $NaHSO_3$ (2×75 mL) and brine (1×75 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 15:1) afforded **10** as a white solid; yield: 1.24 g (1.33 mmol, 98%); mp 148–149 °C; ^{1}H NMR (400 MHz): $\delta = 7.86$ (d, $J =$ 9.0 Hz, 2H), 7.64 (d, $J = 9.0$ Hz, 2H), 7.57 (d, $J = 8.3$ Hz, 2H), 7.37 (td, $J = 7.8$, 1.1 Hz, 2H), 6.91 (t, $J = 7.4$ Hz, 2H), 6.64 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR (100.6 MHz, due to C-F coupling the fluorinated carbons were not visible): $\delta = 157.4$, 154.5, 142.5, 128.7, 125.5, 123.4, 122.4, 121.9, 120.8, 120.3, 113.9, 111.8; IR: $\nu = 3075$, 1426, 1206, 1145, 909. HRMS (FAB+): calcd. for $C_{32}H_{13}F_{18}O_8S_2$ ($M+H^+$): 930.9764; found: 930.9753.

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Optimized Synthesis of (±)-BIFAP (3)

According to cross-coupling method B, using nonaflate **10** (150 mg, 161 μmol), 2.5 equivs. of $HPPh_2$ and stirring the mixture at 140 °C for 19 h. The mixture was concentrated under vacuum and purification by column chromatography (PE:toluene = 2:1) afforded BIFAP **3** as a white solid; yield: 42 mg (57 μmol, 35%). The spectral data were identical to those reported in the literature.[6]

(*S*)-1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic Acid 3′-(Nonafluorobutane-1-sulfonyloxy)-9,9′-bis(toluene-4-sulfonyl)-9*H*,9′*H*-[4,4′]bicarbazolyl-3-yl Ester (12)

To a solution of **11** (2.39 g, 3.28 mmol) in toluene (33 mL) were added TsCl (1.56 g, 8.20 mmol), t-Bu_4NHSO_4 (0.22 g, 0.65 mmol) and aqueous 2.5 N NaOH (66 mL). After stirring the mixture vigorously at room temperature for 5 h, EtOAc (150 mL) was added and the organic phase was washed with water (2 × 150 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude solids were dissolved in THF (66 mL) and $LiAlH_4$ (0.87 g, 22.9 mmol) was added carefully. After stirring at room temperature for 30 min, the reaction was quenched by adding slowly a mixture of water (80 mL), aqueous 2.0 N HCl (250 mL) and EtOAc (250 mL). After removal of the organic phase the aqueous layer was extracted with EtOAc (2 × 180 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 1.5:1→1:1) afforded the free diol as a white solid; yield: 2.09 g (3.11 mmol, 95%); mp 340 °C (decomposition); $[\alpha]_D^{20}$: −3.8 (*c* 1.00, THF); ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.38 (d, *J* = 9.0 Hz, 2H), 8.21 (d, *J* = 8.4 Hz, 2H), 8.15 (br. s, 2H), 7.73 (d, *J* = 8.4 Hz, 4H), 7.32 (d, *J* = 9.0 Hz, 4H), 7.24–7.30 (m, 4H), 6.70 (t, *J* = 7.3 Hz, 2H), 6.23 (d, *J* = 7.9 Hz, 2H), 2.28 (s, 6H); ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 154.2, 146.8, 140.6, 136.0, 134.0, 131.3, 128.5, 128.2, 128.0, 127.9, 125.2, 122.7, 117.7, 117.7, 116.8, 116.5; IR: ν = 3354, 3294, 1365, 1173, 1089, 972 cm^{-1}; HRMS (FAB+): calcd. for $C_{38}H_{29}O_6N_2S_2$ ($M+H^+$): 673.1467; found: 673.1458.

A solution of the diol (2.05 g, 3.05 mmol), triethylamine (1.10 mL, 7.93 mmol) and $FSO_2C_4F_9$ (1.37 mL, 7.62 mmol) in acetonitrile (61 mL) was stirred at 60 °C for 3 h. The reaction was quenched by addition of water (150 mL) and EtOAc (150 mL) and the organic phase was washed with aqueous 0.5 M $NaHSO_3$ (2 × 100 mL) and brine (1 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 4:1→2:1) afforded **12** as a white solid; yield: 3.55 g (2.86 mmol, 94%); mp 87 °C; $[\alpha]_D^{20}$: +148 (*c* 1.03, $CHCl_3$). ^{1}H NMR (400 MHz): δ = 8.67 (d, *J* = 9.2 Hz, 2H), 8.25 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 4H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.33 (td, *J* = 7.9, 1.0 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 4H), 6.70 (t, *J* = 7.5 Hz, 2H), 6.27 (d, *J* = 7.9 Hz, 2H), 2.28 (s, 6H); ^{13}C NMR (100.6 MHz, due to C-F coupling the fluorinated carbons were not visible): δ = 145.4, 143.4, 139.6, 137.7, 134.3, 129.8, 128.7, 127.2, 126.3, 124.4, 124.2, 121.6, 120.5, 120.2, 117.7, 115.1, 21.4; IR: ν = 3113, 1423, 1375, 1209, 1144, 919 cm^{-1}; HRMS (FAB+): calcd. for $C_{46}H_{27}F_{18}N_2O_{10}S_4$ ($M+H^+$): 1237.0261; found: 1237.0227.

(*S*)-1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic Acid 3′-(Diphenylphosphinoyl)-9,9′-bis(toluene-4-sulfonyl)-9*H*,9′*H*-[4,4′]bicarbazolyl-3-yl Ester (13)

To a mixture of **12** (3.10 g, 2.51 mmol), diphenylphosphine oxide (0.71 g, 3.51 mmol), $Pd(OAc)_2$ (56 mg, 0.25 mmol) and dppb (0.11 g, 0.25 mmol) were added DMSO (12.5 mL) and DIPEA (1.53 mL, 8.78 mmol). The mixture was stirred at 110 °C for 4 h upon which the colour of the solution changed from orange to dark purple. After cooling to room temperature the reaction mixture was diluted with EtOAc (100 mL) and washed with aqueous 0.5 M $NaHSO_3$ (2 × 100 mL) and brine (2 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 1:1→1:2) afforded **13** as a white solid; yield: 2.80 g (2.46 mmol, 98%); mp 121–123 °C; $[\alpha]_D^{20}$: −11 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 8.58 (dd, *J* = 8.8, 1.6 Hz, 1H), 8.49 (d, *J* = 9.2 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.70–7.76 (m, 3H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 12.1 Hz, 1H), 7.41 (dd, *J* = 12.1 Hz, 1.2, 1H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.41 (td, *J* = 7.4 Hz, 1.2, 1H), 7.09–7.28 (m, 10H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H), 6.81 (t, *J* = 7.8 Hz, 1H), 6.80 (t, *J* = 7.7 Hz, 1H), 6.55 (t, *J* = 7.4 Hz, 1H), 6.54 (t, *J* = 7.4 Hz, 1H), 5.86 (d, *J* = 8.1 Hz, 2H), 2.35 (s, 3H), 2.28 (s, 3H); ^{31}P NMR (121.5 MHz): δ = 28.0; IR: ν = 3120, 1422, 1373, 1239, 1207, 1177, 1143, 972, 915 cm^{-1}; HRMS (FAB+): calcd. for $C_{54}H_{37}F_9N_2O_8PS_3$ ($M+H^+$): 1139.1306; found: 1139.1281.

(*S*)-1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic Acid 3′-Diphenylphosphanyl-9,9′-bis-(toluene-4-sulfonyl)-9*H*,9′*H*-[4,4′]bicarbazolyl-3-yl Ester (14)

A solution of **13** (2.28 g, 2.00 mmol) in phenylsilane (13 mL) was stirred at 114 °C for 18 h. After addition of EtOAc (40 mL) the mixture was concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 4:1→3:1) afforded **14** as a white solid; yield: 2.15 g (1.92 mmol, 96%); mp 109–110 °C; $[\alpha]_D^{20}$: −7.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 8.62 (d, *J* = 9.2 Hz, 1H), 8.51 (d, *J* = 8.7 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.56–7.60 (m, 3H), 7.51 (dd, *J* = 8.7, 3.0 Hz, 1H), 7.18–7.32 (m, 9H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.84 (td, *J* = 7.2 Hz, 0.9, 1H), 6.65–6.75 (m, 4H), 6.58 (td, *J* = 8.0, 0.7 Hz, 1H), 6.50 (td, *J* = 8.0, 0.7 Hz, 1H), 6.06 (d, *J* = 7.9 Hz, 1H), 5.81 (d, *J* = 7.8 Hz, 1H), 2.32 (s, 3H), 2.28 (s, 3H); ^{31}P NMR (121.5 MHz): δ = −14.0. IR: ν = 3056, 1421, 1373, 1240, 1177, 1143, 1091, 972, 914 cm^{-1}; HRMS (FAB+): calcd. for $C_{54}H_{37}F_9N_2O_7PS_3$ ($M+H^+$): 1123.1357; found: 1123.1307.

(*S*)-3′-Diphenylphosphanyl-3-(diphenylphosphinoyl)-9,9′-bis(toluene-4-sulfonyl)-9*H*,9′*H*-[4,4′]bicarbazolyl (15)

To mixture of **14** (1.86 g, 1.66 mmol), diphenylphosphine oxide (0.54 g, 2.65 mmol), $Pd(OAc)_2$ (37 mg, 0.16 mmol) and dppb (0.71 mg, 0.16 mmol) were added DMSO (8.5 mL) and DIPEA (1.00 mL, 5.80 mmol). The mixture was stirred at 110 °C for 4 h upon which the colour of the solution changed from orange to dark purple. After cooling to room temperature

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the reaction mixture was diluted with EtOAc (100 mL) and washed with aqueous 0.5 M $NaHSO_3$ (2 × 100 mL) and brine (2 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 2:1→1:1) afforded first by-product **16** as a white solid (yield: 0.27 g, 0.33 mmol, 20%) followed by **15** as a white solid; yield: 1.36 g (1.33 mmol, 80%); mp 155–156 °C; $[\alpha]_D$: −65 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 8.55 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.32 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.71–7.78 (m, 7H), 7.60 (dd, *J* = 8.7, 2.9 Hz, 1H), 7.41–7.46 (m, 3H), 7.19–7.35 (m, 9H), 7.06–7.12 (m, 3H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.50–6.59 (m, 4H), 6.45 (t, *J* = 7.6 Hz, 1H), 6.39 (d, *J* = 7.3 Hz, 2H), 6.00 (t, *J* = 7.6 Hz, 1H), 5.71 (d, *J* = 7.9 Hz, 1H), 5.09 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H); ^{31}P NMR (121.5 MHz): δ = 27.0, −16.1. IR: ν = 3054, 1435, 1420, 1371, 1175, 972, 909 cm^{-1}; HRMS (FAB+): calcd. for $C_{62}H_{47}N_2O_5P_2S_2$ ($M+H^+$): 1025.2402; found: 1025.2411.

By-product **16**: mp 136–138 °C; $[\alpha]_D^{20}$: −38 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 8.47 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.74 (dd, *J* = 8.7, 3.0 Hz, 1H), 7.08–7.32 (m, 12H), 6.89–7.01 (m, 5H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.59 (t, *J* = 7.7 Hz, 1H), 6.03 (d, *J* = 7.9 Hz, 1H), 5.91 (d, *J* = 7.9 Hz, 1H), 2.34 (s, 3H), 2.27 (s, 3H); ^{31}P NMR (121.5 MHz): δ = −14.7. IR: ν = 3054, 1371, 1174, 1090, 973, 909 cm^{-1}; HRMS (FAB+): calcd. for $C_{50}H_{38}N_2O_4PS_2$ ($M+H^+$): 825.2011; found: 825.2021.

(*S*)-Ts-BICAP (5b)

A solution of **15** (0.80 g, 0.78 mmol) in phenylsilane (7 mL) was stirred at 125 °C for 48 h. After addition of EtOAc (40 mL) the mixture was concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 5:1→3:1) afforded **5b** as a white solid; yield: 0.74 g (0.73 mmol, 94%); mp 145–147 °C; $[\alpha]_D^{20}$: −69 (*c* 0.61, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 8.46 (d, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 4H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.17–7.20 (m, 14H), 7.05 (t, *J* = 7.5 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 2H), 6.66–6.72 (m, 4H), 6.58 (d, *J* = 7.5 Hz, 2H), 6.57 (t, *J* = 7.6 Hz, 2H), 6.28 (d, *J* = 7.7 Hz, 2H), 5.52 (d, *J* = 7.9 Hz, 2H), 2.31 (s, 6H); ^{31}P NMR (121.5 MHz): δ = −15.8; IR: ν = 3055, 1371, 1175, 971, 908 cm^{-1}; HRMS (FAB+): calcd. for $C_{62}H_{47}N_2O_4P_2S_2$ ($M+H^+$): 1009.2453; found: 1009.2443.

(*S*)-BICAP (5a)

To a solution of **5b** (0.50 g, 0.49 mmol) in THF (25 mL) was added 2 M KOH in MeOH (3.0 mL). The reaction mixture was stirred at 55 °C for 3 h, then quenched by addition of water (30 mL). The product was extracted with EtOAc (2 × 60 mL) and the organic layers were washed with brine (60 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (toluene) afforded **5a** as a white solid; yield: 0.33 g (0.46 mmol, 95%); mp 328–329 °C; $[\alpha]_D^{20}$: −147 (*c* 0.49, THF); ^{1}H NMR (400 MHz, acetone-d_6): δ = 10.56 (br. s, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.93–7.17 (m, 22H), 6.44 (t, *J* = 8.0 Hz, 2H), 6.12 (d, *J* = 8.0 Hz, 2H); ^{31}P NMR (121.5 MHz): δ = −17.7; IR: ν = 3415, 3052, 2925, 15921466, 1433, 1330, 1257 cm^{-1}; HRMS (FAB+): calcd. for $C_{48}H_{35}N_2P_2$ ($M+H^+$): 701.2276; found: 701.2266.

(*S*)-Nf-BICAP (5c)

NaH (14 mg, 0.35 mmol of a 60% dispersion in mineral oil) was added to a solution of **5a** (70 mg, 0.10 mmol) in 1:1 THF/DMF (2.0 mL). After stirring the mixture for 15 min, $FSO_2C_4F_9$ (54 μL, 0.30 mmol) was added and the suspension was heated to 55 °C for 5 h. The reaction mixture was diluted with EtOAc (20 mL) and the organic phase was washed with water (2 × 15 mL), aqueous saturated NH_4Cl (20 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 20:1→10:1) afforded **5c** as a white solid; yield: 84 mg (75 μmol, 75%); mp 66–67 °C; $[\alpha]_D^{20}$: −37 (*c* 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6, 150 °C): δ = 8.27 (d, *J* = 9.0 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.24–7.36 (m, 12H), 6.9 (m, 6H), 6.83–6.88 (m, 4H), 6.66 (m, 2H), 5.87 (m, 2H); ^{31}P NMR (202.4 MHz, DMSO-d_6, 150 °C): δ = −13.2; IR: ν = 2925, 1411, 1238, 1195, 1144 cm^{-1}; HRMS (FAB+): calcd. for $C_{56}H_{33}N_2P_2S_2O_4F_{18}$ ($M+H^+$): 1265.1070; found: 1265.1095.

(*S*)-Me-BICAP (5d)

NaH (23 mg, 0.58 mmol of a 60% dispersion in mineral oil) was added to a solution of **5a** (0.17 g, 0.24 mmol) in 1:1 THF/DMF (4.8 mL). After stirring the mixture for 15 min, methyl iodide (31 μL, 0.50 mmol) was added and the suspension was stirred for another 30 min. The reaction was diluted with EtOAc (20 mL) and the organic phase was washed with water (2 × 15 mL), aqueous saturated NH_4Cl (20 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (pentane:Et_2O = 2:1→1:2) afforded **5d** as a white solid; yield: 0.12 g (0.17 mmol, 71%); mp 324–325 °C; $[\alpha]_D^{20}$: −86 (*c* 0.21, $CHCl_3$); ^{1}H NMR (500 MHz): δ = 7.57 (s, 4H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.02–7.09 (m, 6H), 6.90–7.00 (m, 14H), 6.54 (t, *J* = 7.2 Hz, 2H), 6.13 (d, *J* = 7.9 Hz, 2H), 3.91 (s, 6H); ^{31}P NMR (202.4 MHz): δ = −18.0; IR: ν = 3049, 2929, 1579, 1475, 1433, 1259; HRMS (FAB+): calcd. for $C_{50}H_{39}N_2P_2$ ($M+H^+$): 729.2589; found: 729.2596.

(*S*)-TBS-BICAP (5e)

n-BuLi (0.10 mL, 0.25 mmol of a 2.5 M solution in THF) was added to a solution of **5a** (40 mg, 57 μmol) in 1:3 THF/toluene (2.6 mL). After stirring the mixture for 15 min, TBSCl (31 μL, 0.20 mmol) was added and the suspension was stirred for another 5 h. The reaction mixture was diluted with EtOAc (20 mL) and the organic phase was washed with water (1 × 15 mL), brine (1 × 20 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 15:1→7:1) afforded **5e** as a white solid; yield: 34 mg (37 μmol, 65%); mp 126–127 °C; $[\alpha]_D^{20}$: −103 (*c* 0.73, $CHCl_3$); ^{1}H NMR (400 MHz): δ = 7.73 (d, *J* = 8.7 Hz, 2H), 7.38–7.44 (m, 4H), 7.14–7.17 (m, 4H), 7.06–7.10 (m, 6H), 6.87–7.03 (m, 12H), 6.41 (t, *J* = 7.5 Hz, 2H), 5.94 (d, *J* =

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7.9 Hz, 2H), 1.01 (s, 18H), 0.81 (s, 6H), 0.79 (s, 6H); ^{31}P NMR (202.4 MHz): $\delta = -17.4$; IR: $\nu = 3050$, 2927, 2856, 1569, 1463, 1420, 1271, 966, 822 cm^{-1}; HRMS (FAB+): calcd. for $C_{60}H_{63}N_2P_2Si_2$ ($M+H^+$): 929.4005; found: 929.4019.

(±)-Trifluoromethanesulfonic Acid 9,9′-Bis(trifluoromethanesulfonyl)-3′-trifluoromethanesulfonyloxy-9*H*,9′*H*-[4,4′]bicarbazolyl-3-yl Ester (17)

To a suspension of (±)-BICOL (0.10 g, 0.27 mmol) in CH_2Cl_2 (3 mL) were added LiHMDS (1.57 mL of a 1 M solution in THF, 1.57 mmol) and triflic anhydride (0.32 mL, 1.89 mmol) at −30 °C. The resulting green solution was heated to 40 °C and stirred for 4 h. The mixture was diluted with CH_2Cl_2 (20 mL) and the organic phase was washed with aqueous 0.5 M $NaHSO_3$ (2 × 30 mL) and brine (1 × 30 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE:EtOAc = 15:1) afforded **17** as a white solid; yield: 73 mg (81 μmol, 30%); mp 57–59 °C; ^{1}H NMR (400 MHz, DMF-d_7): $\delta = 8.64$–8.79 (m, 2H), 8.16–8.30 (m, 2H), 7.63–7.67 (m, 2H), 7.10–7.24 (m, 2H), 6.98, 6.92, 6.63, 6.56 (4 d, $J = 8.0$, 7.9, 8.1, 7.3 Hz, intensity ratio 1.1:0.4:0.4:0.1, together 2H); ^{1}H NMR (400 MHz, DMF-d_7, T = 130 °C): $\delta = 8.80$ (d, $J = 9.0$ Hz, 2H), 8.25–8.28 (m, 4H), 7.75 (t, $J = 7.5$ Hz, 2H), 7.30 (t, $J = 7.5$ Hz, 2H), 6.89 (d, $J = 7.0$ Hz, 2H); HRMS (FAB+): calcd. for $C_{28}H_{13}O_{10}F_{12}N_2S_4$ ($M+H^+$): 892.9261; found: 892.9227.

[(*S*)-Me-BICAP]PdCl$_2$ (18)

To a solution of (*S*)-Me-BICAP (30.0 mg, 41 μmol) in CH_2Cl_2 (1.5 mL) was added $PdCl_2(MeCN)_2$ (10.1 mg, 39 μmol) and the resulting solution was stirred for 1 h at room temperature. After evaporation of the solvent, the crude product was recrystallized from a mixture of CH_2Cl_2/EtOAc/*i*Pr_2O, yielding red cubic crystals.

X-Ray Crystallographic Study

All X-ray measurements were carried out on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated CuKα radiation [λ(CuKα) = 1.5418 Å] and ω-2θ scan. Corrections for Lorentz and polarization effects were applied. Absorption corrections were performed (for **17** and **18**) with the program PLATON,[17] following the method of North et al.[18] using Ψ-scans of five reflections, with coefficients in the range 0.759–0.967 (**17**) and 0.491–0.977 (**18**). The structures were solved by the PATTY option of the DIRDIF-99 program system.[19]

Crystal Structure of BICOL Tetratriflate (17)

$C_{28}H_{12}F_{12}N_2O_{10}S_4$, $M_r = 892.7$, triclinic, Pī, $a = 10.497(2)$, $b = 162.542(1)$, $c = 13.426(2)$ Å, $a = 85.35(1)$, $\beta = 70.97(1(3)$, $\gamma = 85.838(9)°$, $V = 1663.5(4)$ Å^3, $Z = 2$, $D_x = 1.78$ g cm^{-3}, μ(CuKα) = 38.19 cm^{-1}, F(000) = 892, −20 °C, Final R = 0.98 for 5030 observed reflections.

A colourless crystal (grown from a solution of EtOAc/PE) with dimensions 0.25 × 0.40 × 0.40 mm approximately was used for data collection. A total of 6827 unique reflections was measured within the range $-12 \le h \le 13$, $-15 \le k \le 15$, $0 \le l 16$. Of these, 5030 were above the significance level of $4\sigma(F_{obs})$ and were treated as observed. The range of (sin θ)/λ was 0.040–0.626 Å ($3.5 \le \theta \le 74.8°$). Two reference reflections ([1 1 0],[0 1 3]) were measured hourly and showed 6% decrease during the 92 h collecting time, which was corrected for. Unit cell parameters were refined by a least-squares fitting procedure using 23 reflections with $40.03 \le \theta \le 41.70$. The hydrogen atoms were calculated. After isotropic refinement of the non-H atoms O4 and O5 had very high atomic displacement parameters. Careful examination of a ΔF synthesis revealed positional disorder for both atoms, so it was decided two split both atoms into two half-occupied positions and keep the ADP's isotropic during further refinement. Full-matrix least-squares refinement on F, anisotropic for the non-hydrogen atoms isotropic for the hydrogen atoms restraining the latter in such a way that the distance to their carrier remained constant at approximately 1.0 Å, converged to R = 0.098, $R_w = 0.089$, $(\Delta/\sigma)_{max} = 0.41$, S = 1.01. A weighting scheme $w = [3.5 + 0.01*(\sigma(Fobs))^2 + 0.01/(\sigma(Fobs))]^{-1}$ was used. The secondary isotropic extinction coefficient[20] refined to g = 518(48). A final difference Fourier map revealed a residual electron density between −1.33 and 1.49 eÅ^{-3} in the vicinity of the disordered atoms. Scattering factors were taken from the International Tables for X-Ray Crystallography.[21] The anomalous scattering of S, and F was taken into account.[22] All calculations were performed with XTAL3.7,[23] unless stated otherwise.

Crystal structure of [(*S*)-Me-BICAP]PdCl$_2$ (18)

$C_{50}H_{38}Cl_2N_2P_2Pd$, $M_r = 906.2$, orthorhombic, $P2_12_12_1$, $a = 14.610(1)$, $b = 15.766(1)$, $c = 17.89(3)$ Å, $V = 3837.0(7)$ Å^3, $Z = 4$, $D_x = 1.46$ g cm^{-3}, μ(CuKα) = 5.85 mm^{-1}, F(000) = 1776, room temperature, Final R = 0.038 for 4367 observed reflections.

A red crystal with dimensions 0.25 × 0.50 × 0.50 mm approximately was used for data collection. A total of 4669 unique reflections was measured within the range $0 \le h \le 18$, $0 \le k \le 19$, $0 \le l \le 22$. Of these, 4367 were above the significance level of $4\sigma(F_{obs})$ and were treated as observed. The range of (sin θ)/λ was 0.042–0.626 Å ($3.7 \le \theta \le 74.7°$). Two reference reflections ([3 0 2], [0 2 2]) were measured hourly and showed no decrease during the 80 h collecting time. Unit cell parameters were refined by a least-squares fitting procedure using 23 reflections with $39.95 \le 2\theta \le 41.94$. The hydrogen atoms were calculated and kept fixed with U = 0.10 Å^2. Full-matrix least-squares refinement on F, anisotropic for the non-hydrogen atoms converged to R = 0.038, $R_w = 0.039$, $(\Delta/\sigma)_{max} = 0.076$, S = 0.94. A weighting scheme $w = [3.5 + 0.01*(\sigma(Fobs))^2 + 0.01/(\sigma(Fobs))]^{-1}$ was used. The secondary isotropic extinction coefficient[20] refined to g = 1183(57). A final difference Fourier map revealed a residual electron density between −0.68 and 0.73 eÅ^{-3} in the vicinity of the heavy atoms. Scattering factors were taken from the International Tables for X-Ray Crystallography.[21] The anomalous scattering of Cl, P and Pd was taken into account.[22] All calculations were performed with XTAL3.7,[23] unless stated otherwise. Refining the inverted structure converged to R = 0.066, thus confirming the correct

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structure. Phenyl group C31-C36 behaves rather anisotropic compared with the other three phenyl groups.

Crystal structure of (*S*)-Me-BICAP (5d)

$C_{50}H_{38}N_2P_2$, $M_r = 728.8$, orthorhombic, $P2_12_12_1$, $a = 9.9515(6)$, $b = 11.4449(8)$, $c = 34.374(3)$ Å, $V = 3915.0(5)$ Å^3, $Z = 4$, $D_x = 1.24$ g cm^{-3}, $\mu(CuK\alpha) = 1.29$ mm^{-1}, $F(000) = 1528$, room temperature, Final $R = 0.056$ for 3864 observed reflections.

A white crystal (grown from a mixture of CH_2Cl_2/PE) with dimensions $0.15 \times 0.20 \times 0.75$ mm approximately was used for data collection. A total of 4524 unique reflections was measured within the range $0 \le h \le 12$, $0 \le k \le 14$, $0 \le l \le 42$. Of these, 3864 were above the significance level of $2.5\sigma(I_{obs})$ and were treated as observed. In addition 865 "Friedel" reflections were measured; these were used in the determination of the absolute configuration. The range of $(\sin\theta)/\lambda$ was 0.029–0.626 Å ($2.6 \le \theta \le 74.7°$). Two reference reflections ([2 1 0], [2 0 4]) were measured hourly and showed no decrease during the 80 h collecting time. Unit cell parameters were refined by a least-squares fitting procedure using 23 reflections with $39.93 \le 2\theta \le 41.84$. Full-matrix least-squares refinement on F, anisotropic for the non-hydrogen atoms, isotropic for the hydrogen atoms restraining the latter in such a way that the distance to their carrier remained constant at approximately 1.0 Å, converged to $R = 0.056$, $R_w = 0.071$, $(\Delta/\sigma)_{max} = 0.11$, $S = 1.08$. A weighting scheme $w = [4.2 + 0.01*(\sigma(Fobs))^2 + 0.01/(\sigma(Fobs))]^{-1}$ was used. The secondary isotropic extinction coefficient[20] refined to $g = 13010(454)$. A final difference Fourier map revealed a residual electron density between -0.32 and 0.38 e Å^{-3}. Scattering factors were taken from the International Tables for X-Ray Crystallography.[21] The anomalous scattering of P was taken into account.[22] All calculations were performed with XTAL3.7,[23] unless stated otherwise. The Flack parameter[24] converged to $Xabs = 0$, thus confirming the correct structure.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 225796 (**17**), No. CCDC 225797 (**18**), No. CCDC 225795 (**5d**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44–1223/336–033; E-mail: deposit@ccdc.cam.ac.uk]

General Procedure for Asymmetric Hydrogenation of Methyl Acetoacetate (21)

To a solution of **21** (0.92 mL, 8.52 mmol) in MeOH (8.5 mL) were added $[RuCl_2(C_6H_6)]_2$ (2.00 mg, 4.0 μmol) and ligand (8.5 μmol). After all the solids were dissolved, a 1 mL sample was transferred into a glass vial, placed in a stainless-steel autoclave and equipped with a stirring bean. The reaction was flushed with hydrogen gas (3×5 bar), pressurized to 100 bar and stirred at 70 °C for 2 h. The autoclave was cooled to room temperature, depressurized and opened. The resulting orange solution was filtered over silica (eluted with CH_2Cl_2) and concentrated under vacuum (at this stage the conversion was determined by ^{1}H NMR). To the crude mixture were added pyridine (3 mL) and benzoyl chloride (0.8 mL) and the solution was stirred at 70 °C for 17 h. After cooling to room temperature the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with aqueous 0.5 M $NaHSO_3$ (1×30 mL) and water (1×30 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (PE : CH_2Cl_2 = 1 : 8→1 : 25) afforded the benzoylated product, which was used to determine to enantiomeric excess by chiral HPLC [Daicel OB, heptane:*i*-PrOH = 9 : 1, 1.0 mL min^{-1}, UV 254 nm: $t_R = 8.56$ (*R*) and 10.6 min. (*S*)].

General Procedure for Asymmetric Hydrogenation of Dimethyl Itaconate (23)

A solution of $Rh(nbd)_2BF_4$ (3.0 mg, 8.02 μmol) and ligand (9.22 μmol) in CH_2Cl_2 (4 mL) was stirred for 30 min. After the itaconate (127 mg, 0.80 mmol) was added, a 1 mL sample was transferred into a glass vial, placed in a stainless-steel autoclave and equipped with a stirring bean. The autoclave was flushed with hydrogen gas (3×5 bar), before the reaction mixture was stirred at room temperature under hydrogen pressure (5 bar) for 15 h. The autoclave was depressurized and opened. The resulting solution was filtered over silica (eluted with CH_2Cl_2) and concentrated under vacuum. At this stage the conversion was determined by ^{1}H NMR and the enantiomeric excess of **24** was checked by chiral GC [Beta-Dex 325 (Supelco), gas flow settings: carrier gas helium 150 kPa, H_2 50 kPa, air 100 kPa, oven temperature program: 70 °C isotherm 40 min.; 30 °C/min up to 190 °C; isotherm 16 min., $t_R = \sim 33$ min. (*R*) and ~34 min. (*S*)].

Acknowledgements

Prof. P. W. N. M. van Leeuwen, Dr. P. C. J. Kamer, F. Ribaudo, B. H. G. Swennenhuis, G. C. Schoemaker, R. P. J. Bronger, and J. A. J. Geenevasen (University of Amsterdam) and A. van den Hoogenband (Solvay Pharmaceuticals, Weesp, The Netherlands) are kindly acknowledged for their support. We thank the National Research School Combination Catalysis (NRSC-C) for financial support.

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