Coordination Chemistry Reviews 353 (2017) 223–246

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

# Coordination and catalytic chemistry of phosphinoferrocene carboxamides

Petr Štěpnička

*Department of Inorganic Chemistry, Faculty of Science, Charles University, Hlavova 2030, 128 40 Prague, Czech Republic*

ARTICLE INFO

*Article history:*
Received 11 August 2017
Received in revised form 3 October 2017
Accepted 4 October 2017

*Keywords:*
Ferrocene
Ligands
Phosphines
Amides
Coordination chemistry
Catalysis

ABSTRACT

Amidation reactions of ferrocene phosphinocarboxylic acids and various simple or functional amines provide access to a range of specific metalloligands combining the soft phosphine moiety with easily changeable, hard-donor amide substituents. Compounds of this type are also accessible in a complementary manner, as demonstrated by the reactions of [1′-(diphenylphosphino)ferrocenyl]methylamine with carboxylic acids (or their derivatives) and isocyanates. Owing to their hybrid nature, phosphinoferrocene carboxamides are versatile ligands for coordination chemistry and catalysis. Applications in such areas particularly benefit from the modular structures of these compounds, which allow the design and synthesis of extensive ligand libraries and, hence, the fine tuning of their properties for a particular use. Moreover, phosphinoferrocene amides can easily be made chiral using either a chiral ferrocene precursor or an attached chiral pendant. The amide linking group stabilizes the phosphinoferrocene moiety towards oxidation and endows phosphinoferrocene amides with the ability to participate in hydrogen bonding interactions and, consequently, form well-defined supramolecular assemblies in the solid state. As a defined linker, the amide moiety can be used to attach phosphinoferrocene moieties onto a larger scaffold (e.g., dendrimers) and thus create multidonor arrays. Furthermore, the presence of the amide moiety renders the phosphinoferrocene carboxamides useful synthetic building blocks.



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## 1. Introduction

Research into the chemistry of ferrocene-based ligands began shortly after the discovery of ferrocene itself [1] and the determination of its real structure [2]. For instance, the iconic diphosphine 1,1′-bis(diphenylphosphino)ferrocene (dppf) was first reported in 1965 [3]. Since then, dppf has been used extensively as a ligand in coordination chemistry and as an essential component of efficient catalysts for a range of transition metal-mediated organic transformations [4].

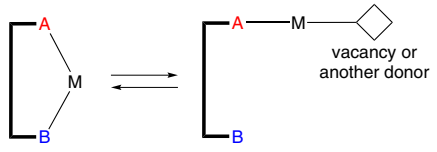
*E-mail address:* petr.stepnicka@natur.cuni.cz

https://doi.org/10.1016/j.ccr.2017.10.003
0010-8545/

Naturally, developments in the area of phosphinoferrocene donors reflect the practical success of "organic" phosphine ligands, which are currently indispensable donors for coordination chemistry and catalysis because of their widely tunable steric and electronic properties and their capability of being easily modified by introducing functional moieties. Although an enormous number of phosphinoferrocene derivatives have been reported to date, two distinct major lines along which such donors are designed can be recognized, namely, the preparation of chiral phosphines for applications in enantioselective catalysis and the synthesis of achiral donors structurally related to dppf [5].

To expand the family of non-chiral phosphinoferrocene donors, the phosphine moieties in the dppf molecule have often been modified. Thus, the replacement of the phenyl substituents in dppf with other groups led, inter alia, to electron-rich dialkylphosphine dppf congeners, the analogous phosphites and even several P-chiral derivatives [6]. Another approach towards the modification of the dppf structure was based on the replacement of one of the phosphine substituents with another functional moiety [7]. This approach allows the preparation of donor-unsymmetrical ligands combining two donor moieties with modified coordination preferences and catalytic properties that are tailored for a certain application. In particular, the functional substituents can be used to modify physicochemical properties of phosphinoferrocene donors (e.g., their solubility); introduce an additional donor moiety, chiral element or a synthetically useful fragment; and append the phosphinoferrocene unit to another small molecule or a larger molecular scaffold. For these reasons, we have directed our research along such a line, focusing first on phosphinoferrocene carboxylic acids [8] and later on their corresponding amides.

Phosphine donors modified by carboxamide substituents [9] represent prototypical examples of the so-called hybrid ligands [10]. The particular combination of donor moieties, which fall into different classes according to the hard and soft acids and bases theory [11], viz. the soft phosphine group and the hard-donor amide moiety, enables phosphino-carboxamide ligands to coordinate a whole range of transition metals in diverse coordination modes (typically as P- or P,O-donors in their native form and as N- or P,N-donors after deprotonation of the amide NH group). The possible hemilabile coordination of phosphino-carboxamides to soft transition metals is particularly interesting, mainly because of its relevance to catalysis. Typically, the phosphine moiety forms strong dative bonds with catalytically active soft metal ions and thus acts as a firmly bound pivot, whereas the relatively weaker coordination bonds to the amide unit (via its oxygen atom in the non-deprotonated state) can be, under certain circumstances, cleaved and formed again. This cleavage can be induced by the addition of another donor with a higher affinity to the metal center than the amide unit. During a catalytic cycle involving a transition metal ligated in a hemilabile fashion, the additional substituting donor may well be the substrate of the catalytic process. Once the metal-mediated transformation is completed and the product is released from the coordination sphere, the bond to the amide moiety can be formed again in a fast intramolecular fashion (Scheme 1), thereby preventing interactions of the metal center with other donors present in the reaction system. In this manner, ligands coordinated in a hemilabile fashion can protect the catalytically active metal species from deactivation and thus increase the catalyst life-time and activity per metal atom.




**Scheme 1.** Schematic representation of the hemilabile coordination of a hybrid ligand (A = strongly binding donor moiety, B = weaker binding donor moiety, M = transition metal).

Another notable feature of phosphino-carboxamide donors is undoubtedly their modular structures and facile synthesis. These compounds are conveniently prepared by amidation reactions of phosphinocarboxylic acids with amines or, in an inverted manner, of carboxylic acids with phosphino-amines (Scheme 2). All these starting materials are either well known or can be newly synthesized by applying general routes previously reported in the literature, and the new molecules can be assembled using conventional synthetic protocols for amide bond formation and coupling methods developed for peptide chemistry [12].

Of course, a number of alternative approaches towards phosphino-carboxamides can also be derived from the synthetic methods developed for the preparation of phosphines, such as nucleophilic substitution of halogenated substrates by phosphide reagents or hydrophosphination (Scheme 2). In this case, however, attention must be paid to the compatibility of the functional groups with the reaction conditions. Nevertheless, possible limitations can be eliminated by choosing the proper synthetic method, using protecting groups and carefully devising a sequence of individual reaction steps.

The virtually unlimited choice of synthetic building blocks and the whole palette of complementary and functional group-tolerant methods available for their combination and subsequent modifications allow a highly modular and practically unrestricted molecular design of phosphino-carboxamides (molecular LEGO) and thus provide rational and reliable access to extensive libraries of chemically related compounds designed for applications in diverse fields. All these developments render phosphino-carboxamides attractive research targets and substantially widen the scope of their possible practical applications.

This review attempts to summarize the developments in the chemistry of phosphinoferrocene carboxamides, particularly those that capitalize on the particular combination of the specific properties of phosphino-carboxamide donors and the unique steric and electronic features of the ferrocene scaffold. The ferrocene unit has a defined, compact cylindrical shape, which is especially important for ligand design. Its cyclopentadienyl rings can rotate along the molecular axis but are relatively resistant to mutual tilting. The ferrocene moiety can easily be made chiral at the cyclopentadienyl plane or via introduced (external) chirality. Lastly, the introduction of a ferrocene moiety into a molecule results in the incorporation of an exceedingly stable, redox-active organometallic fragment, the properties of which can be altered or monitored by changing the oxidation state of the iron center (N.B. although ferrocenyl is a strongly electron-donating group, the corresponding ferrocenium is an electron-withdrawing moiety [13]). Coordination of any ferrocene-based ligand onto a metal fragments inevitably leads to the formation of multinuclear coordination species with possible electronic communication between the metal centers. These aspects, however, are not the main objective of this review. Herein, the focus is predominantly on the synthesis of phosphinoferrocene carboxamides, their applications in coordination chemistry, and use as supporting ligands in conventional as well as enantioselective transition metal-catalyzed transformations of organic substrates.

## 2. Previous work and contributions from other laboratories

When initiating our investigations into the chemistry of phosphinoferrocene carboxamides, we realized that these compounds had received relatively minor attention, with most associated