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Tetrahedron 61 (2005) 6186–6192
Tetrahedron

Enantioselective synthesis of β-amino alcohols and α-amino acids via a copper catalyzed addition of diorganozinc reagents to *N*-phosphinoylimines

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Received 8 November 2004; revised 4 February 2005; accepted 4 March 2005

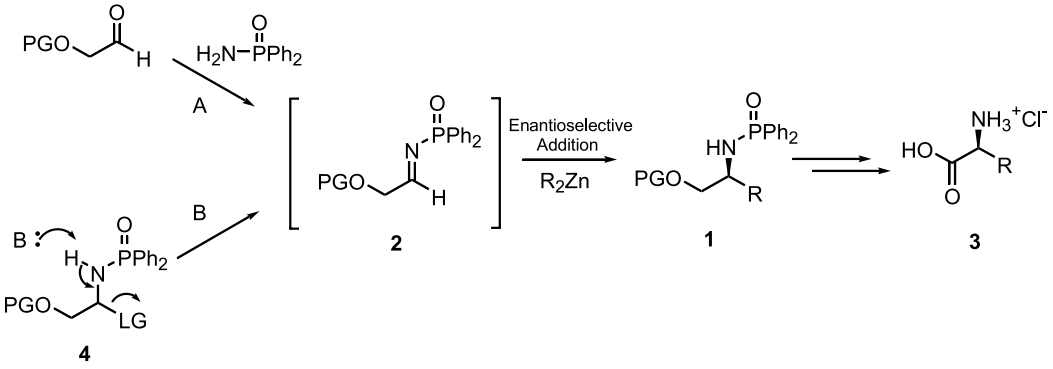
Available online 20 April 2005

Abstract—Enantioenriched β-amino alcohols were prepared via an asymmetric addition of diethylzinc, catalyzed by the BozPHOS·Cu(I) complex, on in situ formed *N*-phosphinoylimines. The nature of the hydroxyl protecting groups was found to affect the enantioselectivities. Subsequent deprotection and oxidation of *N*-phosphinoyl β-amino alcohols afforded optically active α-amino acids (97% ee).

1. Introduction

The synthesis of β-amino alcohols is of considerable current interest as they are important sub-units commonly found in natural products, biologically active molecules, ligands, and chiral auxiliaries, or simply used as building blocks.[1] β-Amino alcohols are also potential precursors for the synthesis of non-proteinogenic α-amino acids. Incorporation of these unnatural compounds into proteins can lead to conformational changes, non-scissile peptide mimics and biologically active molecules with novel properties.[2]

The method we chose to synthesize β-amino alcohols (**1**, Scheme 1) was a nucleophilic addition of diorganozinc reagents to *N*-phosphinoylalkylimines (**2**) substituted with a β-alkoxy functionality. Subsequent oxidation of the deprotected β-amino alcohol will afford α-amino acid (**3**). The *N*-diphenylphosphinoyl protecting group was used due to its facile cleavage under mildly acidic conditions with no racemization. Diastereoselective methodologies were developed to generate β-amino alcohols.[3] One powerful method for preparing β-amino alcohols was a one-pot catalytic enantioselective reaction developed by Hoveyda and Snapper.[4] Excellent ee values were obtained, but this procedure suffered from use of an excess of diorganozinc reagents and a *N*-aryl protecting group that can be cleaved only under oxidizing conditions.



Scheme 1. Strategy to generate *N*-phosphinoylalkylimines, β-amino alcohols and α-amino acids.

Keywords: β-Amino alcohols; α-Amino acids; Enantioselective synthesis; Imines; Copper; Diorganozinc reagents.
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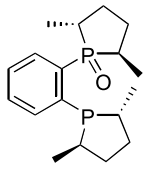
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.113

One drawback of using *N*-phosphinoylalkylimines with α-enolizable protons was the difficulty to isolate them due to their instability. Two strategies were used to solve this problem. The first one (path A) was a one-pot procedure involving generation of the imine from an in situ condensation of the aldehyde and the amide, using the diorganozinc reagent as a dehydrating agent. This approach led to excellent ee values but low conversions. The second (path B), was an in situ formation of the imine from a stable precursor **4** containing a leaving group (–OMe,[5] $-SO_2Ph$,[6] benzotriazoyl,[7] –OTMS,[8] or succinimyl[9]) on the α-position of the *N*-protected amine.

Recently, we reported an efficient methodology to generate the *N*-phosphinoylalkylimines in situ, from sulfinic acid (LG=$-SO_2Tol$) adducts, which was compatible with the BozPHOS (**5**)·Cu asymmetric catalyzed addition of diorganozinc reagents (Fig. 1).[10,11] Because it afforded excellent yields and ee values, we planned to use this strategy (path B) to generate optically active β-amino alcohols (**1**) and α-amino acids (**3**).



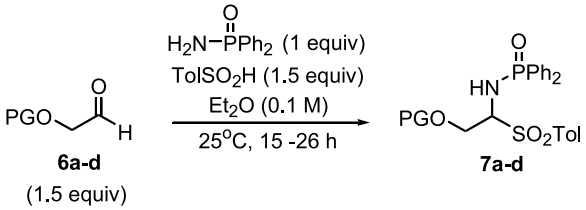
5
(*R*,*R*)-BozPHOS

Figure 1. Structure of (*R*,*R*)-BozPHOS, ((*R*,*R*)-MeDuPHOS monoxide).

2. Results and discussion

We initially identified which hydroxyl protecting group (PG) was the most suitable for the BozPHOS·Cu catalyzed asymmetric addition. Thus, sulfinic acid adducts **7** were prepared with several hydroxyl protecting groups (PG) by mixing the aldehyde **6**, diphenylphosphinic amide and *p*-toluenesulfinic acid in diethyl ether. The benzyl protected substrate **7a** was produced in the highest yield of 97% (Table 1, entry 1). It was found that strictly anhydrous conditions were mandatory to generate the adduct **7b** bearing the trityl moiety. Otherwise, acidic traces of water deprotected the α-trityloxyacetaldehyde **6b** and no desired product precipitated from the reaction mixture. The synthesis of the sulfinic acid adduct **7d** was problematic because it did not lead to any precipitation of the desired product. Consequently, the latter needed to be purified from the crude mixture by flash chromatography and it decomposed upon isolation.

Table 1. One-pot synthesis of sulfinic acid adducts **7**



6a-d
(1.5 equiv)

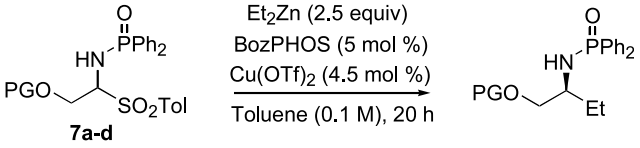
7a-d

Entry	PG	Product	Time (h)	Yield (%)
1	Bn	**7a**	20	97
2[a]	Tr	**7b**	15	70
3	Piv	**7c**	26	54
4	TBDMS	**7d**	15	38[b]

[a] Required strictly anhydrous conditions.
[b] Determined after flash chromatography.

With these compounds **7** in hand, we studied the effect of protecting groups (PG) on the level of enantiocontrol in the Cu-catalyzed diethylzinc addition (Table 2). The sulfinic acid adducts **7** were submitted to the optimized reaction conditions recently developed.[11] As the data summarized in Table 2 illustrate, the BozPHOS·Cu catalyzed addition of diethylzinc was strongly affected by the protecting group. It was found that the bulky trityl group **8b** (entries 4–7) provided best isolated yields (81–92%) and best ee values (75–97%).

Table 2. Enantioselective addition of diethylzinc to sulfinic acid adducts **7**



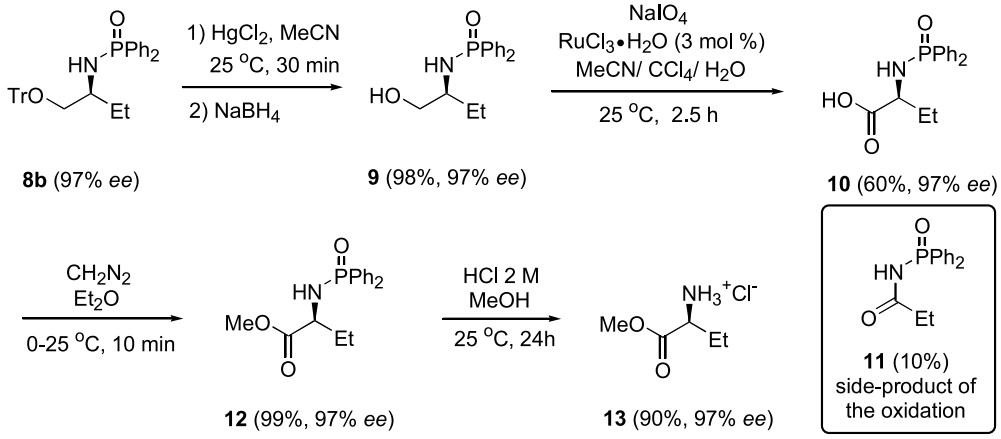
7a-d

Entry	PG	Product	Temperature (°C)	Yield (%)	ee[a] (%)
1[b]	Bn	**8a**	−20	95	84
2			−40	96	86
3			−60	83	89
4	Tr	**8b**	0	92	93
5			−40	81	95
6			−60	84	97
7			−78	89	75
8	Piv	**8c**	10	49	79
9			0	51	92
10			−20	69	87
11	TBDMS	**8d**	0	79	75[c]
12			−60	67	79[c]

[a] Enantiomeric excesses were determined by HPLC on a chiral stationary phase unless otherwise stated.
[b] Results determined after 48 h.
[c] Enantiomeric excesses were determined by SFC on a chiral stationary phase.

The temperature was another parameter that considerably affected the enantiomeric excesses. The most striking example was a 13% ee difference for a variation of 10 °C with the pivaloyl adduct **8c** (entries 8 and 9). In addition, a temperature of −60 °C was required to reach 97% ee with substrate **8b**. Finally, we changed the sulfinate leaving group by a benzotriazoyl substituent (**4**, LG=Bt). Comparable ee values were obtained but, owing to its low solubility, modest yields were obtained.

Removal of both the trityl and the *N*-diphenylphosphinoyl groups from **8b** was possible using HCl/MeOH, affording the free β-amino alcohol in quantitative yield (Scheme 2). However, our goal was to develop reaction conditions to access monoprotected α-amino acids **10** and **13**, which could be more useful in peptidic synthesis. Several conditions were screened for selective trityl deprotection (hydrogenolysis,[12] $ZnBr_2$,[13] BCl_3,[14] BBr_3, BBr_3·DMS, TFA,[15] TFA and TFAA followed by Et_3N[16] and acetyl chloride[17]) but the best procedure was a reductive

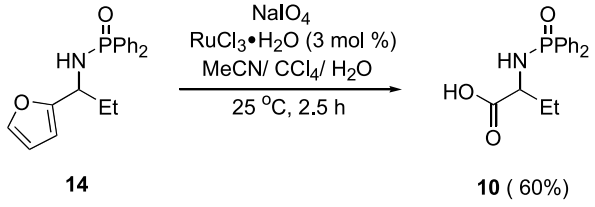


Scheme 2. Synthesis of α-amino acids from **8b**.

demercuration reported by Maltese.[18] A 10-fold excess of $HgCl_2$ was required to afford the β-amino alcohol **9** in 98% yield and 97% ee.

The next challenge was the oxidation of the β-amino alcohol **9** (Scheme 2). The complexity of this step resided in the presence of the protic acid sensitive *N*-phosphinoyl group and the possibility of the chiral center to racemize. Unsuccessful procedures tried included TEMPO free radical with sodium chlorite[19] or with trichloroisocyanuric acid,[20] IBX and 2-hydroxypyridine[21] or PDC[22] and all afforded total or partial degradation of the starting material or of the desired amino acid. The most successful procedure was the Sharpless oxidation[23] with $RuCl_3$ and $NaIO_4$ which generated the α-amino acid **10** in 60% yield without erosion in enantiomeric purity and 10% of the side-product **11** caused by over oxidation. Subsequent esterification with diazomethane and straightforward deprotection of the *N*-phosphinoyl group in mildly acidic conditions afforded the enantioenriched (97% ee) methyl ester hydrochloride derivative **13** of ethylglycine in 89% yield over two steps.

An alternative approach toward α-amino acids was to start from the addition product **14** of the *N*-phosphinoylimine derived from 2-furaldehyde (Scheme 3).[24] The enantioselective synthesis of the latter substrate from the BozPHOS·Cu catalyzed addition of diorganozinc reagents was reported by our research group.[10] By treating compound **14** with the same oxidation conditions mentioned above (Scheme 2), a similar yield of the α-amino acid **10** was obtained.



Scheme 3. Oxidative cleavage of the *N*-phosphinoylimine **14** derived from 2-furaldehyde.

3. Conclusion

In summary, based on the BozPHOS·Cu catalyzed addition of diorganozinc reagents, we have developed a practical procedure for the synthesis of enantioenriched (97% ee) β-amino alcohols.

The latter was an excellent framework for the catalytic enantioselective synthesis of optically active α-amino acids from a nucleophilic addition on imines. This method allowed generation of both enantiomers of α-amino acids, since both enantiomers of the BozPHOS ligand can be prepared, from the two commercially available enantiomers of Me-DuPHOS. We have also previously reported that the reaction was compatible with different dialkylzinc (Me_2Zn, *n*-Bu_2Zn and *i*-Pr_2Zn) or functionalized reagents.[10]

4. Experimental

4.1. General

All non-aqueous reactions were run under an inert atmosphere (argon) with rigid exclusion of moisture from reagents and glassware by using standard techniques for manipulating air-sensitive compounds. All glassware was stored in the oven and/or was flame-dried before use under an inert atmosphere of gas. Anhydrous solvents were obtained either by filtration through drying columns (ether, toluene, acetonitrile, dichloromethane) on a Glass-Contour system (Irvine, CA) or by distillation over sodium/benzophenone (toluene). Analytical TLC was performed on precoated, glass-backed silica gel (Merck 60 F_{254}). Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, ninhydrine, *p*-anisaldehyde or aqueous potassium permanganate. Flash column chromatography was performed by using 230–400 mesh silica [EM Science or Silicycle (Québec City, QC, Canada)] of the indicated solvent system according to standard technique. Melting points were obtained on a Buchi (Flawil, Switzerland) melting point apparatus and are uncorrected. NMR spectra (^1H, ^{13}C, ^{31}P) were recorded on Bruker AV 300, AMX 300, AV 400 or ARX 400 spectrometers.

Chemical shifts for ^{1}H NMR spectra are recorded in ppm with the solvent resonance as the internal standard ($CDCl_3$, δ 7.27 ppm, DMSO-d_6, δ 2.50 ppm or D_2O δ 4.80 ppm). Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; sept, septet; oc, octet; m, multiplet; br, broad), coupling constant in Hz, and integration. Chemical shifts for ^{13}C NMR spectra are recorded in ppm from tetramethylsilane by using the central peak of deuterochloroform (77.00 ppm) or deuterated DMSO (39.52 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. Infrared spectra were taken on a Perkin–Elmer Spectrum One FTIR and are reported in reciprocal centimeters (cm^{-1}). Optical rotations were determined with a Perkin–Elmer 341 polarimeter at 589 or 546 nm. Data are reported as follows: $[\alpha]_D^{temp}$, concentration (c in g/100 mL) and solvent. Combustion analyses were performed by the Elemental analysis Laboratory of the Université de Montréal.

Analytical HPLC was performed on a Hewlett–Packard analytical instrument (model 1100) equipped with a diode array UV detector. Data for determination of the enantiomeric excess are reported as follows: column type, eluent, flow rate, and retention time (t_r). Analytical Supercritical Fluid Chromatography was performed on a Berger SFC Analytical Instrument equipped with a diode array UV detector. Data are reported as follows: column type, eluent, flow rate: retention time (t_r). Analytical gas chromatography was carried out on a Hewlett–Packard 5880A gas chromatograph equipped with a splitless mode capillary injector and a flame ionization dectector. Unless otherwise noted, the injector and detector temperatures were set to 250 °C and hydrogen was used as the carrier gas (63 psi). Data are reported as follows: column type, column length, initial temperature, initial time, rate, final temperature, final time: retention time (t_r).

$Cu(OTf)_2$ and $RuCl_3 \cdot H_2O$ were purchased from Strem Chemicals (Newburyport, MA). Diazomethane was prepared from Diazald®. *p*-Toluenesulfinic acid was formed by dissolving its hydrated sodium salt in a minimum of hot 10% vol/vol HCl (the resulting pH must be lower than 3) and crystallization at 4 °C. Further filtration and drying under vacuum led to white crystals. Diethylzinc was purchased neat from Akzo Nobel and used without purification. All others starting materials were purchased from Aldrich or Alfa Aesar (Ward Hill, MA). Unless otherwise stated, commercial reagents were used without purification. Racemic samples for HPLC analysis were prepared by addition of Et_2Zn/CuCN in toluene to the sulfinic acid adducts. Ligand (*R*,*R*)-BozPHOS was prepared according to literature procedure.[10]

4.2. General procedure for preparation of sulfinic acid adducts 7

A round-bottomed flask equipped with a magnetic stirring bar, was charged with *P*,*P*-diphenylphosphinic amide (1.43 g, 6.6 mmol, 1 equiv). Diethyl ether (70 mL, ~0.1 M) was then added to the flask. The resulting suspension was stirred for 5 min and the aldehyde **6** (10 mmol, 1.5 equiv) was added, then *p*-toluenesulfinic acid (1.56 g, 10 mmol, 1.5 equiv) was added in one portion at room temperature. The reaction mixture was allowed to stir (200 rpm) under closed atmosphere for a specific period of time, during which a white precipitate was slowly formed. The mixture was filtered through a sintered glass funnel and the white solid was washed with diethyl ether and dried under vacuum to afford the sulfinic acid adduct **7**.

4.2.1. *N*-{2-(Benzyloxy)-1-[(4-methylphenyl)sulfonyl]-ethyl}-*P*,*P*-diphenylphosphinic amide (7a). The general procedure was followed (specific conditions: 20 h). The crude compound (white powder) was used without purification for the next step. Yield: 97%. Mp 125.0–126.0 °C (dec); R_f 0.45 (100% EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H), 3.80 (dd, J=10.4, 7.5 Hz, 1H), 3.87 (dd, J=10.4, 3.5 Hz, 1H), 4.38 (d, J=11.7 Hz, 1H), 4.44 (d, J=11.8 Hz, 1H), 4 .78 (m, 1H), 6.49 (t, J=11.7 Hz, 1H), 7.11–7.65 (m, 19H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.2, 67.9, 71.6, 72.3, 127.6, 127.7, 128.1 (d, J_{C-P}=13.0 Hz), 128.2 (d, J_{C-P}=13.2 Hz), 128.2, 129.1, 129.5, 131.2 (d, J_{C-P}=10.1 Hz), 131.4 (d, J_{C-P}=10.0 Hz), 131.6 (d, J_{C-P}=10.0 Hz), 131.6 (d, J_{C-P}=10.2 Hz), 132.3 (d, J_{C-P}=77.1 Hz), 134.0, 134.5 (d, J_{C-P}=73.3 Hz), 137.6, 144.4; ^{31}P NMR (121 MHz, DMSO-d_6) δ 25.3; IR (Neat) 3065, 2877, 1595, 1435, 1289, 1191, 1125, 1085, 865, 725, 692, 666, 583 cm^{-1}. LRMS (APCI) *m*/*z* calcd for $C_{21}H_{20}NO_2P$ $[M-SO_2Tol]^+$: 350.1 found: 350.1.

4.2.2. *N*-[1-[(4-Methylphenyl)sulfonyl]-2-(trityloxy)-ethyl]-*P*,*P*-diphenylphosphinic amide (7b). The general procedure was followed, except that reagents and glassware were dried, anhydrous ether was used and the reaction was run under inert atmosphere (specific conditions: 15 h). The crude compound (white powder) was used without purification for the next step. Yield: 70%. Mp 99.5–100.0 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H), 3.41 (dd, J=8.1, 6.8 Hz, 1H), 3.51 (dd, J=9.8, 4.1 Hz, 1H), 4.74–4.78 (m, 1H), 6.61 (dd, J=12.5, 12.3 Hz, 1H), 7.20–7.30 (m, 17H); 7.40–7.43 (m, 4H), 7.47–7.54 (m, 6H); 7.70 (dd, J=11.8, 7.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.2, 63.3, 73.2, 87.9, 128.0, 128.0, 128.9–129.1 (m), 129.2, 130.1 (d, J_{C-P}=8.2 Hz), 132.3 (dd, J_{C-P}=11.8, 11.4 Hz), 132.5 (d, J_{C-P}=9.5 Hz), 135.0, 135.0 (dd, J_{C-P}=125, 59 Hz), 144.0, 145.3; ^{31}P NMR (161 MHz, DMSO-d_6) δ 27.0; IR (Neat) 3058, 2879, 1314, 1299, 1185, 1154, 1125, 1062, 702, 689 cm^{-1}. Elemental analysis calcd for $C_{39}H_{34}NO_4PS$: C, 72.77; H, 5.32; N, 2.18; S, 4.98 found: C, 72.75; H, 5.55; N, 2.24; S, 4.97.

4.2.3. 2-[(Diphenylphosphoryl)amino]-2-[(4-methylphenyl)sulfonyl]ethyl pivalate (7c). The general procedure was followed (specific conditions: 26 h). The crude compound (white powder) was used without purification for the next step. Yield: 54%. Mp 134.0–135.0 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (s, 9H), 2.39 (s, 3H), 4.21 (dd, J=13.0, 7.5 Hz, 1H), 4.52 (dd, J=11.5, 4.3 Hz, 1H), 4.77–4.80 (m, 1H), 6.64 (dd, J=12.0, 11.8 Hz, 1H), 7.33 (d, J=7.9 Hz, 2H), 7.37–7.55 (m, 4H), 7.44–7.55 (m, 4H), 7.66–7.71 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.2, 27.6, 39.1, 62.9, 71.6, 129.2 (dd, J_{C-P}=27.0, 12.5 Hz), 130.4 (d, J_{C-P}=22.0 Hz), 132.1 (dd, J_{C-P}=19.9, 10.3 Hz), 132.6 (d, J_{C-P}=22.0 Hz), 134.4, 134.7 (dd, J_{C-P}=125.7, 42.7 Hz), 145.8, 178.2; ^{31}P NMR (161 MHz, DMSO-d_6) δ 26.7; IR (Neat) 3061, 2976,

2949, 1729, 1438, 1302, 1291, 1279, 1192, 1165, 1135, 1126, 972, 668 cm^{-1}. LRMS (APCI) *m/z* calcd for $C_{19}H_{22}NO_3P$ $[M-SO_2Tol]^+$: 344.1 found: 344.1.

4.2.4. *N*-{2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[(4-methylphenyl)sulfonyl]ethyl}-*P*,*P*-diphenylphosphinic amide (7d). The general procedure was followed, but the product did not precipitate (specific conditions: 15 h). The reaction mixture was evaporated under reduced pressure, and the crude mixture was purified by flash chromatography (70% EtOAC in hexanes). A white foam was obtained (Yield: 38%) and decomposed upon isolation, so it had to be used immediately for the next step. R_f 0.50 (100% EtOAc); ^1H NMR (400 MHz, DMSO-d_6) δ 0.05 (s, 6H), 0.77 (s, 9H), 2.36 (s, 3H), 3.96 (dd, $J=7.5$, 6.6 Hz, 1H), 4.15 (dd, $J=8.4$, 4.6 Hz, 1H), 4.53–4.62 (m, 1H), 6.36 (dd, $J=11.9$, 11.8 Hz, 1H), 7.29 (d, $J=8.0$ Hz, 2H), 7.35–7.45 (m, 4H), 7.48–7.53 (m, 4H), 7.62 (d, $J=8.0$ Hz, 2H), 7.71 (dd, $J=12.1$, 7.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ −4.6, 18.9, 21.9, 26.8, 62.7, 74.8, 125.5, 129.1 (dd, $J_{C-P}=17.2$, 12.7 Hz), 130.2 (d, $J_{C-P}=45.9$ Hz), 132.2–132.6 (m), 132.5, 134.8 (dd, $J_{C-P}=148.0$, 24.3 Hz), 145.3; ^{31}P NMR (161 MHz, DMSO-d_6) δ 26.6.

4.3. General procedure for the asymmetric addition on sulfinic acid adducts 7

A flame-dried round-bottomed flask equipped with a magnetic stirring bar was charged with $Cu(OTf)_2$ (6.5 mg, 0.018 mmol, 4.5 mol%) and (*R*,*R*)-BozPHOS (6.4 mg, 0.02 mmol, 5 mol %) under argon. Anhydrous toluene (1.5 mL) was added to the flask at room temperature via a syringe. The resulting dark green heterogeneous solution was stirred for 1 h at room temperature and neat diethylzinc (102 μL, 1 mmol, 2.5 equiv) was added at room temperature under argon via a gas-tight syringe (*Caution*: pyrophoric). The resulting dark brown suspension was stirred for 20 min at room temperature. The mixture was cooled to the temperature described in Table 2 and stirred 10 min at that temperature. Substrate **7** (0.4 mmol, 1 equiv) in anhydrous toluene (1.5 mL) was added via a teflon cannula (heterogeneous mixture) under argon. The flask was rinsed with 1 mL, and 0.5 mL of toluene. The reaction mixture was allowed to stir 20 h at the temperature mentioned above under argon. Aqueous saturated ammonium chloride (5 mL) was then added dropwise. The mixture was brought to room temperature and poured into a separatory funnel containing aqueous saturated ammonium chloride (20 mL). The biphasic mixture was extracted with dichloromethane (3× 20 mL). The combined extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography with ethyl acetate 100% to afford compound **8**.

4.3.1. *N*-{1-[(Benzyloxy)methyl]propyl}-*P*,*P*-diphenylphosphinic amide (8a). The general procedure was followed, except that the reaction was run 48 h (specific conditions: −60 °C) to afford **8a** as a white solid. Yield 83%, enantiomeric excess (89% ee) was determined by HPLC analysis (Chiralpak AD-H, 80:20 hexanes–*i*-PrOH, 1.0 mL/min: (*S*)-**8a** $t_r=9.52$ min, (*R*)-**8a** $t_r=11.83$ min). $[\alpha]_D^{21}=-32.2$ (*c* 1.30, CH_2Cl_2); mp 89.0–91.0 °C; R_f 0.20 (100% EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J=$ 7.4 Hz, 3H), 1.69 (oc, $J=7.0$ Hz, 2H), 3.05–3.20 (m, 1H), 3.27 (dd, $J=10.4$, 7.0 Hz, 1H), 3.57 (d, $J=3.8$ Hz, 2H), 4.47 (d, $J=12.0$ Hz, 1H), 4.52 (d, $J=12.0$ Hz, 1H), 7.20–7.30 (m, 5H), 7.30–7.50 (m, 6H), 7.84–7.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 15.2, 27.0 (d, $J_{C-P}=$ 6.2 Hz), 52.5, 72.6 (d, $J_{C-P}=4.1$ Hz), 73.1, 127.5, 127.6, 128.2, 128.4, 131.6 (d, $J_{C-P}=2.3$ Hz), 132.0 (d, $J_{C-P}=$ 7.0 Hz), 132.1 (d, $J_{C-P}=7.0$ Hz), 133.7 (d, $J_{C-P}=10.1$ Hz), 138.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.5; IR (Neat) 3058, 2841, 1435, 1183, 1108, 1049, 998, 721, 691, 573 cm^{-1}. LRMS (ACPI) *m/z* calcd for $C_{23}H_{26}NO_2P$ $[M+H]^+$: 380.1 found: 380.1. Elemental analysis calcd for $C_{23}H_{26}NO_2P$: C, 72.81; H, 6.91; N, 3.69 found: C, 72.71; H, 7.13; N, 3.72.

4.3.2. *P*,*P*-Diphenyl-*N*-{1-[(trityloxy)methyl]propyl}-phosphinic amide (8b). The general procedure was followed (specific conditions: −60 °C) to afford **8b** as a white solid. Yield 84%, enantiomeric excess (97% ee) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexanes–*i*-PrOH, 1.0 mL/min: (*S*)-**8b** $t_r=10.8$ min, (*R*)-**8b** $t_r=13.6$ min). $[\alpha]_D^{20}=-8.1$ (*c* 1.00, CH_2Cl_2); mp 67.5–68.5 °C; R_f 0.35 (70% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, $J=7.4$ Hz, 3H), 1.86 (dqn, $J=34.5$, 7.4 Hz, 2H), 3.08–3.16 (m, 1H), 3.21–3.33 (m, 2H), 3.28 (dd, $J=3.7$, 3.7 Hz, 1H), 7.25–7.51 (m, 21H), 7.79–7.93 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 28.1, 53.4, 65.7, 86.8, 127.5, 128.3, 128.9 (d, $J_{C-P}=12$, 5 Hz), 129.1, 132.1 (dd, $J_{C-P}=8.8$, 2.5 Hz), 132.6 (dd, $J_{C-P}=33.6$, 9.4 Hz), 133.4 (d, $J_{C-P}=71.9$ Hz), 144.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.5; IR (Neat) 3056, 2928, 1437, 1189, 1089, 1068, 1029, 722, 693 cm^{-1}. Elemental analysis calcd for $C_{35}H_{34}NO_2P$: C, 79.07; H, 6.45; N, 2.63 found: C, 78.90; H, 6.63; N, 2.77.

4.3.3. 2-[(Diphenylphosphoryl)amino]butyl pivalate (8c). The general procedure was followed (specific conditions: 0 °C) to afford **8c** as a white solid. Yield 51%, enantiomeric excess (92% ee) was determined by HPLC analysis (Chiralpak AD-H, 80:20 hexanes–i-PrOH, 1.0 mL/min: (*R*)-**8c** $t_r=6.6$ min, (*S*)-**8c** $t_r=7.8$ min). $[\alpha]_D^{21}=-23.3$ (*c* 0.63, CH_2Cl_2); mp 95.5–96.5 °C; R_f 0.18 (70% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, $J=7.4$ Hz, 3H), 1.19 (s, 9H), 1.61–1.66 (m, 2H), 3.01 (dd, $J=10.9$, 6.4 Hz, 1H), 3.20–3.30 (m, 1H), 4.13 (d, $J=3.0$ Hz, 1H), 4.14 (d, $J=2.6$ Hz, 1H), 7.42–7.48 (m, 6H), 7.88–7.91 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 26.9, 27.0, 38.7, 51.6, 66.5, 128.4 (dd, $J_{C-P}=12.5$, 6.4 Hz), 131.7, 131.9 (dd, $J_{C-P}=9.4$, 2.8 Hz), 133.1 (d, $J_{C-P}=21.1$ Hz), 178.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.5; IR (Neat) 2966, 2933, 2873, 1725, 1437, 1282, 1182, 1159, 1121, 1108, 722, 693 cm^{-1}; LRMS (APCI) *m/z* calcd for $C_{21}H_{28}NO_3P$ $[M+H]^+$: 374.2 found: 374.2. Elemental analysis calcd for $C_{21}H_{28}NO_3P$: C, 67.54; H, 7.56; N, 3.75 found: C, 67.24; H, 7.87; N, 3.82.

4.3.4. *N*-[1-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)propyl]-*P*,*P*-diphenylphosphinic amide (8d). The general procedure was followed (specific conditions: −60 °C) to afford **8d** as a colorless oil. Yield 67%, enantiomeric excess (79% ee) was determined by SFC analysis (Chiralpak AD, 10% MeOH, 1.5 mL/min: (*S*)-**8d** $t_r=16.1$ min, (*R*)-**8d** $t_r=$ 18.9 min). $[\alpha]_D^{22}=-20.0$ (*c* 1.40, CH_2Cl_2); R_f 0.42 (100% EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (d, $J=7.7$ Hz,

6H), 0.86 (s, 9H), 1.54–1.71 (m, 2H), 2.97–3.07 (m, 1H), 3.20 (dd, $J=10.5$, 7.1 Hz, 1H), 3.67 (d, $J=4.1$ Hz, 2H), 7.42–7.47 (m, 6H), 7.87–7.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, 10.3, 18.1, 25.7, 26.4, 53.7, 65.2, 128.2 (dd, $J_{C-P}=12.5$, 4.7 Hz), 131.5, 131.9 (dd, $J_{C-P}=20.3$, 9.4 Hz), 133.1 (dd, $J_{C-P}=129.1$, 11.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.6; IR (Neat) 2954, 2928, 2856, 1438, 1253, 1190, 1106, 835, 723, 697, 630 cm^{-1}; LRMS (APCI) *m/z* calcd for $C_{22}H_{34}NO_2PSi$ $[M+H]^+$: 404.2 found: 404.2.

4.3.5. *N*-[1-(Hydroxymethyl)propyl]-*P*,*P*-diphenylphosphinic amide (9). A flame-dried round-bottomed flask equipped with a magnetic stirring bar was charged with compound **8b** (270 mg, 0.50 mmol, 1 equiv) and $HgCl_2$ (1.37 g, 5.07 mmol, 10 equiv) under argon. Anhydrous MeCN (25 mL, 0.02 M) was added to the flask. The colorless solution was stirred for 30 min at room temperature under argon. Small solid portions of $NaBH_4$ were added to the stirred solution and a dark grey precipitate was formed (gas formation). Additions of $NaBH_4$ were stopped when the precipitate formed 3/4 of the solution and no gas was formed. The mixture was stirred 5 min at room temperature, then was brought to 0 °C. Small portions of H_2O (total of 100 mL) were added (gas formation). The mixture was warmed to room temperature and stirred 25 min. The mixture was extracted with DCM (3×80 mL). The combined extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography with 100% DCM to remove the trityl moiety, then with 5% MeOH in DCM to afford 145 mg of the title compound as a white solid (98% yield). Enantiomeric excess (97% ee) was determined by SFC analysis (Chiralpak AD, 15% MeOH, 1.5 mL/min: (*S*)-**9** $t_r=29.3$ min, (*R*)-**9** $t_r=32.1$ min). $[\alpha]_D^{20}=-39.3$ (*c* 1.00, CH_2Cl_2); mp 139.5–141.0 °C; R_f 0.34 (10% MeOH in DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, $J=7.4$ Hz, 3H), 1.44–1.59 (m, 2H), 2.90–3.10 (m, 2H), 3.46 (dd, $J=11.6$, 6.7 Hz, 1H), 3.65 (d, $J=11.2$ Hz, 1H), 4.55–4.60 (br s, 1H), 7.44–7.54 (m, 6H), 7.54–7.97 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 26.9, 57.5, 67.7, 129.0 (d, $J_{C-P}=12.3$ Hz), 132.0 (dd, $J_{C-P}=130.9$, 118.5 Hz), 132.6 (dd, $J_{C-P}=74.1$, 9.4 Hz), 132.5 (dd, $J_{C-P}=9.7$, 2.7 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.4; IR (Neat) 3253, 2961, 2913, 2871, 1436, 1169, 1142, 1112, 1092, 995, 723, 694 cm^{-1}; LRMS (APCI) *m/z* calcd for $C_{16}H_{20}NO_2P$ $[M+H]^+$: 290.1 found: 290.1.

4.3.6. 2-[(Diphenylphosphoryl)amino]butanoic acid (10). A round-bottomed flask equipped with a magnetic stirring bar was charged with compound **9** (170 mg, 0.5876 mmol, 1 equiv). The amino alcohol was dissolved in a 2:2:3 mixture of MeCN (3.6 mL), CCl_4 (3.6 mL) and H_2O (4.8 mL). Solid $NaIO_4$ (502 mg, 2.35 mmol, 4 equiv), then $RuCl_3\cdot H_2O$ (4 mg, 0.017 mmol, 0.03 equiv) were added in one portion to the reaction mixture. The dark brown mixture was vigorously stirred for 2.5 h at room temperature. The mixture was diluted with DCM (20 mL) and washed with H_2O (20 mL). The aqueous layer was extracted twice with DCM (2×20 mL). The crude product was dissolved in EtOAc (15 mL) and extracted with $NaHCO_3$ sat. (3× 40 mL). Combined basic extracts were acidified (pH 1–2) with HCl 10% v/v and extracted quickly with DCM (3× 80 mL). Combined extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford 106 mg of the title compound as a white solid (60% yield). The crude compound was used without purification for the next step. Analytically pure product can be obtained by flash chromatography with 1% AcOH in EtOAc. Enantiomeric excess (97% ee) was determined by SFC analysis (Chiralpak AD, 20% MeOH, 1.5 mL/min: (*S*)-**10** $t_r=36.9$ min, (*R*)-**10** $t_r=41.3$ min). $[\alpha]_D^{20}=-49.5$ (*c* 1.00, CH_2Cl_2); mp 130.0–131.0 °C; R_f 0.47 (1% AcOH in EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, $J=7.3$ Hz, 3H), 1.77 (qn, $J=7.2$ Hz, 2H), 3.73 (dq, $J=21.5$, 5.0 Hz, 1H), 3.91 (dd, $J=10.7$, 3.9 Hz, 1H), 7.43–7.56 (m, 6H), 7.90–7.97 (m, 4H), 12.57–12.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 27.4, 54.3, 130.6 (dd, $J_{C-P}=133.1$, 107.1 Hz), 131.9 (dd, $J_{C-P}=79.1$, 9.8 Hz), 132.1 (dd, $J_{C-P}=3.1$, 3.1 Hz), 174.4; ^{31}P NMR (161 MHz, $CDCl_3$) δ 26.6; IR (Neat) 2877, 2458, 1714, 1438, 1123, 1106, 891, 724, 692 cm^{-1}. Elemental analysis calcd for $C_{16}H_{18}NO_3P$: C, 63.36; H, 5.98; N, 4.62 found: C, 63.50; H, 6.15; N, 4.67.

4.3.7. Methyl 2-[(diphenylphosphoryl)amino]butanoate (12). A flame-dried round-bottomed flask equipped with a magnetic stirring bar was charged with the amino acid **10** (89 mg, 0.2934 mmol, 1 equiv) under argon. Anhydrous DCM (5 mL) was added via a syringe and the colorless solution was cooled to 0 °C. Excess of diazomethane in Et_2O was added at 0 °C under argon until the yellow color persisted. The resulting yellow solution was stirred 5 min under argon at 0 °C and 5 min at room temperature. The solution was evaporated under reduced pressure to afford 93 mg of the title compound as a white solid (99% yield). The crude compound was used without purification for the next step. Analytically pure product can be obtained by flash chromatography with 70–100% EtOAc in hexanes. Enantiomeric excess (97% ee) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexanes–*i*-PrOH, 1.0 mL/min: (*R*)-**12** $t_r=14.3$ min, (*S*)-**12** $t_r=24.5$ min). $[\alpha]_D^{22}=-16.8$ (*c* 1.00, CH_2Cl_2); mp 91.0–92.0 °C; R_f 0.30 (100% EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, $J=7.4$ Hz, 3H), 1.77 (sept, $J=1.0$ Hz, 2H), 3.62–2.67 (m, 1H), 3.68 (s, 3H), 3.77–3.86 (m, 1H), 7.41–7.47 (m, 6H), 7.49–7.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 28.1, 52.0, 54.3, 128.3 (dd, $J_{C-P}=12.6$, 5.6 Hz), 131.8, 131.8 (dd, $J_{C-P}=127.6$, 55.6 Hz), 131.9 (dd, $J_{C-P}=20.9$, 9.7 Hz), 173.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 23.4; IR (Neat) 3110, 2936, 2877, 1732, 1436, 1197, 1184, 1106, 903, 721, 691 cm^{-1}. Elemental analysis calcd for $C_{17}H_{20}NO_3P$: C, 64.35; H, 6.35; N, 4.41 found: C, 64.01; H, 6.45; N, 4.39.

4.3.8. Methyl 2-aminobutanoate hydrochloride (13). A round-bottomed flask equipped with a magnetic stirring bar was charged with substrate **12** (67 mg, 0.211 mmol, 1 equiv). A mixture of methanol (1.7 mL) and aqueous concentrated HCl (0.38 mL) was added to the flask. The resulting bright clear yellow solution was allowed to stir at room temperature under closed atmosphere for 24 h. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in aqueous HCl 10% v/v (4 mL). The precipitate (diphenylphosphinic acid) was removed by filtration on a sintered glass funnel. The acidic filtrate was extracted with diethyl ether (3×10 mL), the acidic layer was then evaporated under reduced pressure or

lyophilized to afford 29 mg of the title compound as an off-white solid (90% yield). Analytically pure product can be obtained by triturating in Et_2O, then in EtOAc or by flash chromatography with 10% DCM in MeOH. Enantiomeric excess (97% ee) was determined by GC analysis (Cyclodex β, 30 m, 30 °C, 0 min, 5 °C/min, 220 °C, 5 min: (*R*)-**13** t_r= 12.8 min, (*S*)-**13** t_r=13.0 min). The absolute configuration *S* of **13** was determined by comparison of the optical rotation with that of the literature data. [lit.[25] $[\alpha]_D^{20}=+14.1$ (*c* 1.00, 95% AcOH)]. $[\alpha]_D^{20}=+13.4$ (*c* 0.32, 95% AcOH); R_f 0.42 (20% MeOH in DCM); The physical and spectroscopic properties were in accordance with those described in the literature.[25]

Acknowledgements

This work was supported by NSERC, Merck Frosst Canada, Boehringer Ingelheim (Canada), and the Université de Montréal. J. N. D. is grateful to NSERC (ES M), F.Q.R.N.T. (B1) and to the Université de Montréal for graduate fellowships. A. C. is grateful to NSERC (ES D) for graduate fellowship.

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