New Coupling Reactions and Phosphorylations Using Organozinc Reagents

Paul Knochel*, Falk Langer, Alexia Longeau, Mario Rottländer, and Thomas Stüdemann

Fachbereich Chemie der Philipps-Universität Marburg
Hans-Meerwein-Straße, D-35032 Marburg, Germany
Fax: (internat.) +49(0)6421-282189
E-mail: Knochel@ps1515.chemie.uni-marburg.de

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This Microreview on the chemistry of organozinc reagents starts by briefly showing the methods of preparation of organozinc compounds and then discusses the considerable synthetic utility of zinc organometallics for the formation of new carbon−carbon bonds in the presence of transition-metal catalysts. Finally, the use of organozinc chemistry for the preparation of polyfunctional and chiral phosphanes is described.

Organozinc reagents have been known for more than 150 years[1]. However, their application to organic synthesis was limited to very specific reactions like cyclopropanation[2] and the aldol reaction[3] due to the moderate reactivity of organozinc compounds. Interest in these compounds was rekindled about 10 years ago when it became clear that the

Paul Knochel (center right), born in 1955, completed his Ph.D. under the supervision of Prof. Dieter Seebach in 1982 (ETH Zürich). He joined the CNRS in Paris and worked in the laboratory of Prof. Jean-François Normant until 1986. After a year of postdoctoral research at Princeton University with Prof. Martin F. Semmelhack, he became assistant professor at the University of Michigan in Ann Arbor (USA) and full professor in 1991. In 1992 he moved back to Europe and accepted a C4 professorship at the Philipps-Universität Marburg (Germany). In 1994 he was awarded the Thieme-IUPAC prize in Synthetic Organic Chemistry, in 1995 the Otto-Bayer prize and in 1996 the Leibniz prize. His research is focussed on the use of organometallic reagents for the development of new synthetic methodologies.

Falk Langer (right), born in 1967, studied chemistry from 1987 to 1993 at the Philipps-Universität Marburg (Germany) and received his Ph.D. under the supervision of Prof. Knochel in 1996. During his Ph.D. studies he developed the boron-zinc exchange reaction and its application in phosphorus chemistry.

Alexia Longeau (center), born in 1971, studied chemistry from 1989 to 1994 at the University of Poitiers, Nantes (France). Since 1994 she has been working in Prof. Knochel's group towards her Ph.D. Her research studies involve phosphorus chemistry and particularly the preparation of chiral phosphines.

Mario Rottländer (center left), born in 1969, studied chemistry from 1990 to 1995 at the Philipps-Universität Marburg (Germany) and UMIST (Manchester, U.K.). Since 1996 he has been working in Prof. Knochel's group towards his Ph.D. His research studies involve palladium-catalyzed cross coupling reactions and combinatorial chemistry.

Thomas Stüdemann (left), born in 1968, studied chemistry from 1989 to 1995 at the Universität Bielefeld (Germany), the University of Michigan in Ann Arbor (USA) and the Philipps-Universität Marburg (Germany). Since 1995 he has been working towards his Ph.D. in Prof. Knochel's group. His research studies involve nickel- and palladium-catalyzed carbometallation and cross coupling reactions.

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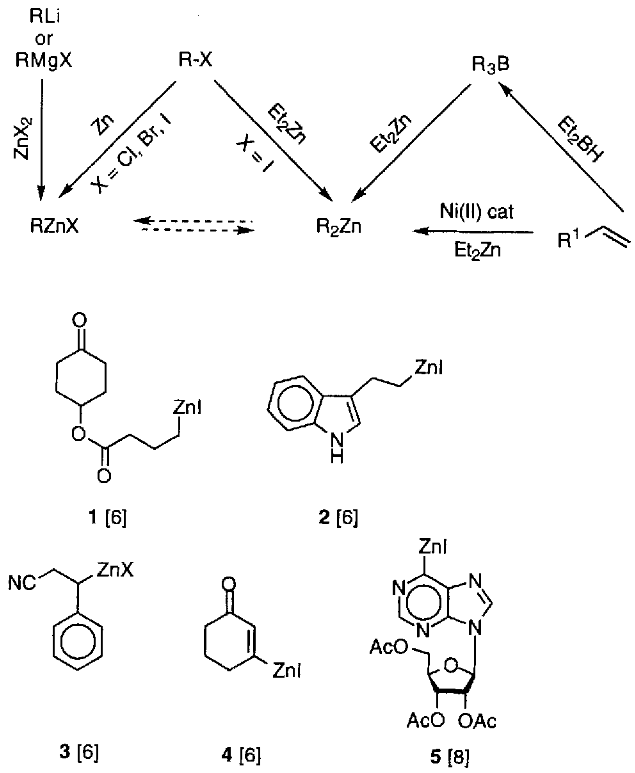
reactivity of organozincs can be dramatically increased by the use of transition-metal catalysis. Negishi[4] first demonstrated that organozincs are ideal reagents for the performance of cross-coupling reactions in the presence of catalytic amounts of palladium(0) complexes. Soon it became clear that the moderate reactivity of the carbon–zinc bond is, in fact, an advantage since it allows the preparation of highly functionalized organozinc reagents[5]. Furthermore, the pioneering work of Negishi could be extended and transition-metal complexes of many transition metals (Ni, Co, Fe, Ti) efficiently catalyze reactions of organozincs with organic electrophiles.

Preparation of Organozinc Compounds

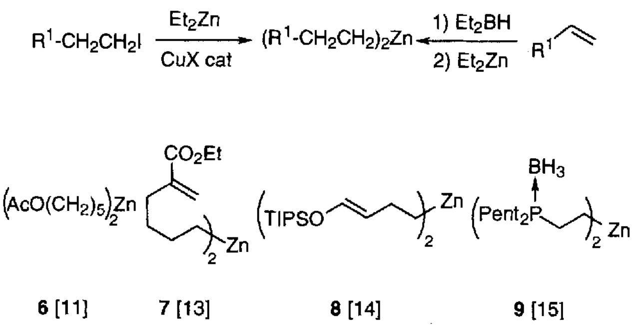
There are two classes of organozinc species: the organozinc halides (RZnX) and the diorganozincs (R_2Zn). The organozinc halides can be prepared either by transmetalations of organolithium or Grignard reagents or, more importantly, by the insertion of zinc into an organic halide[6]. This last method is of special importance since it allows the preparation of a range of polyfunctional organozinc halides[6–8] like **1**–**5** (Scheme 1). Diorganozincs are more reactive than organozinc halides and find numerous applications in asymmetric synthesis[9,10]. They can be prepared by an iodine–zinc exchange reaction[11] starting from a primary alkyl iodide. Treatment of the appropriate alkyl halide at 50°C with Et_2Zn[1] in the presence of a catalytic amount of copper(I) halide gives the desired diorganozinc in good yield. A method of similar utility, but proceeding under milder reaction conditions, is the boron–zinc exchange reaction, which allows olefins to be converted to diorganozincs by a successive one-pot hydroboration followed by a boron–zinc exchange reaction mediated by Et_2Zn[6,7]. Finally, a nickel(II)-catalyzed hydrozincation is also possible, but this reaction suffers from a lack of generality[12]. The iodine– and boron–zinc exchange reactions permit the general preparation of polyfunctional primary diorganozincs like **6**–**9**[13–15] (Scheme 2). Interestingly, by using (*iso*-Pr)$_2$Zn instead of Et_2Zn in the boron–zinc exchange reaction, it was possible to extend this reaction to the preparation of configurationally well defined cyclic organozinc derivatives. After quenching with an electrophile, such as D_2O, a high retention of configuration was observed (Scheme 3)[16].

Scheme 1



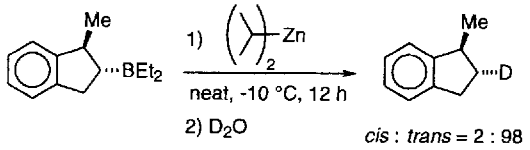
1 [6] **2** [6] **3** [6] **4** [6] **5** [8]

Scheme 2



6 [11] **7** [13] **8** [14] **9** [15]

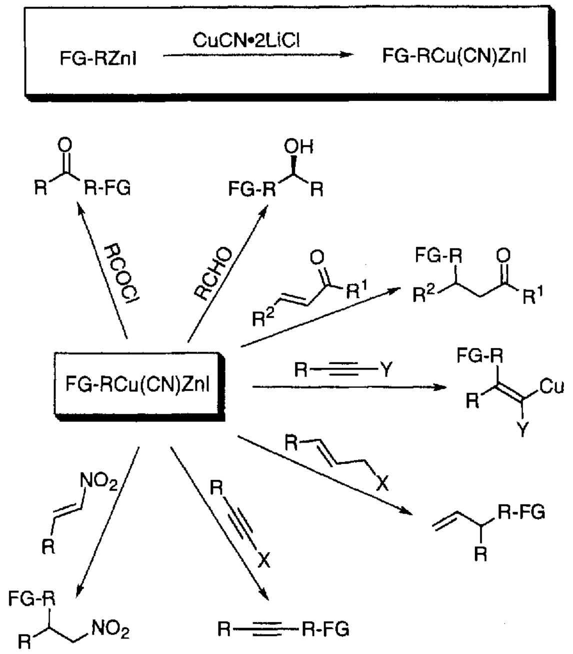
Scheme 3



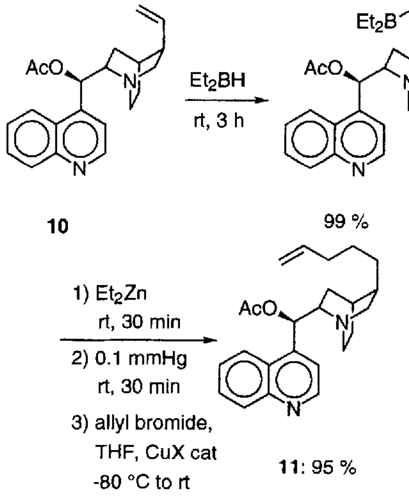
Reactivity of Organozinc Compounds towards Carbon Electrophiles

The reactivity of zinc organometallics can be dramatically increased by adding catalytic or stoichiometric amounts of the THF-soluble salt CuCN · 2 LiCl (Scheme 4)[5]. After this transmetalation, the resulting copper–zinc species display a similar reactivity to copper reagents prepared from organolithium or magnesium reagents. This fact considerably enhances the scope of organocopper chemistry, since the use of organozincs as precursors allows the use of polyfunctional organometallics. The performance of allylation or propargylation reactions is especially efficient (Schemes 5 and 6). Thus the unsaturated alkaloid **10** was hydroborated with Et_2BH[7] and converted to the corresponding zinc compound by treatment with Et_2Zn. After the addition of allyl bromide and a catalytic quantity of the copper salt, the expected allylated product **11** was obtained in 95% yield (Scheme 5)[17]. The zinc compound **12**, derived from a chiral amino acid, reacts with propargyl bromide in the presence of CuCN to give the allenyl amino acid **13** in 55% yield[18].

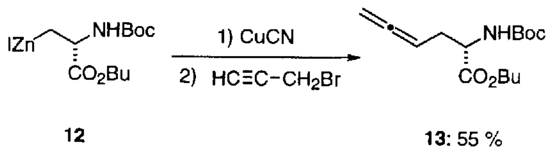
Scheme 4



Scheme 5

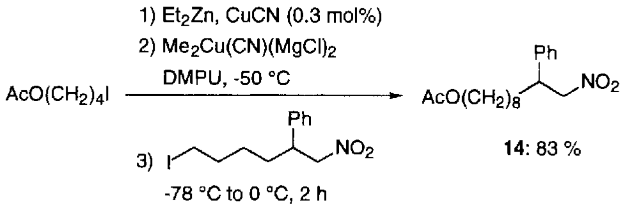


Scheme 6



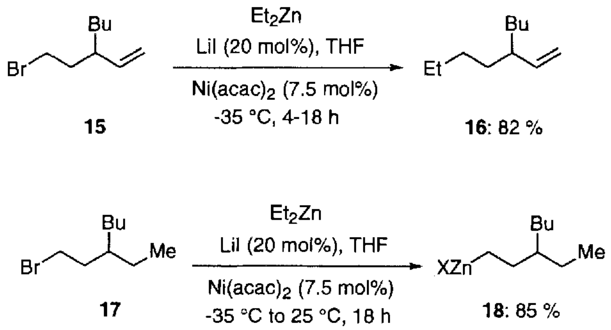
The cross-coupling between Csp^3−Csp^3 is still a challenging problem. The stoichiometric formation of copper reagents derived from organolithium and magnesium compounds has often been used[19]. The preparation of a mixed zincate obtained by the reaction of a diorganozinc with $Me_2CuMgCl \cdot MgCl(CN)$ allows substitution reactions at Csp^3 centers and leads to polyfunctional molecules like **14** in excellent yield (Scheme 7)[20].

Scheme 7

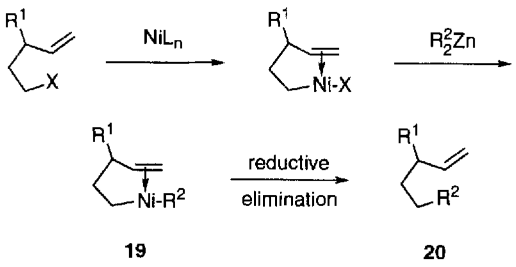


More interesting from a practical point of view are cross-coupling reactions between Csp^3 centers in which a transition metal is used as catalyst. Such a reaction can be accomplished with an Ni(II) catalyst using alkyl bromides bearing a double bond at a remote position. Thus, the reaction of **15** with Et_2Zn at −35°C provides the desired cross-coupling product **16** in 82% yield (Scheme 8). The presence of the double bond in **15** is crucial to the success of the reaction, because in its absence no cross-coupling is observed. The saturated alkyl bromide **17** furnishes only the bromide−zinc exchange product **18**. This behavior can be explained by assuming that the double bond complexes to the intermediate Ni(II) species **19**, as shown in Scheme 9[21]. This complexation removes electron density from the metal center and therefore favors reductive elimination, leading to **20**. This method can be used to prepare polyfunctional molecules like **21**, using catalytic amounts of $Ni(acac)_2$ (7.5 mol%; Scheme 10). Remarkably, these reactions proceed at −35°C, showing that under appropriate reaction conditions, transition-metal-catalyzed cross-coupling reactions at Csp^3 centers can be faster than cross-coupling reactions at Csp^2 centers. Typical reaction conditions of the Negishi reaction lie between 0°C and 50°C[4].

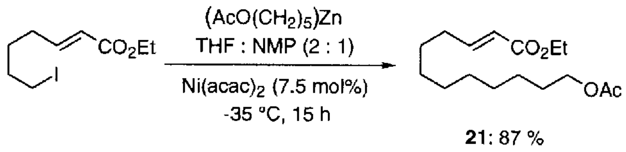
Scheme 8



Scheme 9

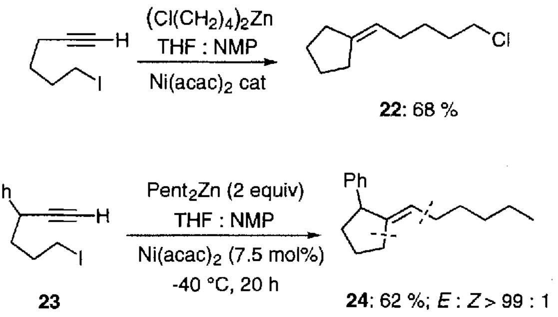


Scheme 10

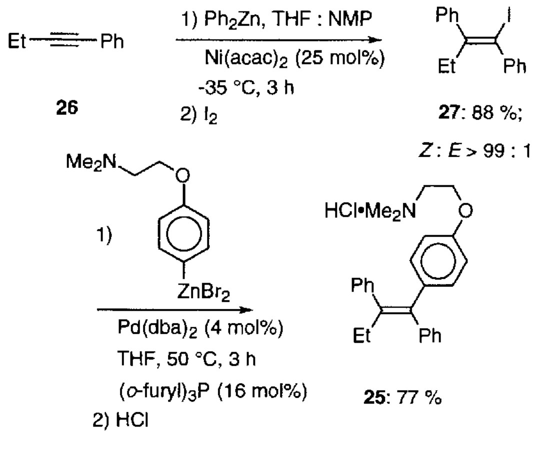


The presence of a triple bond instead of a double bond in the alkyl iodide leads to an intramolecular carbozincation reaction. The coordination of the nickel(II) intermediate obviously activates the triple bond sufficiently for an addition to occur. This reaction provides a short route to functionalized *exo*-alkylidenecyclopentanes like **22** (Scheme 11)[22]. The carbonickelation is highly stereoselective, as demonstrated by the substituted iodoalkyne **23**. Only the cyclopentane **24** is obtained in the cyclization, showing that a *syn*-carbonickelation has occurred with over 99% stereoselectivity. This reaction proceeds well in an intermolecular fashion to give a short stereoselective preparation of the anticancer drug Z-tamoxifen **25**. The key step is the *syn*-carbometalation of **26** leading, after iodolysis, to the *Z*-tetrasubstituted olefin **27** in 88% yield ($E/Z < 1{:}99$, Scheme 12)[23].

Scheme 11

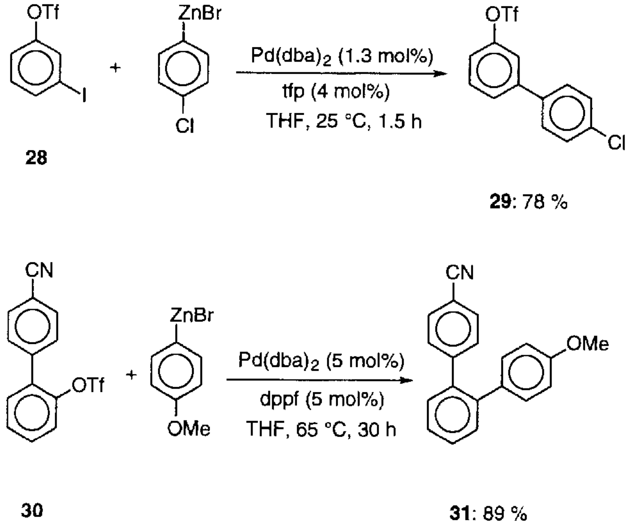


Scheme 12



New developments of the Negishi reaction have also been accomplished by fine tuning the palladium catalyst used, and the contributions of Hayashi[23], Farina[24] and Liebeskind[25] have significantly increased the synthetic potential of this cross-coupling reaction between Csp^2 centers. It has opened the way to the design of aromatic multi-coupling reagents[26] such as **28**. This reagent bears two electrophilic functions, a triflate and an iodo substituent. In the presence of tri-*o*-furylphosphane (tfp) as a phosphane ligand[24,25] and palladium *bis*(dibenzylideneacetone) [Pd(dba)$_2$], only the carbon–iodine bond undergoes a substitution reaction, leading to the functionalized aryl triflate **29** (Scheme 13)[27]. In the presence of the more effective phosphane, 1,1′-bis(diphenylphosphino)ferrocene (dppf), the substitution reaction also occurs with aryl triflates. The bisaryl triflate **30** is converted under these conditions to the teraryl **31** in 89% yield[27].

Scheme 13

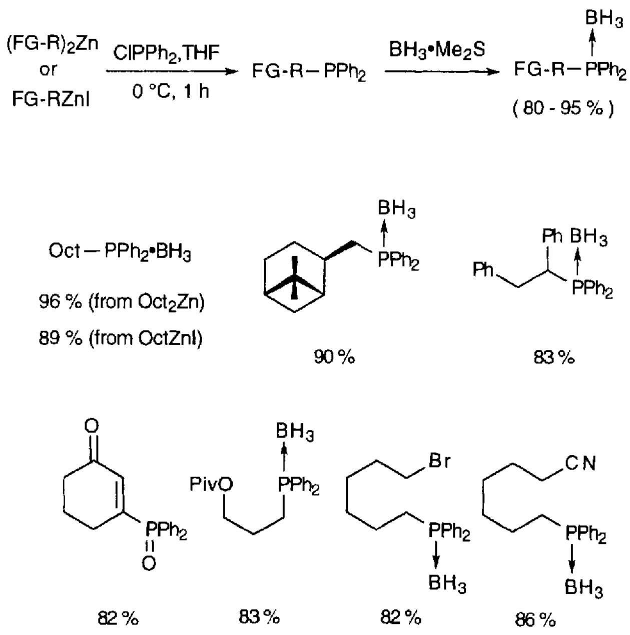


Reactivity of Organozinc Compounds with Phosphorus Electrophiles

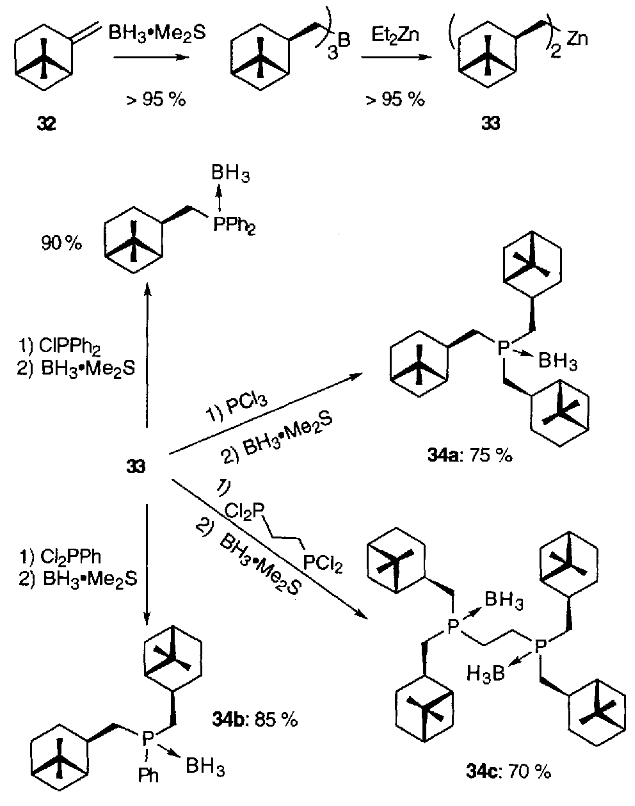
Organozinc halides rarely react with an electrophilic function in the absence of a metal catalyst. However, chlorophosphanes undergo smooth substitution reactions with various functionalized organozinc halides or diorganozincs to give polyfunctional phosphanes in good to excellent yields (Scheme 14)[28]. This method gives direct access to a range of polyfunctional phosphanes of great interest in coordination chemistry. The preparation of chiral phosphanes is readily achieved starting from terpenes. Hydroboration of β-pinene **32** with $BH_3 \cdot Me_2S$ gives trimyrtanylborane which, on treatment with Et_2Zn, gives bis(myrtanylzinc) (**33**) in quantitative yield. In the presence of various chlorophosphanes this zinc reagent affords the expected chiral phosphanes **34a–c** (Scheme 15). The chelating ability of the phosphane **34c** makes this compound of potential interest as a chiral ligand for catalytic asymmetric reactions[29].

The preparation of polyfunctional chlorophosphanes like **35** as phosphorus building blocks led us to react diethylaminodichlorophosphane (**36**)[30] with zinc organometallics. After protection with BH_3[31,32], the readily isolated borane–aminophosphane complexes **37** were obtained. Treatment with HCl in ether provides the desired borane-protected chlorophosphanes **35** in excellent overall yield

Scheme 14



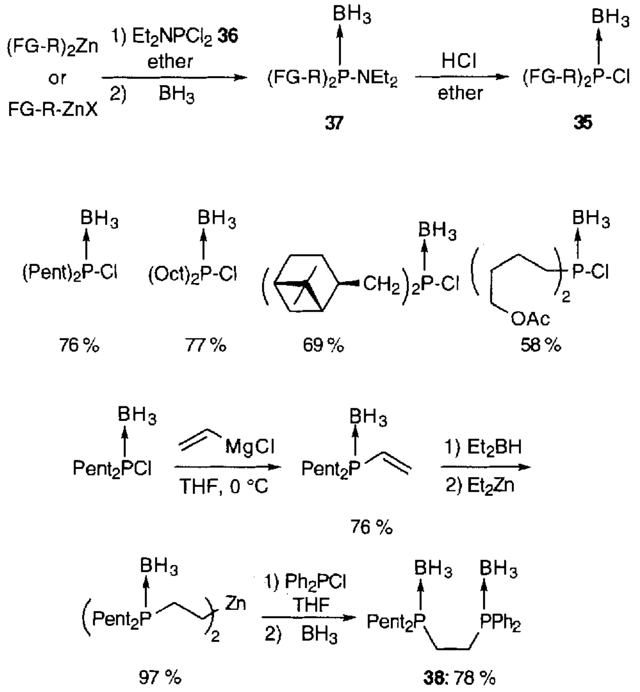
Scheme 15



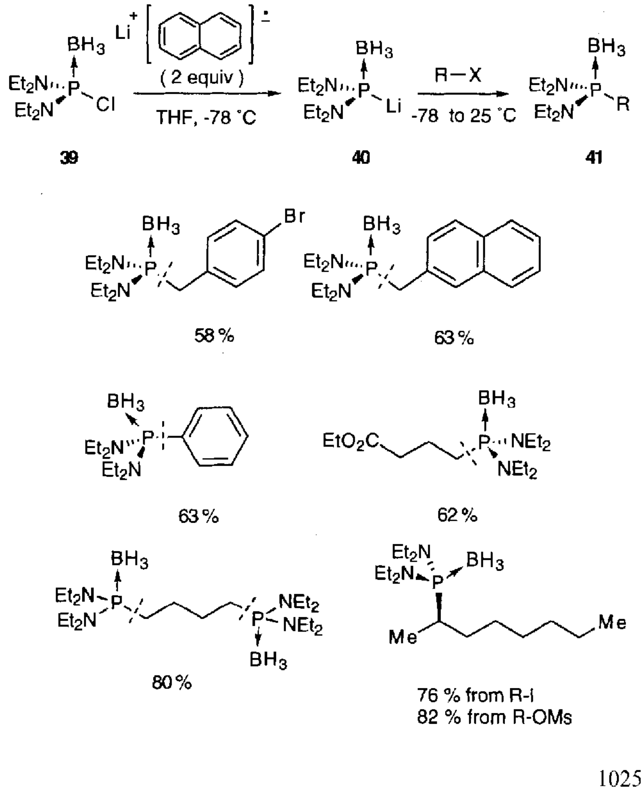
(Scheme 16)[15]. As an example of an application of this reaction the mixed diaryldialkyldiphosphane **38** was prepared by this methodology (Scheme 16).

The need for anionic phosphorus reagents showing a reactivity pattern complementary to those of the electrophilic chlorophosphanes led us to perform a reductive lithiation on the borane–bis(diethylamino)chlorophosphane complex **39** with lithium napththalenide[32] to afford the new anionic phosphorus reagent **40**. The reaction of **40** with various organic halides or mesylates cleanly provides the substitution products of type **41** (Scheme 17)[23]. Remarkably, substitution with iodobenzenes or bromopyridines shows that substitution at Csp^2 centers is also possible (Scheme 17)[33].

Scheme 16

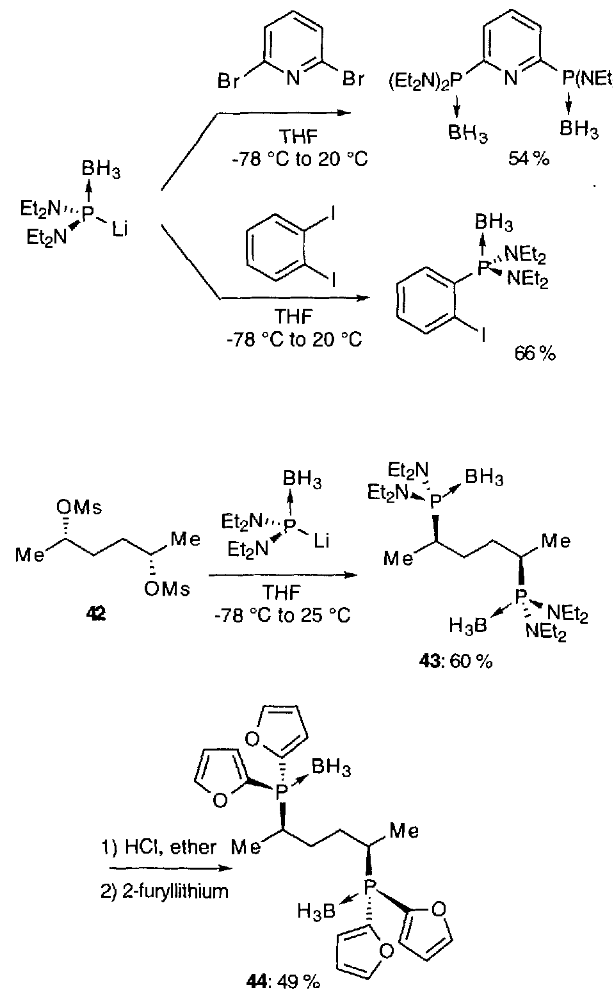


Scheme 17



The reaction of the chiral C_2-symmetrical dimesylate **42** with **40** furnishes the tetraamino-1,4-diphosphane **43** in 60% yield. Treatment with HCl in ether gives the tetrachlorodiphosphane, which can be reacted with a number of organometallic reagents to give chiral diphosphanes. The reaction with 2-furyllithium gives the diphosphane **44** in 49% yield (Scheme 18)[33]. The ligand **44** may be of interest for the performance of asymmetric hydrogenation reactions[34]. Finally, the new methods of phosphane preparation were applied to a convergent synthesis of the C_2-symmetrical diphosphane **45**, starting from readily available (*S,S*)-diacid **46** (Scheme 19)[35].

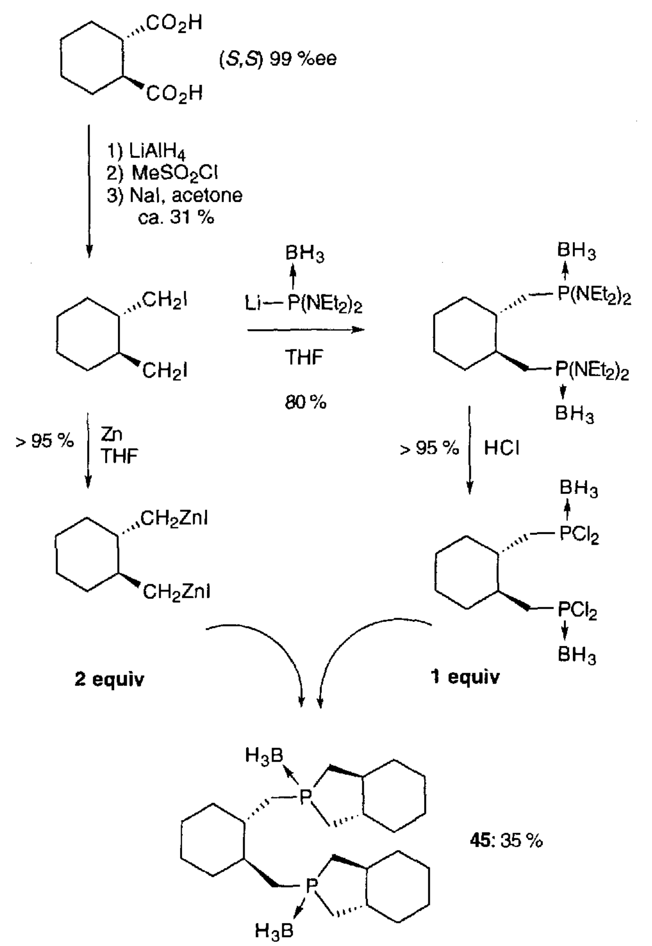
Scheme 18



Conclusion

Zinc organometallics are ideal organometallic reagents for the preparative chemist. The low toxicity of zinc combined with the high functional group compatibility and easy preparation of these organometallic compounds have led to increasing applications in recent years. There are still many synthetic problems that could potentially be solved by zinc reagents and the use of organozinc reagents in synthesis is still in its infancy.

Scheme 19



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