Novel Palladium-Free Synthesis of a Key Quinazolinap Precursor

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Abstract: A novel, short synthetic route has been successfully developed for a key precursor of Quinazolinap ligands. The key step is a Friedel–Crafts-type reaction between 2-naphthol and 4-chloroquinazoline, with moderate to quantitative yields recorded. A variation of this reaction allows for the introduction of an amine group on the naphthalene unit.

Key words: arylation, Lewis acids, ligands, quinazolines, phenols

The expansion of the scope of catalytic asymmetric synthesis relies heavily on the design, preparation and evaluation of chiral ligands for transition metal complexes.[1] Chiral P–N ligands have proven over the years to form a synthetically useful class of ligands,[2] in which QUINAP (**1**) holds a central place. Developed by Brown in 1993, it opened the way to a class of atropisomeric chiral P–N ligands.[3] Today, applications exist in most of the fields of organometallic catalysis (hydroboration,[4] alkyne addition,[5] diboration,[6] and azomethine cycloaddition[7]). Our group has since then developed our own series of atropisomeric P–N ligands, Quinazolinap (**2**; Figure 1) which has been successfully applied to the rhodium-catalysed hydroboration of vinylarenes and palladium-catalysed allylic alkylation, with enantiomeric excesses up to 99% in the former application.[8]

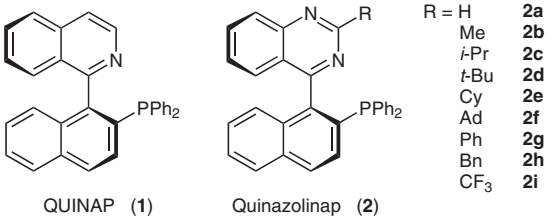
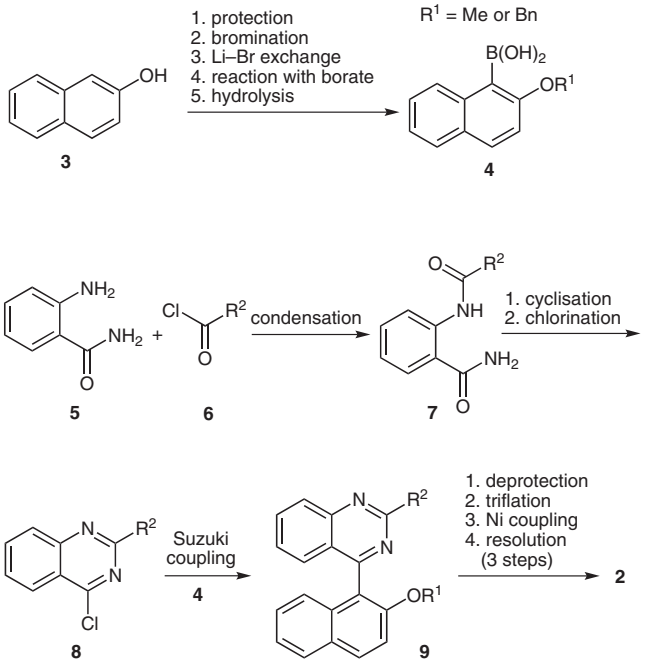


Figure 1

However, one of the obstacles to the widespread use of the Quinazolinap (**2**) ligands is the length of their synthesis. Overall fifteen steps were required to obtain the resolved ligand **2** (Scheme 1).[8] One of the key steps is the attachment of the upper and lower rings systems by a Suzuki–Miyaura reaction between a 4-chloroquinazoline **8** and a 2-alkoxynaphthalen-1-yl boronic acid **4**.

A first hint to a possible alternative route was given by Pal, Yeleswarapu and co-workers with their 4-substituted phthalazin-1(2*H*)-one synthesis.[9] They relied on a Friedel–Crafts-type reaction in order to react 1,4-dichlorophthalazine with various aromatic compounds, notably 2-naphthol (**3**). They found that the reaction was tolerant to free hydroxyl groups, and that 2-naphthol (**3**) was substituted exclusively in the 1-position. This idea was applied to the development of the PINAP class of ligands by Carreira and co-workers, which were used with impressive results in the field of alkyne additions.[10]



Scheme 1

In addition, the reaction of 4-chloroquinazoline **8** and 2,4-dichloroquinazoline with 1-naphthol to afford 4-(4-hydroxynaphthalen-1-yl)quinazoline and 2,4-bis(4-hydroxynaphthalen-1-yl)quinazoline, respectively, has been reported in the patent literature.[11] The reaction was selective for substitution at the 4-position of 1-naphthol. Similar conditions have been used recently with 2-naphthol (**3**) and 2,4-dichloroquinazoline, and afforded the expected product (substitution at the 1-position).[12]

The reaction conditions employed in the later process (3 equiv Lewis acid at 80 °C in DCE for 3.5 h) were tested on 4-chloroquinazoline (**8a**) and 2-naphthol (**3**) and we were pleased to obtain a good yield of 70% of the required product **9a** (Table 1, entry 1). The use of two equivalents of Lewis acid only slowed the reaction; whereas the use of

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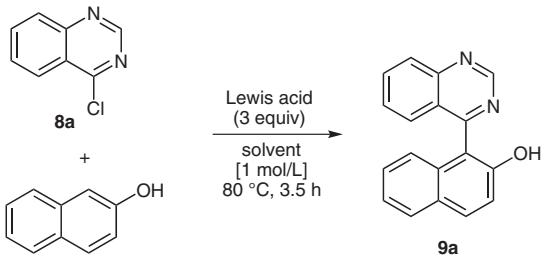
four equivalents had no beneficial effect (entries 2 and 3). Replacing $AlCl_3$ by other Lewis acids or the use of other solvents gave either no reaction (entry 4) or lowered the yield of the reaction (32–53%, entries 5–8).

Table 1 Reaction of 4-Chloroquinazoline (**8a**) and 2-Naphthol (**3**)



Entry	Lewis Acid	Solvent	Yield (%)
1	$AlCl_3$	DCE	70
2[a]	$AlCl_3$	DCE	43
3[b]	$AlCl_3$	DCE	68
4	$BF_3{\cdot}Et_2O$	DCE	0
5	$FeCl_3$	DCE	49
6	$AlCl_3$	DMSO	32
7	$AlCl_3$	Toluene	46
8	$AlCl_3$	CH_2Cl_2	53

[a] 2 equiv of Lewis acid were used.
[b] 4 equiv of Lewis acid were used.

As expected, the selectivity was excellent for the 1-position of the naphthalene unit and no other substitution pattern was observed. Moreover, no alkoxidation product was observed even though reports of such reactions exist with 4-chloroquinazolines, but neutral or basic conditions and high temperatures are required for the nucleophilic aromatic substitution to occur.[13]

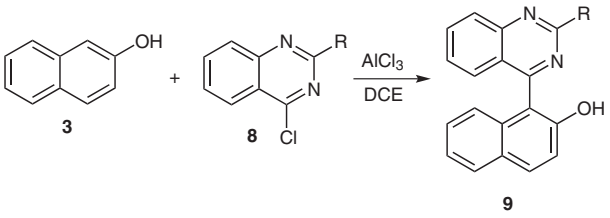
Compounds **8a–h** were obtained from anthranilamide and the corresponding acid chloride, followed by chlorination with phosphorus oxychloride according to the established procedure.[8]

The trifluoromethyl-substituted analogue **8i** was obtained in 74% yield starting with anthranilamide and trifluoroacetic anhydride. Biaryls **9a–i** were then prepared using the optimum conditions from Table 1, entry 1, in yields ranging from 55% to quantitative.

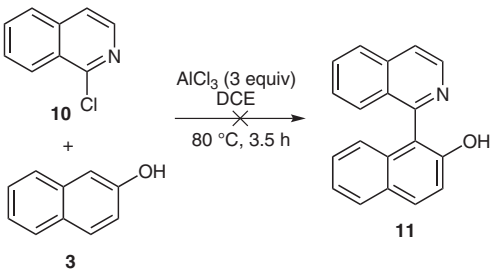
Steric hindrance appears to play an important role as the yields increase with the size of the R groups (Table 2, entries 2–6). Electronic effects seem also to play a role as substituents of similar size gave better results when they were more electron-withdrawing (Table 2, compare entries 2 and 9).

In an attempt to extend this methodology to the synthesis of QUINAP (**1**), 1-chloroisoquinoline (**10**) was tested as a substrate with our optimised arylation protocol (Scheme 2). However, despite variations of solvents, Lewis acid and temperatures, this did not allow for the formation of QUINAP precursor **11**. Reports of arylation between 2-naphthol (**3**) and 2- and 3-position substituted 1-chloroquinazoline do exist, but in these cases the reaction was promoted by UV irradiation.[14]

Table 2 Reaction of 2-Naphthol (**3**) and Various 4-Chloroquinazolines **8**

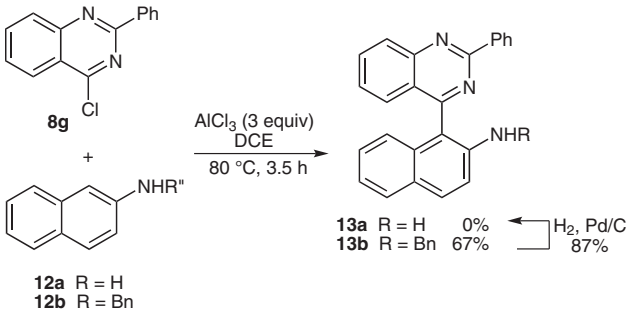


Entry	R	Product	Yield (%)
1	H	**9a**	70
2	Me	**9b**	55
3	*i*-Pr	**9c**	58
4	*t*-Bu	**9d**	85
5	Cy	**9e**	100
6	Ad	**9f**	100
7	Ph	**9g**	51
8	Bn	**9h**	100
9	CF_3	**9i**	100



Scheme 2

A preliminary study on the scope of our arylation protocol extended the substrates to 2-naphthylamines. The desired product **13a** was not obtained when 2-naphthol (**3**) was replaced by 2-aminonaphthalene (**12a**; Scheme 3). A mixture of compounds was obtained, and no single component could be isolated for identification. However, a benzyl-protected amine **12b** afforded compound **13b** in 67% yield. It was then successfully deprotected by palladium-catalysed hydrogenation to give the primary amine **13a** in 87% yield. Furthermore, this approach avoids the handling of 2-aminonaphthalene (**12a**) which is a known carcinogen.



Scheme 3

In conclusion, a robust new method has been developed to obtain the Quinazolinap scaffold.[15] Overall, five steps have been removed from the previous synthetic route as the nucleophilic component of the Suzuki reaction, the boronic acid, is no longer required because the biaryl is formed directly from 2-naphthol. The 2-trifluoromethyl-substituted intermediate **5i** is currently being progressed to give a novel Quinazolinap ligand. The approach reported herein is now the favoured method for the preparation of this class of ligand.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are procedures and spectroscopic data for previously unreported compounds **8i**, **9i**, **13a** and **13b**.

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(15) **Typical Procedure**: 2-Naphthol (1 mmol), 4-chloroquinazoline (1 mmol) and $AlCl_3$ (3 mmol) were suspended in DCE (3 mL) in a Schlenk tube under a nitrogen atmosphere. The mixture was heated at 80 °C for 3.5 h and then diluted with CH_2Cl_2 (15 mL). The mixture was washed with 1 M NaOH solution (15 mL), sat. NH_4Cl solution (15 mL), H_2O (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product could be directly used in the subsequent steps of the synthesis without significant loss of yield compared to the use of pure compound. Nevertheless, purification was achievable by column chromatography using silica gel and CH_2Cl_2 as eluent. Compounds were identical to known samples.