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Synthesis and resolution of 2-methyl-Quinazolinap, a new atropisomeric phosphinamine ligand for asymmetric catalysis

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Abstract

The preparation in a five-step sequence of 2-methyl-Quinazolinap, a new atropisomeric ligand for asymmetric catalysis, is described. Diastereomeric palladacycles derived from racemic ligand and (+)-di-μ-chlorobis[(*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C_2,*N*]dipalladium(II) were separated by fractional crystallisation. Displacement of the resolving agent by reaction with DPPE afforded enantiopure 2-methyl-Quinazolinap. © 2000 Elsevier Science Ltd. All rights reserved.

Of the atropisomeric ligands reported to date, the diphosphine BINAP and numerous analogues have proven most successful in a wide range of enantioselective metal-catalysed transformations.[1] Recently, interest in atropisomeric phosphinamine ligands has increased as asymmetry can be induced by a combination of steric and electronic effects on reactions occurring within the co-ordination sphere of the transition metal to which they are bound.[2] The first example to be applied in asymmetric catalysis was Quinap **1**,[3] followed by the vaulted analogue Phenap **2**,[4] both from Brown's group. We recently reported the preparation and resolution of 1-(3,6-dimethylpyrazin-2-yl)(2-naphthyl)diphenylphosphine **3**.[5] However, **3** racemised at room temperature and we reverted to a biaryl unit design which we felt was going to be essentially inert to racemisation, namely one linking a naphthalene and a quinazoline. Thus, we prepared and resolved[6,7] 2-phenyl-Quinazolinap **4** and we successfully applied this ligand to the rhodium-catalysed hydroboration of styrenes[8] and in palladium-catalysed allylic substitutions.[9]

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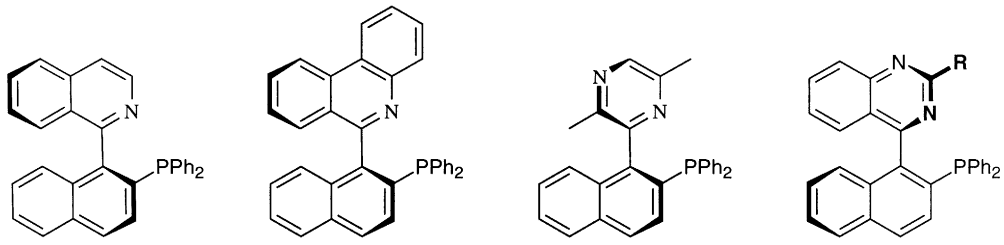
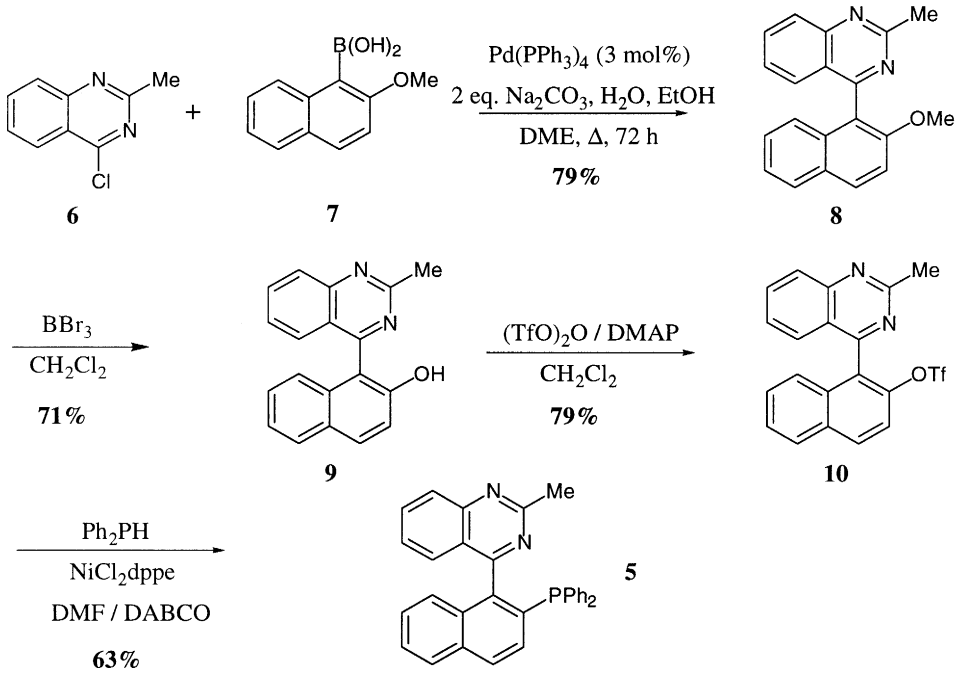


1 **2** **3** **4** R = Ph, **5** R = Me

During a mechanistic investigation of the latter process with 2-phenyl-Quinazolinap **4**, we determined that the 2-phenyl group takes up a position in space leading to ligand–reactant steric interactions which have a major influence on the sense of the asymmetric induction observed.[8a,9] In light of this observation we wished to determine the influence of a smaller substituent than a phenyl group at the 2-position. Therefore, we now wish to report in this letter the synthesis and resolution of 2-methyl-Quinazolinap **5**, the second member of this class of the quinazoline-containing atropisomeric phosphinamine ligand.[10]

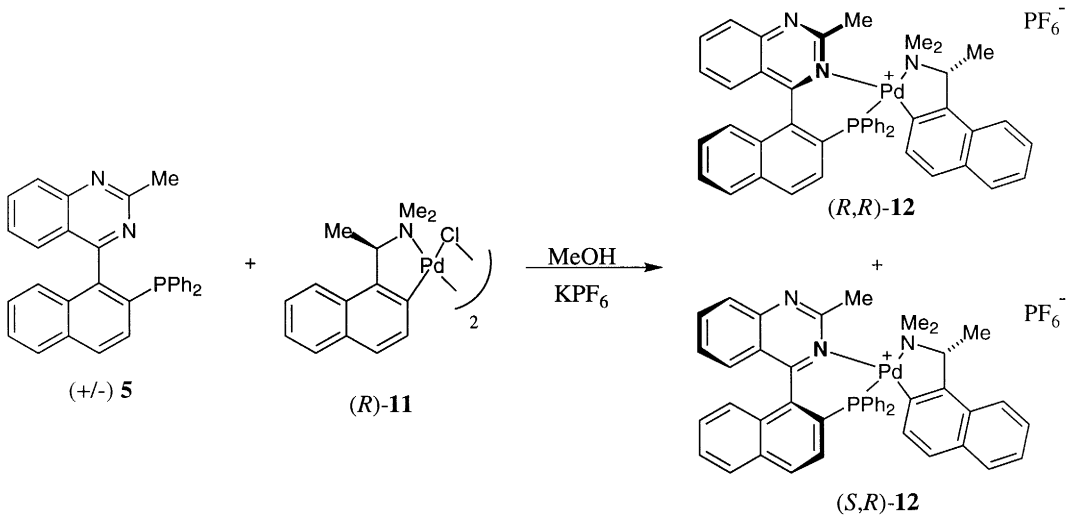
The synthetic approach to ligand **5** is similar to that used for ligands **1**–**4** with two key metal-catalysed reactions of the biaryl linkage and introduction of the diphenylphosphino group. The electrophilic component of the Suzuki coupling, 4-chloro-2-methyl-quinazoline **6**, was prepared in 66% yield from 2-methyl-4(3*H*)-quinazolinone and phosphorous oxychloride.[11]



Scheme 1.

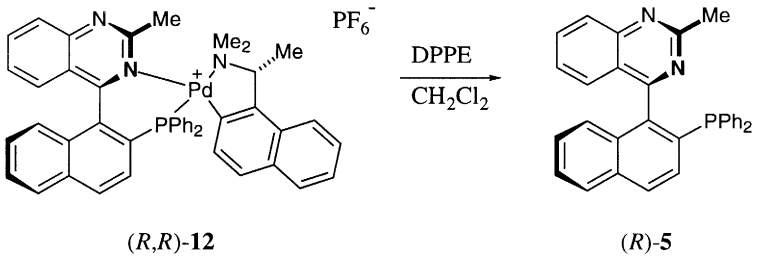
The coupling of **6** and 2-methoxy-1-naphthylboronic acid **7**,[3a] catalysed by tetrakis(triphenylphosphine) palladium(0), gave 2-methyloxy-1-(2-methylquinazolin-4-yl)naphthalene **8** in 79% yield, Scheme 1. The next two steps involved the conversion of the ether **8** into the triflate component for the carbon–phosphorus bond formation by first converting it into 1-(2-methylquinazolin-4-yl)naphthalen-2-ol **9** in 71% yield by reaction with boron tribromide in dichloromethane.[12] Alcohol **9** was reacted with trifluoromethanesulfonic anhydride in the presence of 4-dimethylaminopyridine to

give 1-(2-methylquinazolin-4-yl)-2-naphthyl(trifluoromethyl)sulfonate **10** in 79% yield. The coupling of **10** with diphenylphosphine, to afford 2-methyl-Quinazolinap **5** in 63% yield, was catalysed by [1,2-bis(diphenylphosphino)ethane]dichloro nickel(II) in the presence of DABCO as base.[13]



Scheme 2.

Our initial attempts at resolving **5** focused on the preparation and separation of diastereomeric complexes derived from **5** and (+)-di-μ-chlorobis[(*R*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C_2,*N*]dipalladium(II) **11**, the latter being a successful resolving agent in the resolution of a wide range of phosphorus-containing ligands.[14] As the steric demand of 2-methyl-Quinazolinap **5** approximates to a mid-point between Quinap **1** and Phenap **2**, the resolution procedures successful for them were attempted in the present study. In the absence of KPF_6 we observed no precipitation, whereas, after the addition of KPF_6 both diastereomers precipitated, Scheme 2 (as this behaviour is similar to that observed with Quinap **1**, we suggest that the palladacycles are bound through both donor atoms which would be confirmed by X-ray analysis). A range of solvent systems were investigated to effect separation until the use of $CHCl_3$/diethyl ether mixtures afforded a diastereomerically pure material (^{31}P NMR showed peaks at 41.41 and 37.53 ppm for the diastereomers but only a peak at 37.53 ppm after separation).



Scheme 3.

Enantiopure ligand was obtained after decomplexation of the separated diastereomer by the addition of DPPE in dichloromethane at ambient temperature followed by separation on a short silica column, Scheme 3. The free ligand thus obtained had an optical activity of $[\alpha]_D^{23}$ −94.08 (*c* 1.06, CH_2Cl_2).[15] In line with Quinap **1**, Phenap **2** and 2-phenyl-Quinazolinap **4**, this sign of optical rotation suggests we have the (*R*)-enantiomer of ligand **5** and hence the diastereomer we obtained from the fractional crystallisation was (*R*,*R*)-**12**.

In conclusion, we have prepared and resolved a new member of the Quinazolinap class of atropisomeric phosphinamine ligand for asymmetric catalysis. Further studies on the application of this ligand in asymmetric catalysis and on the preparation and application of other Quinazolinap analogues are in progress and will be reported by us in due course.[16]

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15. The spectroscopic properties of all new compounds are in agreement with the assigned structures. Physical data for **5**: m.p. 195–197°C. Found: C, 81.5; H, 5.1; N, 6.1. $C_{31}H_{23}N_2P$ requires: C, 81.9; H, 5.1; N, 6.2%; ^{1}H NMR (270 MHz): δ ($CDCl_3$) 8.04 (d, 1H, J=8.4 Hz, H_8), 7.92 (d, 1H, J=8.6 Hz, H_4), 7.90 (d, 1H, J=8.25 Hz, $H_{5'}$), 7.81 (dt, 1H, J_1=7.4 Hz, J_2=1.9 Hz, H_7), 7.50 (dt, 1H, J_1=7.6 Hz, J_2=1.2 Hz, $H_{6'}$), 7.41 (dd, 1H, $J_{H,H}$=8.5 Hz, $J_{P,H}$=3.2 Hz, H_3), 7.34–7.08 (m, 14H, aromatic H) and 2.79 (s, Me); ^{13}C NMR (67.8 MHz): δ ($CDCl_3$) 169.3 (d, $J_{P,C}$=6.4 Hz, $C_{4'}$), 163.8 (C-2′), 150.5 (C-9′), 141.4 (d, $J_{P,C}$=32.3 Hz, C_2), 135.7 (d, $J_{P,C}$=28.9 Hz, C-*i*′′), 135.5 (d, $J_{P,C}$=34.4 Hz, C-*i*′), 131.7 (d, $J_{P,C}$=7.5 Hz, C-1), 133.7 (d, $J_{P,C}$=15 Hz, C-*o*), 133.4 (d, $J_{P,C}$=14 Hz, C-*o*′), 133.1 (d, $J_{P,C}$=14.6 Hz, C-3), 129.81–126.04 (CH, Aromatic C), 123.33 (4°C), 123.28 (4°C) and 26.38 (Me); ^{31}P NMR (101.3 MHz): δ ($CDCl_3$) −12.6; ν_{max} (KBr): 3058 (Ar-H), 1637 (m) (Ar-H), 1556 (s) (Ar-H), 1429 (s) (P-Ph), 743 (s) (Ar-H), 696 (s) (Ar-H) cm^{-1}; *m/z* (EIMS, 70 eV) 454 (M^+, 29%), 377 (100), 300 (19) and 77 (16).
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