ORGANIC LETTERS

2003
Vol. 5, No. 3
297−300

Direct Synthesis of Ferrocenylmethylphosphines from Ferrocenylmethyl Alcohols and Their Application as Ligands for Room Temperature Pd(0)-Catalyzed Suzuki Cross-Couplings of Aryl Bromides

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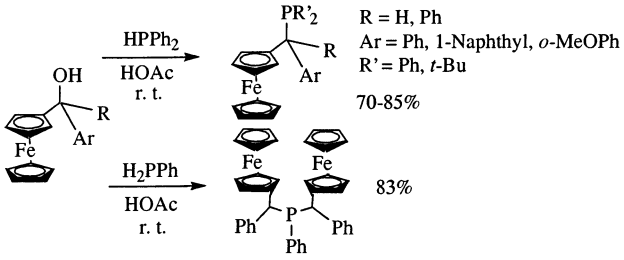
Received November 10, 2002

ABSTRACT



The direct, high-yield conversion of readily available ferrocenylmethyl alcohols to ferrocenylmethylphosphines and the application of ferrocenylmethylphosphines as efficient ligands for room temperature Suzuki cross-coupling reaction of aryl bromides with phenylboronic acid are reported. The procedure of directly converting ferrocenylmethyl alcohols to ferrocenylmethylphosphines described here should find applications in the synthesis of many metallocenylmethylphosphines including optically active ones.

The study of using bulky, electron-rich monophosphines as ligands for transition metal-catalyzed reactions has attracted much attention in recent years since they have been demonstrated as unique, highly efficient ligands for a number of transition metal-catalyzed transformations.[1−6] For example, Fu and others showed that tri-*tert*-butylphosphine (**1**) is a highly efficient ligand for palladium(0)-catalyzed cross-coupling reactions of Suzuki coupling, Heck coupling, Stille coupling, and aminations.[1,2] Miyaura demonstrated the uniqueness of **1** for Rh-catalyzed arylation of aldehydes.[3] Buchwald and co-workers developed a series of dialkylarylphopshines as represented by **2** for the room temperature Suzuki cross-coupling reactions and aminations.[4] Hartwig and co-workers showed that ferrocenylphosphines such as

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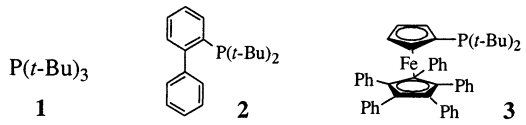
10.1021/ol0272601 CCC: $25.00
Published on Web 01/04/2003

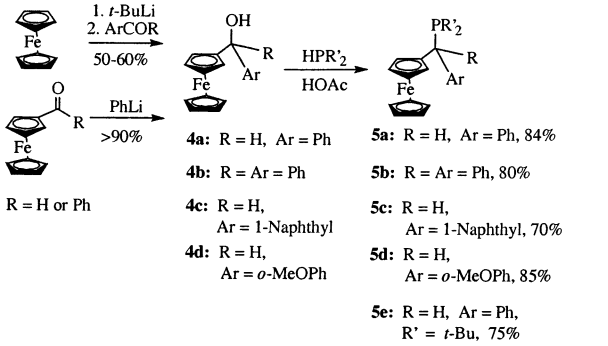
3 are also very effective ligands for arylation and amination reactions.[5] However, only a few examples of electron-rich monophosphines have been developed to date.[1−6] It is thus of continuing interest to develop new electron-rich monophosphines including optically active ones for transition metal catalysis.



In our efforts to develop highly efficient ligands for transition metal-catalyzed reactions, we are interested in developing a system that will allow us to access a family of monophosphines including optically active ones. We have elected to synthesize ferrocenylmethylphosphines from ferrocenylmethyl alcohols based on the following considerations: (a) ferrocenylmethyl alcohols including optically active forms are readily available, (b) the unique retentive S_N1 reaction at the α-position would allow the easy access of a family of ferrocenylmethylphosphines including optically active ones,[7] and (c) the steric and electronic properties of ferrocenylmethylphosphines can be systematically tuned. Although directly converting ferrocenylmethyl alcohols to ferrocenylmethylphosphines is the most efficient way to synthesize ferrocenylmethylphosphines, this process was only realized in low yields and has not been established as a synthetically useful method.[8] Instead, indirect methods involving two or more steps, i.e., converting ferrocenylmethyl alcohols to ferrocenylmethyl acetates or ferrocenylmethylamines followed by conversion to ferrocenylmethylphosphines, have been developed and used.[9,10] We reasoned that if ferrocenylmethyl carbocations, which are involved as the intermediates in the indirect methods, can be efficiently formed directly from ferrocenylmethyl alcohols in the presence of phosphines, it is possible to directly convert ferrocenylmethyl alcohols to ferrocenylmethylphosphines in synthetically useful yields. Achieving this would provide a highly efficient method to access a large family of potentially useful ferrocenylmethylphosphines. Herein the direct conversion of ferrocenylmethyl alcohols to ferrocenylmethylphosphines and the application of ferrocenylmethylphosphines as efficient ligands for the room temperature Suzuki cross-coupling of phenylboronic acid with aryl bromides are reported.

We began our study by preparing ferrocenylmethyl alcohols. Three methods have been used for this purpose: the procedure developed by Kagan,[11] the reaction of ferrocenecarboxaldehyde or ferrocenyl ketones with aryllithium reagents,[9a] and reduction of ferrocenyl ketones.[12,13] By following Kagan's method, reaction of ferrocene with *t*-BuLi in THF at 0 °C followed by treatment with aldehydes or benzophenone generated alcohols **4** in 33−78% yields, along with the disubstituted products which are separable from **4** by flash chromatography. Since ferrocenecarboxaldehyde and ferrocenyl ketones are readily available, we have also explored their reaction with lithium reagents. This route gave higher yields than Kagan's procedure. For example, reaction of ferrocenecarboxaldehyde or benzoylferrocene with phenyllithium generated **4a** and **4b** in 91% and 92% yield, respectively (Scheme 1).

Scheme 1. Synthesis of Ferrocenylmethylphopshines **5**



Acetic acid has been demonstrated as a suitable reaction media (proton source and solvent) for reactions involving ferrocenylmethyl carbocation intermediates and has been demonstrated to be compatible with phosphines.[9,10,14] For example, Richards reported the conversion of ferrocenylmethyl alcohols to ferrocenylmethyl methyl ethers using acetic acid as the proton source.[14] Togni reported the synthesis of ferrocenylmethylphosphines from ferrocenyl-

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(10) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Lander, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

(11) (a) Guillaneux, D.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 2502. (b) Rebiere, F.; Samuel, O.; Kagan, H. B *Tetrahedron Lett.* **1990**, *31*, 3121.

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(13) Wright, J.; Frambes, L.; Reeves, P. *J. Organomet. Chem.* **1994**, *476*, 215.

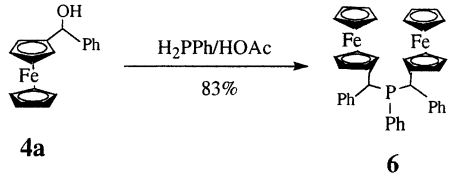
(14) (a) Locke, A. J.; Gouti, N.; Richards, C. J.; Hibbs, D. E.; Hursthouse, M. B. *Tetrahedron* **1996**, *52*, 1461. (b) Locind, A. H.; Richards, C. J. *Tetrahedron Lett.* **1996**, *37*, 7861.

methylamines in acetic acid.[10] Acetic acid was thus selected as solvent and proton source for the conversion of ferrocenylmethyl alcohols **4** to ferrocenylmethylphosphines **5**. We found that **4** smoothly reacted with diphenylphosphine in acetic acid to afford **5** in 70−85% yields (Scheme 1). Although the reaction was initially carried out at 60 °C, we later found the conversion occurred smoothly at room temperature. As an example, the synthesis of **5a** is given here: under nitrogen, to a solution of **4a** (1 mmol) in acetic acid (8 mL) was added diphenylphosphine (4 mL, 10% in hexanes) at room temperature. The solution turned from reddish yellow to yellow immediately and a precipitation, which was confirmed as the product by ^{1}H and ^{31}P NMR, was observed within 5 min. After the mixture was stirred for 4 h, the solvent was evaporated and the solid was collected by filtration and washing with hexanes and methanol. After the solid was dried under vacuum, **5a** was obtained as a yellow solid in 83% yield. The ^{31}P NMR spectrum of **5a** shows a singlet at 4.8 ppm (H_3PO_4 as standard). Other ferrocenylmethylphosphines **5b**−**d** were prepared in a similar manner. **5a**−**d** are air-stable solids, but can be gradually oxidized in solution under air.

When **4a** reacted with di-*tert*-butylphosphine, trialkylphosphine **5e** was obtained (Scheme 1). Like other trialkylphosphines, **5e** is air-sensitive. For easy handling, **5e** was protected as the **5e**·BH3 complex.[15,16]

The successful realization of diphenylphosphine with ferrocenylmethyl alcohols to form ferrocenylmethylphosphines in high yields encouraged us to synthesize bis(ferrocenylmethyl)phosphines such as **6** directly from ferrocenylmethyl alcohols.[8] Thus, reaction of **4a** with phenylphosphine in acetic acid at room temperature smoothly yielded **6** as a yellow solid in 83% (Scheme 2). The ^{31}P NMR

Scheme 2. Synthesis of Bis(ferrocenylmethyl)phosphine **6**

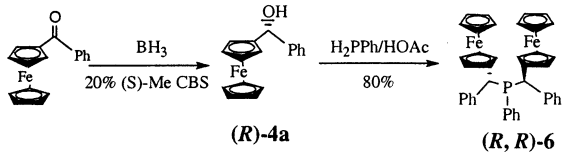


4a **6**

spectrum of **6** showed two singlets at 17.4 and 19.2 ppm, corresponding to the two isomers (*R*,*R*/*S*,*S* and *R*,*S*). The almost 1:1 ratio of the two singlets suggests that the initially formed chiral (ferrocenylphenylmethyl)phenylphosphines further react with (*R*)- or (*S*)-ferrocenylmethyl alcohol **4a** at similar rates.

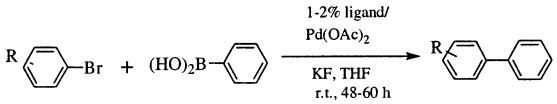
It has been established that the nucleophilic substitution at the α-position of the ferrocenyl group is configurationally retentive.[17] This unique retentive S_N1 reaction pattern implies that optically active ferrocenyl monophosphines could be readily accessible from optically active ferrocenylmethyl alcohols which are readily available by asymmetric reduction of ferrocenyl ketones.[13] We have carried out the direct conversion of optically active ferrocenylmethyl alcohol (*R*)-**4a** to optically active bis(ferrocenylmethyl)phosphine (*R*,*R*)-**6** (Scheme 3). (*R*)-**4a** was prepared in 98% ee by the asymmetric reduction with (*S*)-methyl oxazaborolidine (CBS) as the chiral catalyst.[13] When (*R*)-**4a** was treated with phenylphosphine in acetic acid at room temperature, (*R*,*R*)-**6** was obtained in 80%. The ^{31}P NMR spectrum of (*R*,*R*)-**6** shows a predominant singlet at 17.4 ppm and a minor peak at 19.2 ppm in a 53:1 ratio. The ratio corresponds to a 99% portion of (*R*)-ferrocenylmethyl and a 1% portion of (*S*)-ferrocenylmethyl based on the assumption that the initially formed chiral (ferrocenylphenylmethyl)phenylphosphines further re-

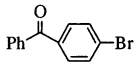
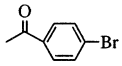
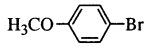
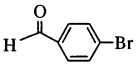
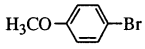
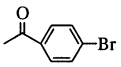
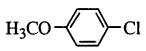
Scheme 3. Synthesis of Optically Active Ferrocenylmethylphosphine (*R*,*R*)-**6**



(*R*)-4a **(*R*, *R*)-6**

Table 1. Room Temperature Pd(0)-Catalyzed Suzuki Cross-Coupling Reaction of Aryl Bromides with Phenylboronic Acid[a]



entry	Ar-Cl	ligand	yield
1		**5a**	95%
2		**5a**	85%
3		**5a**	99%
4		**5a**	86%
5		**5a**	99%
6		**5b**	90%
7		**5c**	90%
8		**5a**	0%

[a] Reaction conditions: aryl bromide (1.0 equiv), phenylboronic acid (1.5 equiv), KF (3 equiv), ligand (1−2%), THF (2 mL), room temperature. Reaction times have not been minimized.

(15) Mckinstry, L.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 7655.
(16) Recently, Fu reported the use of HBF_4 as a protection reagent: Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.
(17) Reference 8, Chapter 4, p 173. See also: refs 10 and 12a,b.

act with (*R*)- or (*S*)-**4a** at the same rates. Therefore, the conversion of (*R*)-**4a** to (*R*,*R*)-**6** is not accompanied by racemization.

Pd(0)-catalyzed Suzuki cross-coupling reactions of aryl halides with arylboronic acids represent one of the most powerful transformations in organic synthesis.[18] Among numerous protocols developed, relatively few examples of Suzuki cross-coupling reactions of aryl bromides occur at room temperature and most of them involve the use of dialkyl or trialkyl monophosphines as ligands.[19] We have employed monoalkylphosphines **5a**−**c**, which are less electron-rich than dialkyl or trialkyl monophosphines, as ligands for the room temperature Suzuki cross-coupling reactions of aryl bromides. Our results showed that these ferrcenylmethylphosphines are highly efficient ligands for this transformation. As shown in Table 1, (1−2%) **5a**−**c**/Pd(0) complexes (1:1 or 2:1) can smoothly catalyze the coupling reaction between aryl bromides including electron-rich ones and phenylboronic acid. The cross-coupling reaction of less active *p*-chloroanisole with phenylboronic acid catalyzed by 2% **5a**/$Pd(OAc)_2$ (1:1 or 2:1) was also carried out and no reaction was observed.

In summary, we have demonstrated that ferrocenylmethylphosphines including monoalkyl, dialkyl, and trialkyl ones can be directly synthesized in high yields from readily available ferrocenylmethyl alcohols. Monoalkyl ferrocenylmethylphosphines have been used as efficient ligands for room temperature Suzuki cross-coupling reaction of aryl bromides with phenylboronic acid. The method of directly converting ferrocenylmethyl alcohols to ferrocenylmethylphosphines should find applications in the synthesis of many ferrocenylmethylphosphines and metallocenylmethylphosphines, including optically active ones. The synthesis and application of these monophosphines are under active investigation and the results will be reported in due course.

Acknowledgment. This work was supported by the Department of Chemistry, College of Staten Island-City University of New York (CUNY). Partial support from the Petroleum Research Fund administered by the American Chemical Society and Professional Staff Congress-CUNY Research Award Programs is gratefully acknowledged.

Supporting Information Available: Synthesis of **4**, **5**, and **6**, and procedure for the Suzuki cross-couplings. This material is available free of charge via the Internet at http://pubs.acs.org.

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