Asymmetric synthesis of *trans*-disubstituted cyclopropanes using phosphine oxides and phosphine boranes†

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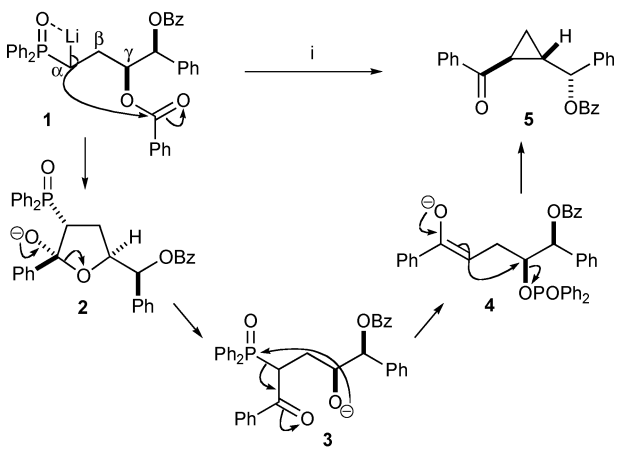
The stereocontrolled synthesis of *trans*-disubstituted cyclopropylketones has been achieved from β-alkyl, γ-benzoyl phosphine oxides *via* a three-step cascade reaction incorporating an acyl transfer, phosphinoyl transfer and cyclisation to form the cyclopropane. Using Evans' chiral oxazolidinone auxiliary and by masking the phosphine oxide moiety as a phosphine borane we have extended the method to the synthesis of enantiomerically-enriched *trans*-disubstituted cyclopropyl ketones.

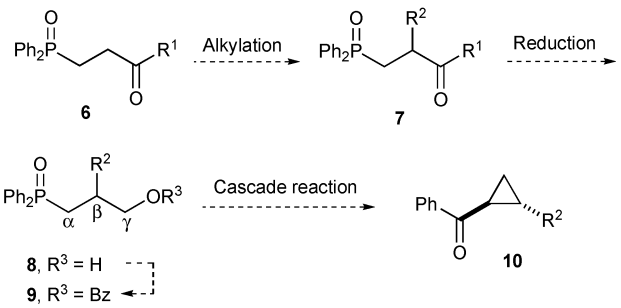
The rigidity of the cyclopropane ring makes it an appealing structural motif for the preparation of molecules with defined orientation of pendant functional groups whilst maintaining the hydrophobic character of linear alkyl chains. The stereocontrolled synthesis of cyclopropanes has therefore been the centre of much research effort.[1] Cascade ring closing reactions involving phosphorus transfer, to generate both nucleophile and leaving group, have yielded cyclopropanes generally with high stereospecificity and selectivity. Phosphine oxides,[2–5] phosphonates,[6–8] and phosphonium salts[9] have been employed in this manner. Studies on diphenylphosphine oxide mediated cyclopropanation cascade reactions have shown that a variety of differentially substituted cyclopropanes can be produced with excellent stereocontrol (Scheme 1, eq. 1). We have achieved the synthesis of di- and trisubstituted cyclopropanes in this manner by including substituents at the α- and γ-positions[5,10] and also at the β- and γ-positions[11,12] of the cyclisation substrates. Recently, we reported the asymmetric synthesis of disubstituted *trans*-cyclopropyl ketones[3,13] and protected *trans*-cyclopropane amino acids[14] using γ-substituted cyclopropane precursors (Scheme 1, eq. 1).

However, to date the effect of β-substituents has been investigated only in the presence of γ-substituents.[11,12] In order to investigate the effect of substituents β to the phosphine oxide group on the stereoselectivity of the cyclopropanation step, it was necessary to find a method of introducing a substituent at this carbon whilst keeping the α- and γ-positions unsubstituted. 3-Diphenylphosphinoyl propionic acid derivatives **6** have a carbon backbone of the required length whilst having a group on the β-carbon capable of directing deprotonation and alkylation (**7**). Importantly, this could provide a route to enantiomerically-enriched cyclopropane precursors (**9**) based on a chiral auxiliary strategy (Scheme 1, eq. 2, R^1 = auxiliary). We now wish to report our results on the racemic synthesis of disubstituted *trans*-cyclopropanes

Eq. 1



Eq. 2



Scheme 1 (i) LDA, THF, −78 to 0 °C, 95% (>95% ee)[3] R^1 = OR or chiral auxiliary.

(**10**) utilising β-substituted phosphine oxides. Moreover, we have extended this methodology to the enantioselective synthesis of *trans*-cyclopropanes using phosphine boranes and a phenylalanine based oxazolidinone auxiliary developed by Evans and Gage.[15,16] We decided to study the cyclopropanation cascade reaction using the β-unsubstituted phosphine oxide **21** and three β-substituted phosphine oxides **22** to **24** (Scheme 2).

Diphenylmethyl phosphine oxide **11** was alkylated with *tert*-butyl bromoacetate to give phosphinoyl ester **12**. LHMDS in THF is known not to lithiate diphenyl alkyl phosphine oxides,[17] but does

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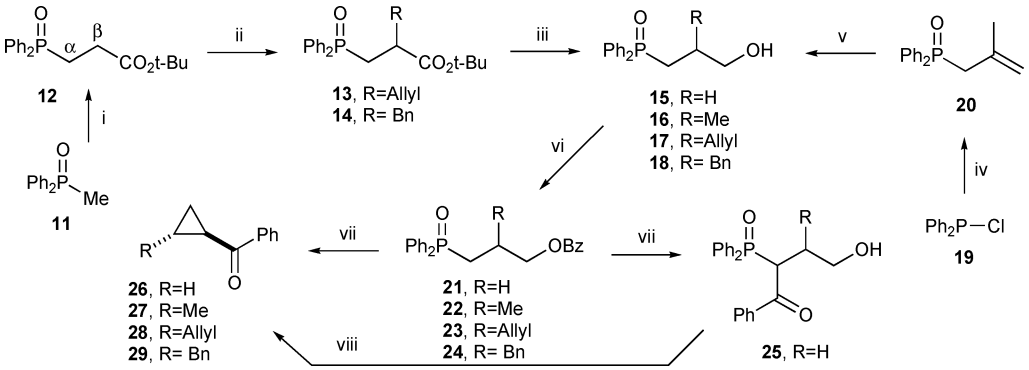
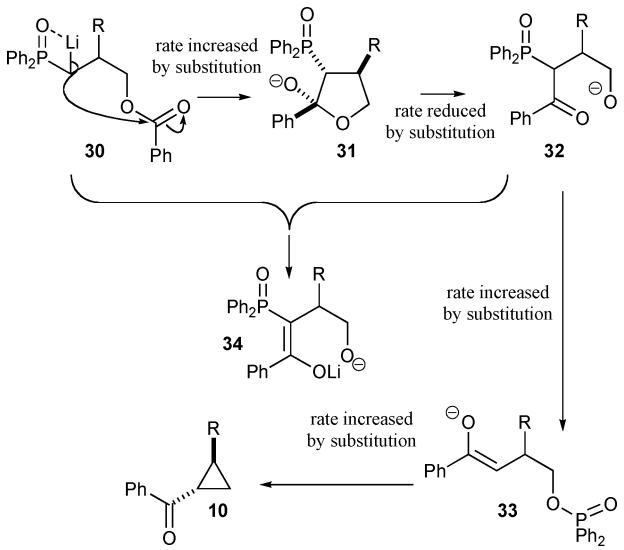
† Electronic supplementary information (ESI) available: experimental and analytical details for all compounds, and coordinates and energies of calculated structures. See DOI: 10.1039/b817433d



Scheme 2 (i) *n*-BuLi, *tert*-butyl bromoacetate, THF, −78 °C to room temperature, 40%; (ii) LHMDS, THF, −78 °C to room temperature, **13** 48%, **14** 64%; (iii) $LiAlH_4$, THF, **15** 77%, **17** 56%, **18** 94%; (iv) 2-methyl-propenol, pyridine, 0 °C to reflux, 28%; (v) BH_3, THF; H_2O_2, NaOH (aq), 68%; (vi) PhCOCl, Et_3N, DMAP, CH_2Cl_2, **21** 76%, **22** 91%, **23** 84%, **24** 42%; (vii) LDA, THF, −78 °C to room temperature, **25** 77%, **27** 54%, **28** 76%, **29** 99%; (viii) *t*-BuOK, *t*-BuOH, 35 °C, 87%.

enolize standard esters. This reactivity allowed for the selective alkylation of ester **12** adjacent to the carbonyl group giving derivatives **13** and **14**. Reduction of esters **12** to **14** with $LiAlH_4$ and benzoylation of the resulting alcohols gave the desired carboxylic esters **21**, **23** and **24**. In the case of the methyl substituted phosphine oxide **22** an alternative synthetic route was used starting from chlorodiphenylphosphine **19** and 2-methyl-propenol producing olefin **20** by an allylic Arbuzov rearrangement. Hydroboration of olefin **20** followed by benzoylation of the resulting alcohol **16** gave the required carboxylic ester **22**.

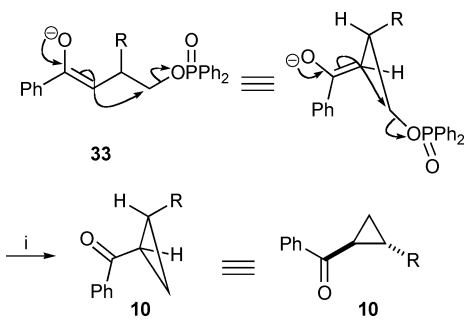
The four phosphine oxides were treated with the conditions that we have developed for the phosphine oxide mediated cyclopropanation cascade reaction.[3] The cyclopropanation results highlight the importance of substitution for driving the cascade reaction to completion: unlike the other substrates, unsubstituted **21** (Scheme 2) produces no cyclopropane under the standard reaction conditions but only acyl transfer product **25**. The Thorpe–Ingold effect suggests that increased substitution on the forming ring should encourage and stabilise ring closures (*e.g.* **30** to **31** and **32** to **33**) (Scheme 3). Lithiation and ring closure of all substrates occurs, but substitution at the β-position slows the ring opening of



Scheme 3

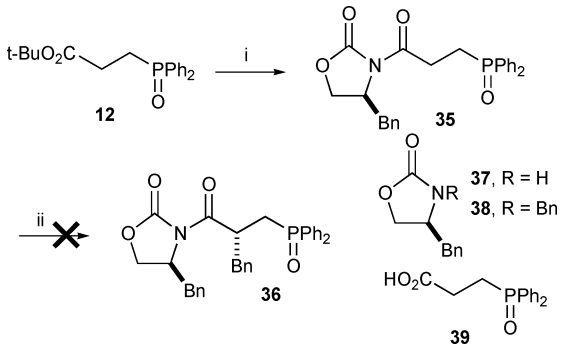
the tetrahedral intermediate **31** compared to its rate of formation. The alkoxy-keto-phosphine oxides **32** are significantly more acidic than the non-keto phosphine oxide starting materials and so it is likely that any ketone formed will be deprotonated by any open-chain lithiated starting material **30** producing an inactive enolate **34**, incapable of further phosphinoyl transfer. Backbone substitution should increase the rates of phosphinoyl transfer and cyclopropanation reactions due to stabilisation of their cyclic transition states. This is consistent with the increase in yield of cyclopropanes **27** to **29** as the size of the substituent increases. The acyl transfer product **25** could, however, be converted to the desired mono-substituted cyclopropane **26** upon treatment with *t*-BuOK in *t*-BuOH.

In every case, only *trans*-cyclopropane **10** was observed. Diastereoselectivity induced by the β-substituent is in accordance with the proposed transition state (Scheme 4) where steric interactions are minimised in enolate **33** if the substituent R can lie *trans* to the phenyl ketone during ring formation.



Scheme 4 (i) LDA, THF −78 °C to room temperature.

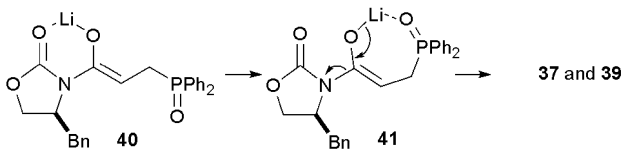
Having established that this approach is a viable route to *trans*-cyclopropanes, we decided to investigate if the method could be applied to the asymmetric synthesis of *trans*-cyclopropanes by performing the required β-alkylations using the Evans oxazolidinone auxiliary.[15,16] The required oxazolidinone **35** was easily prepared from phosphine oxide **12** in two steps by deprotection of the *tert*-butyl ester followed by coupling with the chiral auxiliary (Scheme 5). However, alkylation of oxazolidinone **35** with benzyl bromide using LHMDS in THF to give phosphine oxide **36** was



Scheme 5 (i) a. TFA, CH_2Cl_2, 99%; b. *t*-BuCOCl, Et_3N, THF, (*S*)-(−)-4-benzyl-2-oxazolidinone, *n*-BuLi, −78 °C to room temperature, 62%; (ii) LHMDS, THF, BnBr, 0%.

unsuccessful, producing only free auxiliary **37**, alkylated auxiliary **38** and carboxylic acid **39**.

Similar auxiliary alkylation products have been observed by both Seebach and Hintermann[18] and Davies *et al*.[19] Both proposed that the enolate fragments *via* a ketene decomposition pathway to generate a lithiated auxiliary and that this is then alkylated under the reaction conditions. Seebach and Hintermann improved benzylation yields using sodium and zinc enolates.[18] Attempted alkylations of phosphine oxide **35** using either a potassium base or by transmetallation with zinc, however, also failed suggesting that enolate reactivity was not the problem. Phosphine oxides are good Lewis bases and in the (*Z*)-enolate **40** (Scheme 6) the phosphine oxide lies on a flexible side chain *cis*- to the *exo*-oxygen and could possibly complex the lithium. If this coordination of the phosphine oxide to the lithium is competitive with that of the carbonyl of the auxiliary (**40**), then the lithium could be removed from its conventional chelation site (**41**) making the auxiliary a better leaving group than when coordinated in chelate **40**.



Scheme 6 Plausible mechanism for decomposition of enolate **40**.

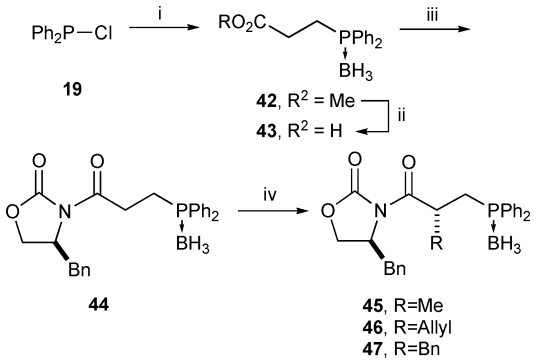
Successful alkylation of phosphine oxide **35** requires the 6-membered chelate **40** to be more stable relative to the 7-membered structure **41**. This could possibly be achieved by reducing the Lewis basicity of the phosphine oxide functionality. Phosphine boranes would not be expected to chelate lithium as well as the corresponding oxides. Moreover, phosphine boranes are easily deprotected with trialkylamines under mild conditions and reoxidised to the corresponding phosphine oxides.[20] Hence we decided to synthesise phosphine borane **44** (Scheme 7) as a protected form of the required phosphine oxide.

Phosphine borane **42** was synthesised *via* reduction[21] of chlorodiphenylphosphine to diphenylphosphine borane, and conjugate addition to methyl acrylate. Hydrolysis of the carboxylic ester and coupling to Evans' auxiliary gave phosphine borane **44** in good yield. As anticipated, alkylation of phosphine borane **44** using LHMDS and a variety of electrophiles gave the desired products **45** to **47** (Table 1). The stereochemistry of the alkylation

Table 1 Alkylation of oxazolidinone **44**

Entry	Base	RX	Product	Yield (%)[a]
1	LHMDS	MeI	**45**	76
2	LHMDS	CH_2=$CHCH_2Br$	**46**	46
3	LHMDS	BnBr	**47**	57
4	NHMDS	MeI	**45**	53

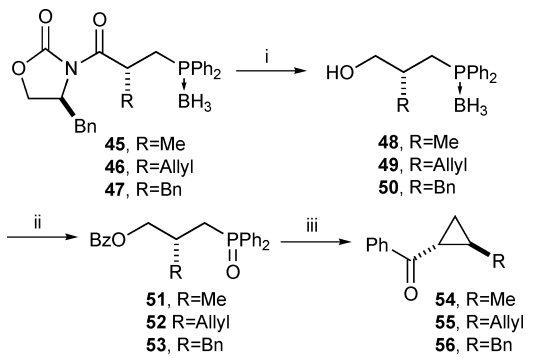
[a] Isolated yield of pure major diastereoisomer.



Scheme 7 (i) a. BH_3, THF, $LiAlH_4$, THF; b. methyl acrylate, MeOH, NaOMe, 0 °C, 96%; (ii) KOH, MeOH, H_2O, 78%; (iii) pivaloyl chloride, Et_3N, THF, (*S*)-(−)-4-benzyl-2-oxazolidinone, *n*-BuLi, −78 °C to room temperature, 71%; (iv) LHMDS or NHMDS, THF, RX, −78 °C to room temperature. See Table 1 for yields.

products was assigned based on the model proposed by Evans and co-workers.[22]

Small quantities of free auxiliary **37** and carboxylic acid **39** were present in the crude reaction mixtures. Even though their diastereoselectivities, the alkylated products could be isolated as single diastereoisomers after purification. Extending the reaction time from 18 to 42 h at 0 °C resulted in a slight reduction in yield. Using NHMDS (entry 4) instead of LHMDS also resulted in a drop in yield. Next, alkylation products **45** to **47** were reduced by the method of Roques and co-workers using sodium borohydride and lithium chloride to give primary alcohols **48** to **50** in moderate to excellent yield (Scheme 8).[23]



Scheme 8 (i) $NaBH_4$, LiCl, EtOH, **48** 99%, **49** 57%, **50** 95%; (ii) a. DABCO, PhMe, 40 °C; b. H_2O_2; c. BzCl, Et_3N, DMAP, **51** 96%, **52** 70%, **53** 46%; (iii) LDA, THF, −78 to 0 °C, **54** 60%, **55** 77%, **56** 72%.

Pellon and co-workers' method of phosphine decomplexation employing DABCO in toluene[20] was used with our substrates **48**

to **50** and the resulting crude phosphines oxidised with hydrogen peroxide to give the corresponding phosphine oxides that were benzoylated, without prior isolation, to give carboxylic esters **51** to **53**. Subjecting enantiomerically enriched cyclopropane precursors **51** to **53** to the standard cyclopropanation conditions completed the three-step cascade reaction to give the desired cyclopropanes **54** to **56** in good yield. As previously observed for the racemic cyclopropanation (Scheme 2), only *trans*-cyclopropane product was isolated.

Molecular modelling

The high levels of stereoselectivity frequently observed in Evans' enolate reactions are proposed to occur due to the significant difference in steric hindrance of the approach of an electrophile to each face of the enolate. The six-membered chelate in the enolate controls the position of the orientation of the auxiliary relative to the enolate, and may also stabilise the enolate by inhibiting the departure of the auxiliary anion. DFT energy minimisations using PC-GAMESS[24] (B3LYP/6-31G(d))[25–30] of simplified versions of the phosphine oxide Evans lithium enolate **57** provided five stable enolate monomers chelated by one dimethyl ether molecule with a range of energies (with the lowest energy structure **57** arbitrarily taken as zero) of 0 to 4.9 kJ mol^{-1} (see ESI for details†). Structures in which the lithium is chelated between the enolate oxygen and the phosphine oxide were also modelled and found to have energies of −28.8 to −28.7 kJ mol^{-1} compared to Evans' chelate structure **57**. The lowest energy conformation **58** is shown in Fig. 1.

The significant drop in energy from Evans' chelate **57** to seven-membered chelate **58** indicates that the phosphine oxide is an excellent ligand for lithium. A further set of structures in which the auxiliary carbonyl, the enolate oxygen and the phosphine oxide are all chelated to the lithium were also found. These are even more stable (−48.5 to −44.5 kJ mol^{-1} compared to **57**), and have a structure where the π-systems of the auxiliary and the enolate are not coplanar (**59** in Fig. 1). The tilting of the auxiliary out of the plane of the enolate may block the approach of an electrophile from one side, while the phosphine oxide blocks the other side (Fig. 1). The lack of experimentally observed reactivity of these phosphine-oxide-containing enolates is therefore explained by their propensity to form potentially unreactive chelates such as structure **59**.

A similar study shows that the three different classes of chelates also exist for the phosphine borane enolates (Fig. 2). In this case, however, the auxiliary–enolate chelates such as **60** (0 to 2.3 kJ mol^{-1}) are more stable than the enolate–phosphine borane chelates such as **61** (+20.8 to +21.1 kJ mol^{-1}). This indicates that the phosphine borane is a significantly worse ligand for lithium than the phosphine oxide. The third class of chelate in which both the auxiliary and the borane are chelated (*e.g.* **62**) is more stable than the corresponding Evans chelates (−13.4 to −8.7 kJ mol^{-1}), but this difference is much less than in the phosphine oxide series. The phosphine borane chelates have similar structural features to the phosphine oxides, but with the B–H bonds coordinating to the lithium *via* agostic-type interactions which are much weaker than the lone pair coordination of the phoshine oxide.

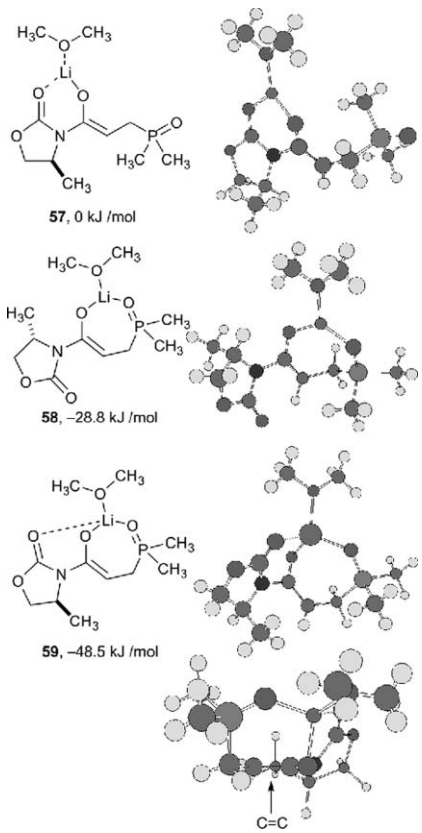


Fig. 1

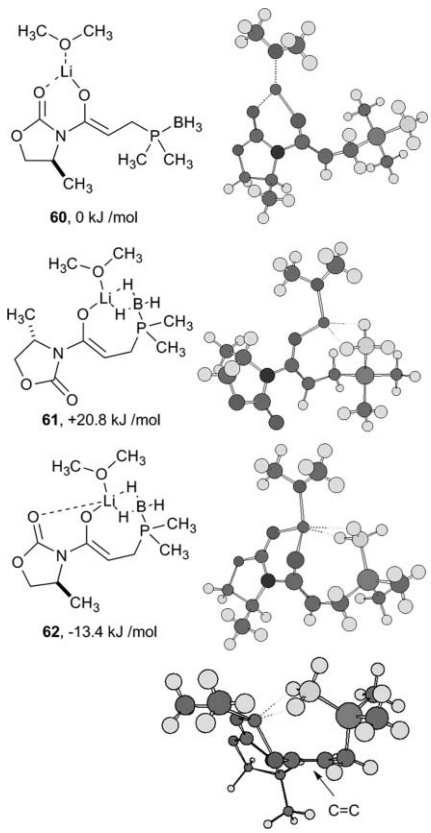


Fig. 2

It should be noted that no account of the change in conformational entropy has been made here, and no absolute equilibrium positions have been calculated. The calculations, however, imply that far less of the phosphine borane enolate will be trapped in an unreactive chelate than the equivalent phosphine oxide, and this is why the enolate alkylation occurs in the former case. In addition, warming of the enolates may increase the proportion of less stable chelates. For the phosphine oxide, the next most stable structure lacks chelation of the auxiliary, and this may explain why the enolate decomposes with loss of, and subsequent alkylation of, the oxazolidinone. For the phosphine borane enolates, however, loss of chelation to the auxiliary carbonyl is energetically unfavourable, which is consistent with the increased observed stability, and stereocontrolled alkylation, of the borane enolate.

In brief, we have demonstrated that β-substituted phosphine oxides undergo the phosphine oxide mediated cyclopropanation cascade reaction to produce *trans*-disubstituted cyclopropyl ketones in good yield. Moreover, we have extended the method to the enantioselective synthesis of cyclopropyl ketones by employing Evans' oxazolidinone auxiliary and masking the phosphine oxide as a phosphine borane.

Experimental procedures

A representative sequence of reactions for the conversion of compound **44** into compound **54** is given below:

(4*S*,2′*R*)-3-[3′-(Boronatodiphenylphosphinyl)-2′-methylpropionyl]-4-(phenylmethyl)oxazolidin-2-one 45

To a solution of hexamethyldisilazane (0.23 cm^3, 1.1 mmol) in dry THF (6 cm^3), stirred at −78 °C under argon, was added *n*-butyllithium (1.5 M solution in hexanes, 0.68 cm^3, 1.05 mmol). After 20 min, a solution of (*S*)-3-[3′-(boronatodiphenylphosphinyl)propionyl]-4-(phenylmethyl)oxazolidin-2-one **44** (0.43 g, 1.0 mmol) in dry THF (6 cm^3), at −78 °C under argon, was added *via* cannula. After 1 h, methyl iodide (0.12 cm^3, 2.0 mmol) was added and the reaction mixture allowed to warm to room temperature. After 42 h, the solvent was removed *in vacuo* and the residue partitioned between dichloromethane (50 cm^3) and water (25 cm^3). The organic layer was dried (Na_2SO_4), filtered and the solvent removed *in vacuo.* The residue was purified by flash column chromatography (SiO_2, EtOAc–hexane 1 : 3, v/v) to give oxazolidinone **45** (0.34 g, 76%) as an oil; $[\alpha]_D^{23}$ (c = 0.5, $CHCl_3$) +58.3; IR ν_{max} (film)/cm^{-1} 2926 (C–H), 2380 (B–H), 1776 and 1694 (C=O), 1605 (C=C, Ph) and 1437 (P–Ph); δ_H (500 MHz; $CDCl_3$) 7.74–7.70 (2H, m, PPh_2 *ortho*), 7.67–7.63 (2H, m, PPh_2 *ortho*), 7.51–7.38 (6H, m, PPh_2), 7.31–7.28 (2H, m, Ph), 7.26–7.23 (1H, m, Ph *para*), 7.15–7.13 (2H, m, Ph), 4.37 (1H, ddt, J 9.5, 7 and 3.5, CHN), 4.15–4.03 (3H, m, CH_2O and C*H*Me), 3.17–3.10 (2H, m, CH_AH_BPh and PCH_AH_B), 2.74 (1H, dd, J 13.5 and 9.5, $PhCH_AH_B$), 2.26 (1H, ddd, J 14.5, 12 and 2.5, PCH_AH_B), 1.30 (3H, dd, J 7 and 1, Me) and 1.12–0.64 (3H, m, BH_3); δ_C (125 MHz; $CDCl_3$) 175.2 (d, J 2.5, *C*ONCO$_2$), 152.7 (CON*C*O$_2$), 135.1 (Ph *ipso*), 132.5 (d, J 9, PPh_2 *ortho*), 132.5 (d, J 9.5, PPh_2 *ortho*), 131.4 (d, J 2.5, PPh_2 *para*), 131.1 (d, J 2.5, PPh_2 *para*), 129.4 (Ph), 129.3 (d, J 55.0, PPh_2 *ipso*), 128.9 (d, J 10, PPh_2 *meta*), 128.9 (Ph), 128.9 (d, J 55, PPh_2 *ipso*), 128.6 (d, J 10, PPh_2 *meta*), 127.3 (Ph *para*), 66.2 (CH_2O), 55.3 (CHN), 37.8 (Ph*C*H$_2$), 33.3 (d, J 2, *C*HMe), 29.0 (d, J 36, PCH_2) and 20.9 (d, J 11.5, Me); δ_P (162 MHz; $CDCl_3$) 15.6–15.3 (m); m/z (ESI) 468 (65%, MNa^+), 454 (51, MNa – BH_3), 446 (33, MH) and 369 (100, MH – Ph) (Found: MNa^+, 468.19000. $C_{26}H_{29}NO_3PBNa$ requires M, 468.18758).

(*R*)-Diphenyl(3-hydroxy-2-methylpropyl)phosphine borane 48

By the method of Roques *et al.*,[23] to a suspension of sodium borohydride (27 mg, 0.72 mmol) and lithium chloride (31 mg, 0.72 mmol) in ethanol : THF (2.9 cm^3 : 2.9 cm^3), stirred at 0 °C under nitrogen, was added a solution of (4*S*,2′*R*)-3-[3′-(boronatodiphenylphosphinyl)-2-methylpropionyl)]-4-(phenylmethyl)oxazolidin-2-one **45** (80 mg, 0.18 mmol) in ethanol : THF (0.72 cm^3 : 0.72 cm^3). The resulting mixture was stirred for 18 h, allowing to warm to room temperature slowly. The mixture was treated with acetone (1 cm^3) and the solvents removed *in vacuo.* The residue was partitioned between EtOAc (2 × 25 cm^3) and water (15 cm^3) and the combined organic layers dried (Na_2SO_4), filtered and the solvents removed *in vacuo* to give an oil. The oil was purified by flash column chromatography (SiO_2, EtOAc–hexane 1 : 1, v/v) to give alcohol **48** (50 mg, 99%) as an oil; R_f 0.3 (EtOAc–hexane, 1 : 1, v/v); $[\alpha]_D^{23}$ (c = 0.5, $CHCl_3$) −4.7; IR ν_{max} (film)/cm^{-1} 3372 (br, O–H), 2925 (C–H), 2381 (B–H), 1589 (C=C, Ph) and 1436 (P–Ph); δ_H (500 MHz; $CDCl_3$) 7.73–7.68 (4H, m, Ph), 7.49–7.40 (6H, m, Ph), 3.51 (1H, ddd, J 11, 5 and 1.5, CH_AH_BO), 3.40 (1H, dd, J 11 and 6, CH_AH_BO), 2.58–2.50 (1H, m, PCH_AH_B), 2.09–2.02 (2H, m, CH and PCH_AH_B), 1.53 (1H, br s, OH), 1.32–0.70 (3H, m, BH_3) and 0.93 (3H, d, J 6.5, Me); δ_C (125 MHz; $CDCl_3$) 132.2 (d, J 9, PPh_2 *ortho*), 132.0 (d, J 9, PPh_2 *ortho*), 131.2 (d, J 2.5, PPh_2 *para*), 131.1 (d, J 2.5, PPh_2 *para*), 130.1 (d, J 55.5, PPh_2 *ipso*), 130.0 (d, J 54.5, PPh_2 *ipso*), 128.8 (d, J 10, PPh_2 *meta*), 67.8 (d, J 9.0, CH_2O), 31.8 (CH), 28.8 (d, J 36, PCH_2) and 18.6 (d, J 5.5, Me); δ_P (162 MHz; $CDCl_3$) 14.9–14.4 (m); m/z (ESI) 295 (58%, MNa^+) and 281 (100, MNa – BH_3) (Found: MNa^+, 295.14000. $C_{16}H_{22}OPBNa$ requires M, 295.13990).

(*R*)-[3-(Benzoyloxy)-2-methylpropyl]diphenylphosphine oxide 51

By the method of Pellon *et al.*,[20] a solution of (*R*)-diphenyl(3-hydroxy-2-methylpropyl)phosphine borane **48** (0.14 g, 0.50 mmol) in toluene (1.5 cm^3) was treated with DABCO (56 mg, 0.50 mmol) and the resulting mixture heated at 40 °C for 18 h. The mixture was treated with excess hydrogen peroxide solution and the residue quenched with sodium metabisulfite. The mixture was partitioned between dichloromethane (15 cm^3) and water (15 cm^3), the organic layer dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give crude (*R*)-diphenyl(3-hydroxy-2-methylpropyl)phosphine oxide. δ_H (400 MHz; $CDCl_3$) 7.79–7.69 (4H, m, Ph *ortho*), 7.56–7.42 (6H, m, Ph), 3.61 (1H, dd, J 11 and 4, CH_AH_BO), 3.45 (1H, dd, J 11.5 and 7.5, CH_AH_BO), 2.36 (1H, dd, J 14 and 8.5, PCH_AH_B), 2.32 (1H, dd, J 8.5 and 4, PCH_AH_B), 2.14–2.04 (1H, m, PCH_2CH) and 0.98 (3H, dd, J 7 and 1.5, Me); δ_C (125 MHz; $CDCl_3$) 133.1 (d, J 99.5, Ph *ipso*), 131.9 (d, J 2.5, Ph *para*), 131.8 (d, J 98, Ph *ipso*), 130.9 (d, J 9, Ph *ortho*), 130.6 (d, J 9.5, Ph *ortho*), 128.8 (d, J 11.5, Ph *meta*), 128.7 (d, J 11.5, Ph *meta*), 68.3 (d, J 4.5, CH_2O), 35.7 (d, J 69.5, PCH_2), 32.1 (d, J 4, PCH_2CH) and 19.9 (d, J 13, Me); δ_P (162 MHz; $CDCl_3$) 35.4; m/z (ESI) 275 (55%, MH^+) (Found: MH^+, 275.1190. $C_{16}H_{20}O_2P$ requires M, 275.1201). The

spectroscopic data are consistent with that reported previously.[31] The crude product was dissolved in dichloromethane (4.5 cm^3) and triethylamine (0.10 cm^3, 0.70 mmol), DMAP (30 mg, 0.25 mmol) and benzoyl chloride (0.08 cm^3, 0.70 mmol) were added. The resulting solution was stirred at room temperature under argon for 32 h. The mixture was washed with water (25 cm^3) and the aqueous layer extracted with ethyl acetate (4 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and the solvents removed *in vacuo*. The residue purified by flash column chromatography (SiO_2, CH_2Cl_2–MeOH 19 : 1, v/v) to give phosphine oxide **51** (0.18 g, 96%) as an oil; $[\alpha]_D^{23.5}$ (c = 0.5, $CHCl_3$) +8.5; δ_H (500 MHz; $CDCl_3$) 7.98–7.96 (2H, m, $PhCO_2$ *ortho*), 7.78–7.73 (4H, m, PPh_2 *ortho*), 7.55 (1H, t, *J* 7.5, Ph *para*), 7.51–7.39 (8H, m, Ph), 4.21–4.15 (2H, m, CH_2O), 2.56 (1H, ddd, *J* 15, 10.5 and 4.5, PCH_AH_B), 2.53–2.45 (1H, m, PCH_2CH), 2.22 (1H, ddd, *J* 15, 12.5 and 8.5, PCH_AH_B) and 1.17 (3H, d, *J* 7, Me); δ_C (125 MHz; $CDCl_3$) 166.3 (CO_2), 133.8 (d, *J* 98, PPh_2 *ipso*), 133.0 ($PhCO_2$ *para*), 132.8 (d, *J* 98, PPh_2 *ipso*), 131.8 (d, *J* 3, PPh_2 *para*), 131.7 (d, *J* 3, PPh_2 *para*), 130.8 (d, *J* 9, PPh_2 *ortho*), 130.6 (d, *J* 9.5, PPh_2 *ortho*), 130.1 ($PhCO_2$ *ipso*), 129.5 ($PhCO_2$), 128.7 (d, *J* 11, PPh_2 *meta*), 128.7 (d, *J* 12, PPh_2 *meta*), 128.2 ($PhCO_2$), 69.7 (d, *J* 12, CH_2O), 33.2 (d, *J* 71.5, PCH_2), 28.3 (d, *J* 3.5, PCH_2CH) and 18.6 (d, *J* 4.5, Me); δ_P (162 MHz; $CDCl_3$) 31.6; *m*/*z* (ESI) 379 (100%, MH^+) (Found: MH^+, 379.1472. $C_{23}H_{24}O_3P$ requires M, 379.1463).

(1′*R*,2′*R*)-(2′-Methylcyclopropyl)phenyl methanone 54

LDA was prepared by the addition of *n*-butyllithium (1.6 M solution in hexanes, 1.25 cm^3, 2.0 mmol) to a solution of diisopropylamine (0.28 cm^3, 2.0 mmol) in dry THF (8.5 cm^3), stirred at −78 °C under nitrogen. After 1 h, a solution of (*R*)-[3-(benzoyloxy)-2-methylpropyl]diphenylphosphine oxide **51** (38 mg, 0.1 mmol) in dry THF (0.4 cm^3), stirred at −78 °C under nitrogen, was treated with the LDA solution (0.2 mol dm^{-3} solution in THF, 0.6 cm^3, 0.12 mmol). After 1 h, the mixture was allowed to warm to 0 °C and stirred for 48 h at this temperature. The reaction was quenched with water (1 cm^3) and the solvent removed *in vacuo*. The residue was partitioned between water (2 cm^3) and ethyl acetate (3 × 5 cm^3), the combined organic extracts dried (Na_2SO_4), filtered and the solvents removed *in vacuo*. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2) to give cyclopropane **54** (10 mg, 60%) as an oil; $[\alpha]_D^{22}$ (c = 0.42, $CHCl_3$) −77.1; R_f 0.5 (CH_2Cl_2); IR ν_{max} (CH_2Cl_2)/cm^{-1} 1664 (C=O); δ_H (500 MHz; $CDCl_3$) 8.00–7.97 (2H, m, Ph *ortho*), 7.55 (1H, tt, *J* 7 and 1.5, Ph *para*), 7.48–7.45 (2H, m, Ph *meta*), 2.39 (1H, dd, *J* 8 and 4, CHCO), 1.64–1.56 (1H, m, C*H*Me), 1.48 (1H, ddd, *J* 8.5, 4.5 and 3.5, CH_AH_B), 1.21 (3H, d, *J* 6, Me) and 0.88 (1H, ddd, *J* 7.5, 6.5 and 3.5, CH_AH_B); δ_C (125 MHz; $CDCl_3$) 200.1 (CO), 138.1 (Ph *ipso*), 132.6 (Ph *para*), 128.4 and 127.9 (Ph), 26.4 and 21.3 (CH), 20.1 (CH_2) and 18.3 (Me); *m*/*z* (EI) 160 (36%, M^+) and 105 (100, PhCO) (Found: M^+, 160.08832. $C_{11}H_{12}O$ requires M, 160.08882).

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