Bidentate P,N Ligands

A Staudinger Approach towards Binol-Derived MAP-Type Bidentate P,N Ligands**

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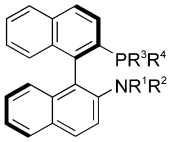
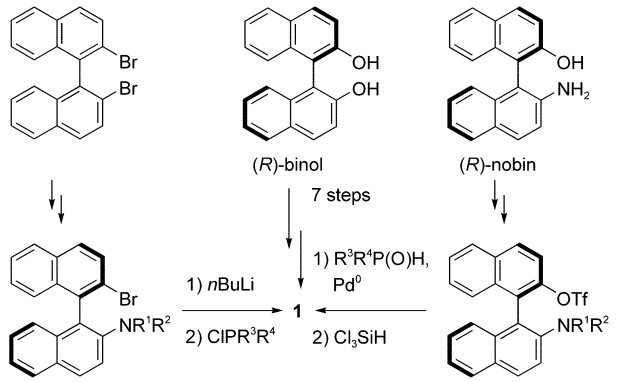
Ligands based on nonsymmetrically 2,2′-substituted 1,1′-binaphthyl compounds find widespread use in homogeneous catalysis.[1] Within this class, the heterobidentate MAP-type ligands **1** stand out because of their high reactivities and selectivities in several transition-metal-catalyzed reactions, such as Hartwig–Buchwald amination reactions, (enantioselective) Suzuki–Miyaura coupling reactions, and the formation of aryl ethers.[2] For the synthesis of enantiopure MAP-type ligands, binol seems the most logical choice as both enantiomers are commercially available. To date, only one direct synthesis of a MAP-type ligand from binol has been reported, namely, the synthesis of **1** ($R^1 = R^2 =$ Ph, $R^3 = R^4 = H$) by Noyori and co-workers in 7 steps (Scheme 1).[3] Alternative routes towards optically pure



1: MAP-type ligand



Scheme 1. Syntheses of MAP-type ligands **1**.

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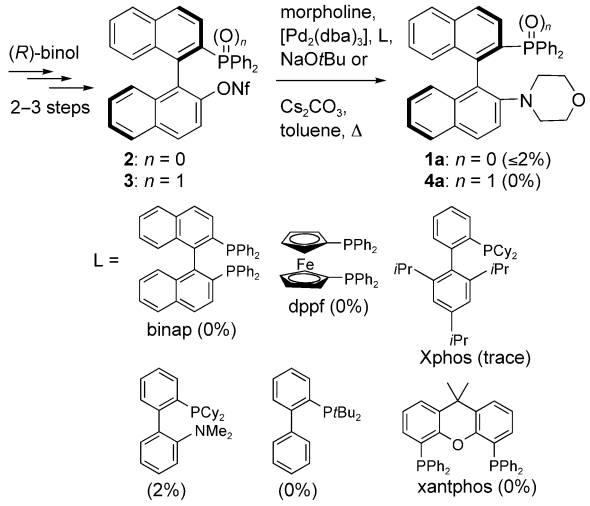
MAP ligands have been disclosed starting from 2,2′-dibromo-1,1′-bisnaphthalene[4] or nobin.[5,6] A common feature of these routes is that the introduction of the amino group precedes phosphane or phosphane oxide installation (Scheme 1).

For the synthesis of a series of MAP ligands which vary in the amine substituent, we decided to start from binol and to reverse the order of reactions by introducing the phosphorus moiety first to give **2**, followed by introduction of the amino group by using the Buchwald–Hartwig amination reaction (Scheme 2). The required phosphanyl nonaflate **2** was prepared in three steps from (*R*)-binol based on literature procedures for the triflate analogue in an overall yield of 89%.[7] The feasibility of this approach is suggested by several reports describing the successful introduction of phosphane, phosphane oxide, and aryl groups into the triflate analogue of **2** by transition-metal catalysis.[8] Although we tried the most powerful ligands known to date, used sets of several conditions, started both from **2** and the oxide **3**, and used morpholine as the nucleophile, only when Xphos[9] or the P,N ligand [2′-(Dicyclohexylphosphanyl)biphenyl-2-yl]dimethylamine[10] were used as the ligand could traces (2% at maximum) of **1a** be detected by ^{1}H NMR spectroscopy.[11]



Scheme 2. Attempts towards Pd^0-catalyzed amine introduction. For each ligand L, the yield is given in brackets. Nf = nonaflate = nonafluorobutanesulfonate.

From the experience gained with our work on intramolecular Staudinger ligations for the synthesis of cyclopeptides we envisioned at this stage the possibility of amine introduction by a similar strategy—the reaction of phosphane **2** with alkyl or aryl azides.[12] In this approach intramolecular nucleophilic aromatic substitution of the nonaflate substituent by the iminophosphorane unit in **6** would yield an aminophosphonium salt **7**, thus providing, after basic hydrolysis, MAP(O)-type compounds **4** (Scheme 3).[13] Herein we show the usefulness of iminophosphorane nitrogen atoms as nucleophiles in an unprecedented intramolecular S_NAr reaction that provides efficient access to MAP ligands.

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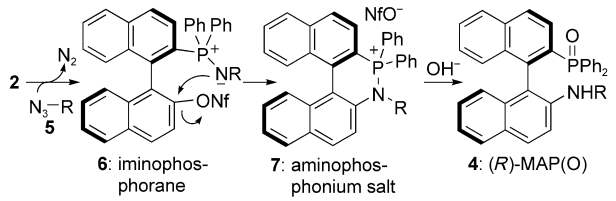
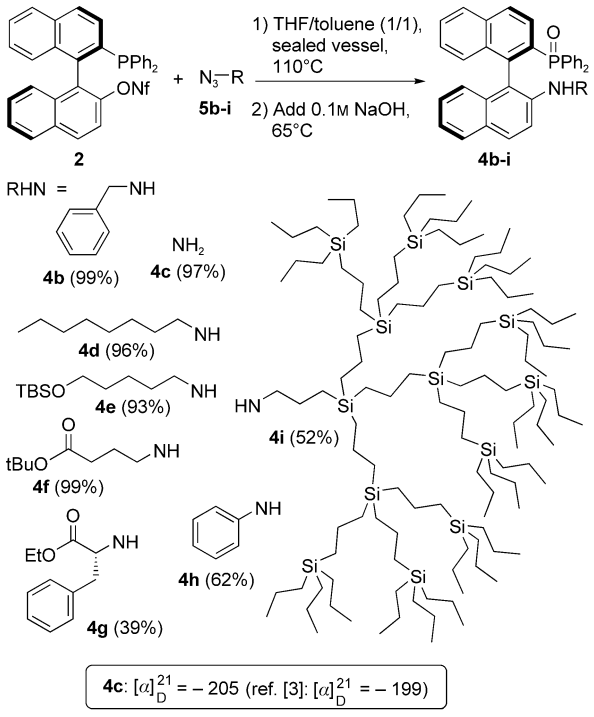


Scheme 3. A Staudinger approach towards P,N ligands.

In a first attempt, equimolar amounts of **2** and benzyl azide (**5b**) were heated at reflux in toluene. Much to our satisfaction, ^{31}P NMR spectroscopic analysis of the reaction mixture after 8 h revealed, besides some starting material and iminophosphorane **6b**, the anticipated aminophosphonium salt **7b** (Scheme 3, R = Bn). After heating for an additional 10 h, only aminophosphonium salt **7b** could be detected. Evaporation of the solvent yielded **7b** as an air-stable off-white viscous oil. Hydrolysis of the P–N bond was accomplished by refluxing **7b** in a mixture of EtOH/THF/aqueous 0.1M NaOH (1/1/1) to provide **4b**. Under optimized conditions (see Scheme 4) **4b** could be isolated almost quantitatively. It was observed that in the THF/toluene mixture iminophosphorane formation already proceeded at room temperature, whereas in toluene heating was required.[14]

To show the broad synthetic scope of this approach towards 2-amino-2′-diphenylphosphinoyl-1,1′-binaphthyl compounds **4** we treated **2** with azides **5b–i** (Scheme 4). To introduce a primary amino group, commercially available Me_3SiN_3 (12 equiv, added in 3 portions at 12-hour intervals) was stirred with **2** in THF/toluene (1/1) to give **4c** almost

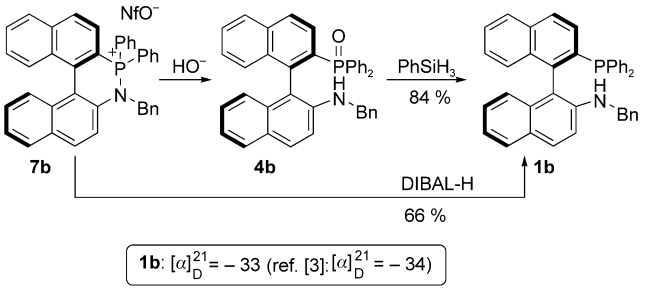


Scheme 4. A new approach to MAP(O)-type ligands. For each amino substituent RNH, the yield is given in brackets.

quantitatively. Thus, by using this Staudinger ligation method, des-dimethyl MAP(O) (**4c**), which is an important intermediate for the synthesis of MAP-type ligands, was synthesized from binol in 4 steps in an overall yield of 87%.[3] Comparison of the optical rotation of **4c** with literature data revealed that no racemization had taken place during the reaction sequence (see Scheme 4).[3] Also, we did not observe any change in the optical rotation after heating **4c**, which bears the small NH_2 group and is thus most prone to racemization, for 10 min at 300 °C. Prolonged heating led to decomposition of the product. These experiments show that racemization under the normal reaction conditions is very unlikely.

Azides with benzyl, *n*-alkyl, ether, or ester functionalities all reacted readily to provide **4b**, **4d**, **4e**, and **4f** in yields of 99, 96, 93, and 99%, respectively. The phenylalanine-derived α-azido ester **5g**, which was prepared from Phe-OEt by a diazo transfer, gave **4g** in 39% yield. The diazo-transfer reactions were performed as described in ref. [19]. Despite the lower nucleophilicity of its intermediate *N*,*N*-diaryliminophosphorane nitrogen atom, phenyl azide **5h** reacted smoothly to give **4h** in 62% yield. A very bulky third-generation carbosilane dendritic wedge featuring an azide in the focal point could also be introduced to give **4i** in 52% yield.[15]

For applications of **4a–i** in catalysis, reduction to the corresponding phosphane is required. As an example **4b** was treated with phenylsilane at 114 °C for 17 h to provide **1b** (84%, Scheme 5). A more convenient method would be the

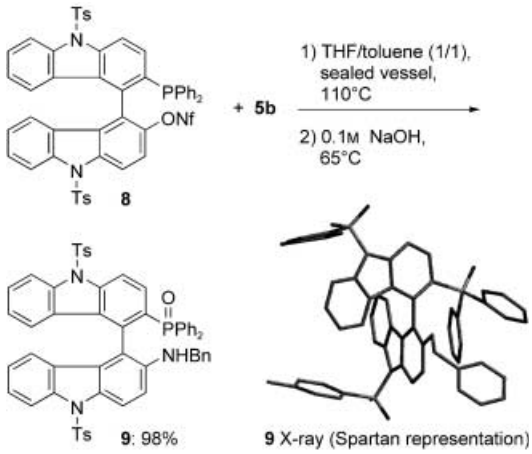


Scheme 5. Two routes to phosphanes derived from **4**. DIBAL-H = diisobutylaluminum hydride.

direct hydride-promoted cleavage of the P–N bond of the intermediate phosphonium salts **7**. Indeed, upon treatment of **7b** with DIBAL-H clean reduction occurred to provide optically pure **1b** (66% yield, Scheme 5).[3]

Finally, reaction of the racemic phosphanyl nonaflate of the structurally related bicol[16]-derived biscarbazole **8**[17] with benzyl azide (**5b**), followed by hydroxide treatment (Scheme 6) gave phosphane oxide **9** (98% yield), the structure of which was confirmed by X-ray analysis.[20]

In conclusion, we have shown that the synthetic potential of the 85-year-old Staudinger reaction[18] between phosphanes and azides is still far from being exhausted. The Staudinger reaction between 2-diphenylphosphanyl-2′-nonaflyloxy-1,1′-biaryl compounds and azides provides, through an unprecendented S_NAr reaction, a wide range of MAP(O)-type ligands in high yields and enantiomerically pure form in only 4 steps



Scheme 6. Synthesis and structure of **9**.

from binol. This strategy is especially attractive because the phosphorus atom is an essential element in the product instead of waste as in usual Staudinger approaches. Furthermore, the required number of synthetic steps is significantly decreased compared to the current synthetic routes towards MAP-type P,N ligands. Finally, this new method provides access to analogues which until now could only be prepared with great difficulty or not at all.

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[20] CCDC 239743 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

