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Scalable synthesis of dihydroxyterphenylphosphine ligands

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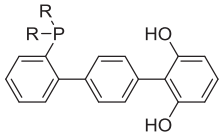
ABSTRACT

We have developed an improved method for the synthesis of dihydroxyterphenylphosphines (DHTPs), which are important ligands used in the palladium-catalyzed *ortho*-selective cross-coupling of dihalophenols or dihaloanilines. This method is simple, easily scalable, and has been used to produce multigram quantities of Cy-DHTP·HBF_4 and Ph-DHTP in five steps.

1. Introduction

Palladium-catalyzed cross-coupling is a powerful tool for carbon–carbon bond formation and has various synthetic applications in academia and industry.[1] Mono-cross-coupling of organic dihalides or pseudohalides such as triflates is a hugely important tool for the synthetic chemist and is used extensively, both in the synthesis of important final products and in the production of useful intermediates. It is widely used to achieve chemoselective coupling in which the selectivity depends on the intrinsic reactivity of the two different halo groups. However, site-selective coupling between two identical halo groups is more challenging, and much effort has been devoted to improving the efficiency and application of this reaction.[2] In most examples of site-selective cross-coupling, the selectivity is controlled by the substrates used. However, site-selective cross-coupling in which the selectivity is controlled by catalysts has recently attracted growing interest, and several types of ligands, including phosphines, have been used to achieve good results.[3]

We have previously reported the development of hydroxylated oligoarene-type phosphine ligands.[4] The design of these phosphines was based on biphenylphosphines developed by Buchwald et al.,[5] with the hydroxy groups expected to allow the molecules to perform as bifunctional ligands.[6] During our investigations, we found that the catalysts derived from palladium and dihydroxyterphenylphosphines (DHTPs, Fig. 1) showed excellent *ortho*-selectivity in the Kumada–Tamao–Corriu coupling of dihalophenols or dihaloanilines with Grignard reagents.[7] Cy-DHTP was also found to be effective for the *ortho*-selective Sonogashira coupling of dichlorophenols or *N*-tosyl-dichloroanilines with terminal alkynes, yielding a product, which could be cyclized to the corresponding chlorobenzo[*b*]furan[8] or chloroindole.[9] These *ortho*-selective cross-coupling reactions can only be achieved using DHTPs, due to their ability to form effective bimetallic (palladium/magnesium or palladium/lithium) species during the reaction.[10] This unique function makes DHTPs attractive ligands for the further development of practical, site-selective cross-coupling methods.



Cy-DHTP (R = Cy)
Ph-DHTP (R = Ph)

Fig. 1. Dihydroxyterphenylphosphines.

While DHTPs were found to be effective ligands, their synthesis was cumbersome and difficult to scale up. The original synthetic route[7a] to DHTPs is shown in Scheme 1. Starting from 1-bromo-2-iodobenzene, a phosphino group was first introduced and then oxidized to the corresponding phosphine oxide to protect against partial oxidation during the synthesis. After construction of the terphenyl backbone by Suzuki–Miyaura coupling,[11] demethylation and reduction of the phosphine oxide afforded the desired phosphine ligand. This route successfully afforded Cy-DHTP with 38%

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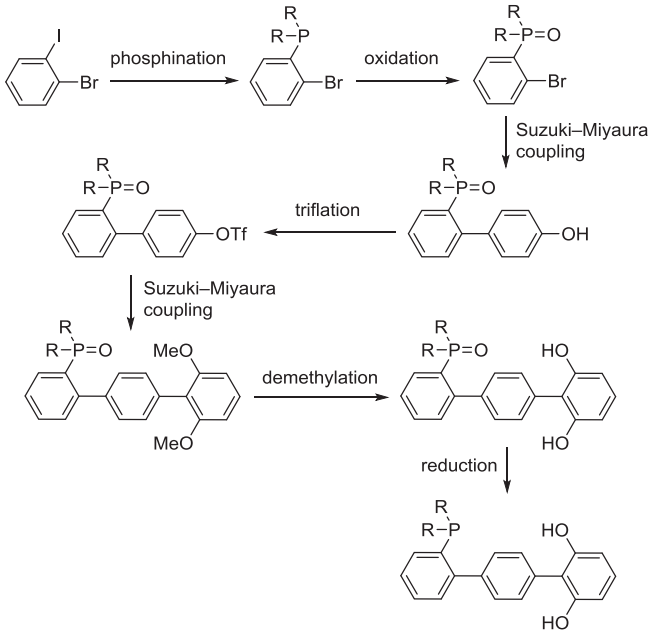


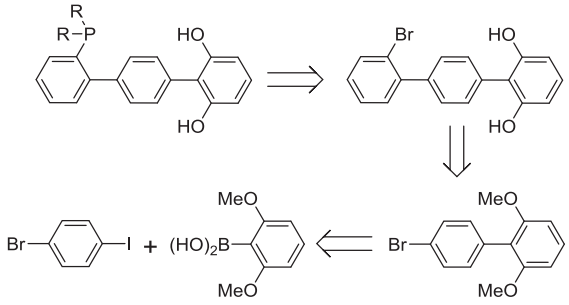
Scheme 1. Original synthetic route to DHTPs.

total yield, and Ph-DHTP with 45% total yield. However, the total number of steps is increased due to the oxidation/reduction of the phosphino group. The necessity for a sealed tube in the reduction step and the need for time-consuming column chromatography in several steps also limited the practicality of this synthetic route. To develop the application of DHTP, a more facile and practical method for their synthesis was desirable. Herein, we present an operationally simple and scalable synthesis of DHTPs, in which they are prepared in five steps.

2. Results and discussion

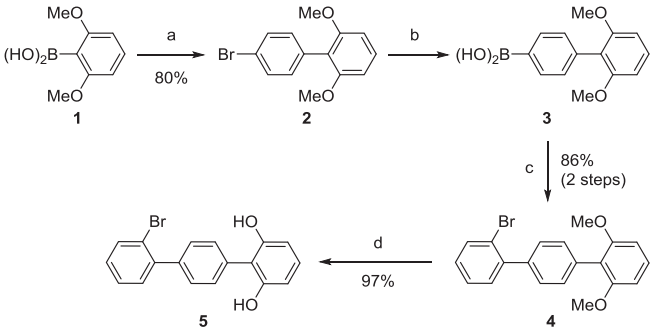
2.1. Synthesis of Cy-DHTP

To make the production of DHTPs more practical and scalable, we designed a new synthetic route (Scheme 2). In this route, the terphenyl backbone is constructed first and the phosphino group is introduced in the final stage, thus avoiding the additional oxidation/reduction steps for the phosphino group, and reducing the total number of steps. It should also be noted that DHTPs with different phosphino groups can be synthesized easily from the common intermediate merely by changing the phosphinating agents used in the final step. The Li–Br exchange followed by phosphination with R_2PCl was chosen for the final step, although this reaction in the presence of the two OH groups was challenging. We also investigated alternative purification methods in each step in order to avoid the use of column chromatography.



Scheme 2. Retrosynthetic analysis for a new route to DHTPs.

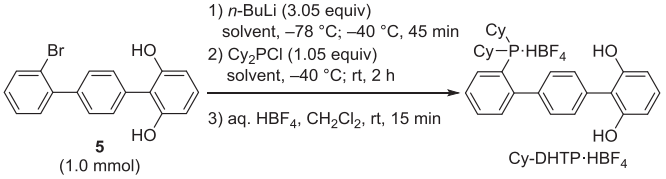
The synthesis commenced with the commercially available 2,6-dimethoxyphenylboronic acid (**1**, Scheme 3). Suzuki–Miyaura coupling of **1** and 1-bromo-4-iodobenzene was performed under the conditions reported by Sherburn et al.[12] Biphenyl **2** was obtained after purification by recrystallization from hexane. Biphenyl **2** was then converted to boronic acid **3**, which was coupled with 1-bromo-2-iodobenzene to give terphenyl **4**. Recrystallization from CH_2Cl_2/hexane gave pure **4** in good yield. Demethylation of **4** with BBr_3 proceeded quantitatively, and purification by passing through a short pad of silica gel afforded hydroxylated terphenyl **5** in excellent yield. All the reactions can easily be conducted at the multigram scale, and the phosphination-step precursor **5** was obtained in four steps.



Scheme 3. Synthesis of **5**. Reagents and conditions. (a) 1-Bromo-4-iodobenzene, $Pd(PPh_3)_4$, Cs_2CO_3, toluene/MeOH, 100 °C, 18 h; (b) *n*-BuLi, THF, −78 °C to −50 °C, 0.5 h; $B(OiPr)_3$, −50 °C to rt, 3 h; (c) 1-Bromo-2-iodobenzene, $Pd(PPh_3)_4$, Cs_2CO_3, toluene/MeOH, 100 °C, 24 h; (d) BBr_3, CH_2Cl_2, rt, 3 h.

With precursor **5** afforded with high purity and in excellent yields, we investigated the introduction of the dicyclohexylphosphino group to synthesize Cy-DHTP (Table 1). The conditions were optimized at the 1 mmol scale. Deprotonation of the hydroxy groups of **5** by NaH prior to lithiation of the bromo group was ineffective and did not give the desired product (Table 1, entry 1). The use of 3.05 equiv of *n*-BuLi for both deprotonation and lithiation was attempted. To prevent lithiation before complete deprotonation of the two phenolic hydroxy groups, a two-solvent system (Et_2O/THF)[13] was employed. However, the yield was low due to the low solubility of the resulting lithium salt of **5** (Table 1, entry 2). Increasing the amount of the solvents and the ratio of Et_2O/THF greatly improved the yield (Table 1, entry 3). The reaction in Et_2O gave a poorer result (Table 1, entry 4). However, the reaction in THF afforded the product in higher yield, and the optimal concentration

Table 1
Conditions used for the introduction of the dicyclohexylphosphino group



Entry	Solvent	Concentration (M) in the second step	Yield (%)[a]
1[b]	THF	0.12	Trace
2	Et_2O/THF (1/2)	0.20	6
3	Et_2O/THF (1/1)	0.05	49
4	Et_2O	0.03	31
5	THF	0.06	50
6	THF	0.03	57
7	THF	0.01	54

[a] Isolated yields.
[b] NaH (2.05 equiv), THF, rt, 1 h; *n*-BuLi (1.05 equiv), −78 °C to −10 °C, 45 min; Cy_2PCl (1.0 equiv), rt, 2 h; aq HBF_4, CH_2Cl_2, rt, 15 min.