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TETRAHEDRON: *ASYMMETRY*

Synthesis of 2-heterosubstituted quinazolinone atropisomeric phosphine ligands by direct lithiation of a 2-unsubstituted quinazolinone system

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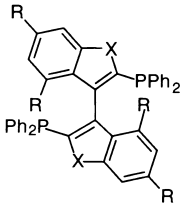
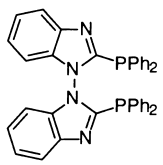
Abstract

The syntheses of 2-heterosubstituted atropisomeric quinazolinone phosphine ligands **7e**–**g** have been achieved in good yield by the straightforward direct lithiation of the 2-unsubstituted quinazolinone ligand **7d** followed by electrophilic substitutions.

Recent syntheses of some atropisomeric phosphine ligands (**1a**–**c**, **2**, and **3**) demonstrated that direct metalation[1] of five-membered heteroaromatic rings (in particular, indoles and imidazoles) was an efficient methodology for obtaining chiral ligands.[2]



1a: X = S, R = CH_3; **1b**: X = S; R = H; **1c**: X = O; R = H



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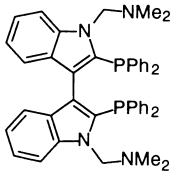

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However, direct lithiation of six-membered aromatic heterocycles, particularly for diaza compounds, is a less studied topic, possibly because of their high reactivity toward nucleophilic addition. Lithiation of pyrimidine using lithium alkylamides such as LDA (lithium diisopropylamide) or LTMP (lithium 2,2,6,6-tetramethylpiperidylamide) which are less prone to nucleophilic addition than alkyl- or aryllithium have been reported. However, to our knowledge, there is no report on direct lithiation of a 2-unsubstituted 3-aryl-4(3*H*)-quinazolinone ring system.[3]

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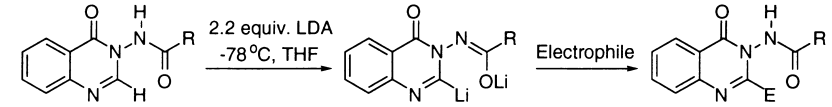
Recently, Smith et al. reported the synthesis of 2-substituted 4(3*H*)-quinazolinone by *ortho*-directed lithiation of 2-unsubstituted quinazolinones (**4a** and **4b**, Scheme 1) with LDA followed by reaction of the resulting intermediate **5** with a variety of electrophiles.[4] They claimed that the *ortho*-directing groups (the 3-pivaloylamino group and the 3-acetylamino group) were necessary for the lithiation of quinazolinones **4a** and **4b** to take place.

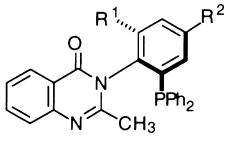


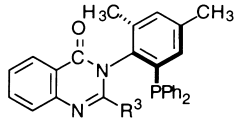
4a: R = *t*-Bu; **4b**: R = Me **5** **6**

Scheme 1.

In the case of compound **4b**, it is interesting that lithiation of the 2-position occurred in the presence of the acidic α-protons of the 3-acetylamino group. Deprotonation of the α-protons of simple acetanilides occurs readily and accounts for the preferred use of the pivaloylamino group in directed lithiation reactions.[5] The regioselective lithiation of compound **4b** suggests that the proton at the 2-position is more acidic than the methyl protons of the 3-acetylamino group.

The successful syntheses and resolutions of ligands **7a–c**[6] encouraged us to develop 2-heterosubstituted quinazolinone phosphine ligands, such as **7e–g**. The heteroatoms at the 2-position of the quinazolinone ring together with the PPh_2 group on the 3-aryl ring are designed to chelate metals in a similar way as BINAP. Many variations of bidentate ligands have been shown to associate strongly with the metal centers and thereby bring metals closer to the chiral environment provided by the ligands. This feature underlies their enhanced stereoselectivity in asymmetric catalysis.[7]

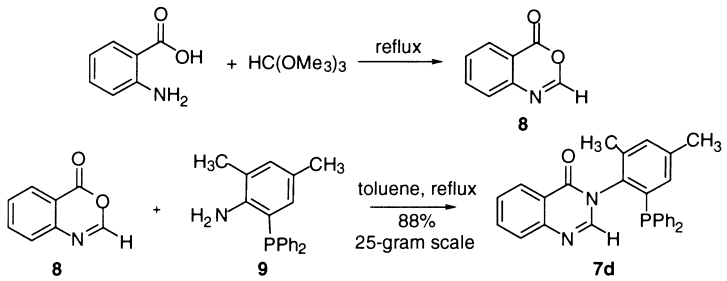




7a $R^1 = R^2 = H$; **7b** $R^1 = H$, $R^2 = CH_3$; **7c** $R^1 = R^2 = CH_3$ **7d** $R^3 = H$; **7e** $R^3 = PPh_2$; **7f** $R^3 = SH$; **7g** $R^3 = SMe$

We anticipated that the proton at the 2-position of quinazolinone ligand **7d** would be acidic enough to be directly lithiated without an apparent directing group. If the regioselective lithiation could be realized, subsequent quenching of the carbanion with electrophiles (such as PPh_2Cl, S_8, and MeSSMe) would afford chelating ligands **7e–g** in a straightforward fashion.

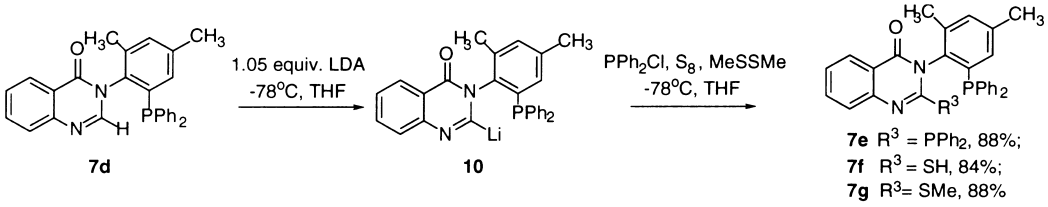
The synthesis of 2-unsubstituted ligand **7d** was initiated with the formation of 4*H*-3,1-benzoxazin-4-one (**8**) by the condensation of 2.2 equiv. anthranilic acid with 5.0 equiv. trimethyl orthoester following the method reported by Khajavi et al.[8] After removal of the excess orthoester, the crude **8** was mixed with a solution of 1.0 equiv. aminophosphine **9**[6] in toluene. The mixture was heated to reflux for 6 h to afford quinazolinone **7d** (88%, 25 g scale) (Scheme 2).



8 **8** **9** **7d**

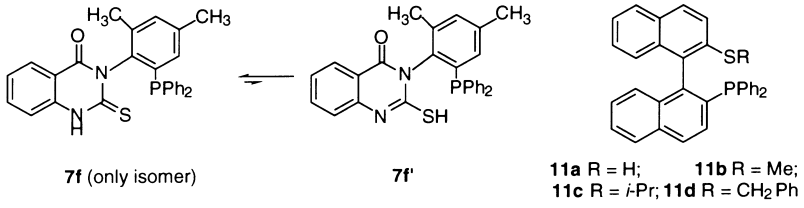
Scheme 2.

As we expected, the lithiation of ligand **7d** using LDA proceeded readily at −78°C in THF under argon to give a yellow solution of anion **10** without the pivaloylamino or acetylamino *ortho*-directing groups (Scheme 3). Anion **10** was found to be unstable at temperatures higher than −20°C. Hence, the subsequent addition of electrophiles (neat chlorodiphenylphosphine (PPh_2Cl), solid sulfur (S_8), and dimethyl disulfide (MeSSMe)) was carried out at −78°C. The reaction mixture was stirred at −78°C for 1 h before warming slowly to room temperature. Normal workup procedures afforded ligands **7e**–**g** in good isolated yield (84–88%). All of the reactions were carried out on a 3 g scale and ligands **7e**–**g** were fully characterized.[9]



Scheme 3.

Based on ^1H NMR and ^{13}C NMR analyses, ligand **7f** is only in the thioamide form (Scheme 4).[10] To our knowledge, only one class of P–S atropisomeric ligand (**11a**–**d**, Scheme 4) has been thus far developed from binaphthol by multiple-step transformations.[11,12]

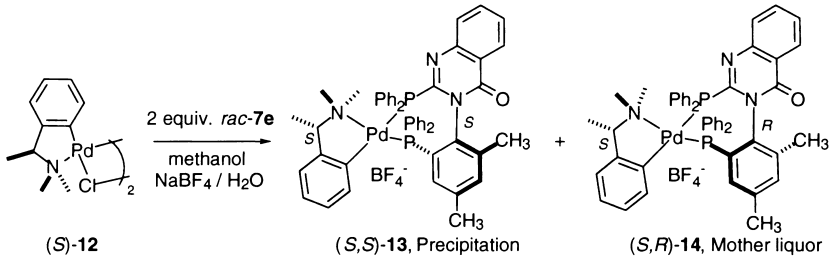


Scheme 4.

Racemic ligand **7d** can be resolved by (−)-di-μ-chlorobis[(*S*)-dimethyl-(1-naphthylethyl)-aminato-C^2,*N*]dipalladium(II)[13] using a similar resolution procedure as for ligands **7a**–**c**.[6,14] Therefore, enantiomers of ligands **7e**–**g** could be derived from enantiomers of ligand **7d**.

We further found that diphosphine ligand **7e** could be directly resolved using (−)-di-μ-chlorobis[(*S*)-dimethyl-(1-phenylethyl)aminato-C^2,*N*]dipalladium(II) (**12**) according to the literature procedure (Scheme 5).[15] The white precipitate, formed from the methanol solution of racemic ligand **7e** and complex **12** upon addition of aqueous $NaBF_4$ solution was recrystallized from benzene. X-Ray crystallography analysis of the colorless prisms revealed that only the (*S*)-**7e** enantiomer and the resolving agent formed the less soluble complex **13**.[16] The PPh_2 group on the 3-aryl ring of ligand (*S*)-**7e** was *trans* to the dimethylamino group; the PPh_2 group at the 2-position was *cis* to the dimethylamino group, suggesting that the two phosphine groups are electronically different. This feature may have special utility for the catalyst design. Treatment of complexes **13** and **14** with ethylenediamine in CH_2Cl_2 released free ligand (*S*)-(−)-**7e** and (*R*)-(+)-**7e**, respectively.[17]

The concise one-pot syntheses of ligands **7e**–**g** from ligand **7d** offers an efficient access to a new class of P–S and P–P chelate atropisomeric ligands. This discovery has also added a new tool for the structural modification of the quinazolinone ring system.



Scheme 5.

Acknowledgements

The authors thank Dr. William Davis for solving the crystal structure of complex **13**.

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9. Data for ligand **7d**: mp 140–142°C; R_f=0.38 (silica, 1:2 ethyl acetate:hexane); FTIR (thin film, cm^{-1}) 3049, 1686, 1607, 1471, 1434, 1289, 1272, 909, 775, 744, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, 1H, *J*=1.4, 7.9 Hz), 7.76 (ddd, 1H, *J*=1.5, 6.8, 8.3 Hz), 7.70 (dd, 1H, *J*=1.8, 8.2 Hz), 7.62 (d, 1H, *J*=1.6 Hz), 7.47 (ddd, 1H, *J*=1.7, 6.7, 7.9 Hz), 7.17–7.40 (m, 11H), 6.80 (dd, 1H, *J*=2.2, 3.2 Hz), 2.27 (s, 3H), 2.10 (s, 3H); $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ −15.1 (s); HRMS 434.15476 (calcd for $C_{28}H_{23}N_2OP$ 434.15480). Data for ligand **7e**: mp 238–241°C; R_f=0.58 (silica, 1:2 ethyl acetate:hexane); FTIR (thin film, cm^{-1}) 3051, 1687, 1542, 1468, 1434, 1246, 1193, 742, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, 1H, *J*=1.5, 7.8 Hz), 7.77 (ddd, 1H, *J*=1.5, 7.1, 8.1 Hz), 7.62 (dd, 1H, *J*=1.2, 8.1 Hz), 7.46–7.55 (m, 4H), 7.30–7.45 (m, 12H), 7.10–7.38 (m, 5H), 6.97 (d, 1H, *J*=1.5 Hz), 6.82 (dd, 1H, *J*=2.0, 3.4 Hz), 2.30 (s, 3H), 1.29 (s, 3H); $^{31}P\{^1H\}$ NMR (202.3 MHz, $CDCl_3$): δ −2.16 (d, *J*=71.38 Hz), −12.70 (d, *J*=71.38 Hz); HRMS 618.19810 (calcd for $C_{40}H_{32}N_2OP$ 618.19899). Data for ligand **7f**: mp: >300°C; R_f=0.43 (silica, 1:2 ethyl acetate:hexane); FTIR (thin film, cm^{-1}) 3248, 3037, 1701, 1666, 1618, 1528, 1484, 1396, 1199, 743, 694; ^1H NMR (300 MHz, $CDCl_3$) δ 10.96 (br s, 1H), 7.99 (dd, 1H, *J*=1.0, 7.8 Hz), 7.60 (tdd, 1H, *J*=1.5, 7.3, 8.3 Hz), 7.35–7.42 (m, 2H), 7.16–7.52 (m, 10H), 7.14 (d, 1H, *J*=8.3 Hz), 6.96 (dd, 1H, *J*=2.0, 3.9 Hz), 2.28 (s, 3H), 2.18 (s, 3H); $^{31}P\{^1H\}$ NMR (202.3 MHz, $CDCl_3$): δ −17.0 (s); HRMS 466.12644 (calcd for $C_{28}H_{23}N_2OPS$ 466.12687). Data for ligand **7g**: mp 130–132°C; R_f=0.55 (silica, 1:2 ethyl acetate:hexane); FTIR (thin film, cm^{-1}) 3052, 1684, 1546, 1467, 769, 743, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, 1H, *J*=1.46, 7.81 Hz), 7.72 (ddd, 1H, *J*=1.46, 6.84, 8.30), 7.66 (dd, 1H, *J*=1.46, 8.30), 7.15–7.42 (m, 12H), 6.99 (dd, 1H, *J*=1.46, 3.42), 2.51 (s, 3H), 2.31 (s, 3H), 2.18 (s, 3H); $^{31}P\{^1H\}$ NMR (202.3 MHz, $CDCl_3$): δ −16.72 ppm; HRMS 480.14240 (FAB, 3-nitrobenzyl alcohol) (calcd for $C_{29}H_{25}N_2OP$ 480.142524).
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14. Data for ligand (*R*)-(−)-**7d**: mp 168–170°C (white needles); $[\alpha]_D$=−189 (*c*=1.09, $CHCl_3$) (99% ee based on chiral HPLC analysis, Chiralcel-OD column, 98:2 hexane:2-propanol, flow rate 0.50 mL/min, λ=295 nm, t_R=32.4 min). Data for ligand (*S*)-(+)-**7d**: mp 169.5–170.5°C (white needles); $[\alpha]_D$=+204 (*c*=1.01, $CHCl_3$), (>99.5% ee based on chiral HPLC analysis, same conditions as for ligand (*R*)-(−)-**7d**, t_R=17.8 min).
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16. X-Ray data for complex **13** ($C_{50}H_{46}BF_4N_3OP_2Pd$; M_W=960.10): orthorhombic system, space group $P2_12_12_1$, *a*=15.6576(3) Å, *b*=16.1037(4) Å, *c*=19.6933(3) Å and *Z*=4. A total of 14 973 reflections were collected at −90°C using a Siemens SMART/CCD diffractometer. Least squares refinement of the data using 4640 reflections converged upon the structure with *R*=0.0932 and a goodness of fit=1.061. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
17. Data for ligand (*S*)-(−)-**7e**: mp 238–240°C (white bricks); $[\alpha]_D$=−21.2 (*c*=1.20, $CHCl_3$), (98% ee based on chiral HPLC analysis, Daicel Chiralcel-OD, 98:2 hexane:2-propanol, flow rate 0.50 mL/min, λ=295 nm, t_R=17.8 min). Data for ligand (*R*)-(+)-**7e**: mp 238–240°C (white bricks); $[\alpha]_D$=+16.8 (*c*=1.46, $CHCl_3$) (90% ee based on chiral HPLC analysis, same conditions as for ligand (*S*)-(−)-**7e**, t_R=19.4 min).