N-Heterocyclic Carbenes

N-Phosphine Oxide-Substituted Imidazolylidenes (PoxIms): Multifunctional Multipurpose Carbenes

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Abstract: This article discusses the concept of N-heterocyclic carbene (NHCs) equipped with more than one functional moiety, which allows using these NHCs for multiple purposes. A pioneering example for such NHCs is N-phosphine oxide-substituted imidazolylidene (PoxIm)s, and their synthesis and strategic use are highlighted. The utility of PoxIm s by far exceeds the conventional use as multidentate ligands for metal complexes on account of the synergic functionalities of the carbene and the N-phosphine oxide group(s).

Introduction

Novel functionalized molecules are always of great interest for chemists, since these molecules often reveal unprecedented reactivity that may eventually lead to epoch-making applications. As such molecules, N-heterocyclic carbene (NHCs) have received considerable attention since the first report on the isolable and crystalline NHC (Figure 1).[1, 2a] Much effort was devoted to understand their electronic and steric natures,[2b, g] which contributed to the design of other types of stable carbene,[3] as well as to the functionalization of NHCs.[4] Today, NHCs are widely employed as for example ligands for transition metals,[2a, 3a] organocatalysts,[2f] and Lewis basic partners for the stabilization of reactive main-group species.[2c, h]

Figure 1. A conceptual illustration of multifunctional multipurpose NHCs.

Practical and reliable methods have been established for the synthesis of multifunctional NHCs by the introduction of substituents on either the nitrogen atom(s) or on the backbone of the NHCs.[2, 4] In this article, multifunctional NHCs are defined as NHCs that contain at least one functional group in addition to the carbene moiety, for example a Lewis acidic/basic, a Brønsted acidic/basic, or a nucleophilic/electrophilic substituent. However, despite the inherent versatility of the additional groups, multifunctional NHCs have so far been used predominantly as multidentate ligands for metals.[4] There are few experimental demonstrations that both the carbene and the additional substituent(s) in the multifunctional NHCs are strategically used in a multipurpose fashion (Figure 1).[5, 6] Beyond satisfying the natural curiosity of the research chemist, multifunctional multipurpose NHCs should contribute to the further development of especially organic and organometallic chemistry, since these carbene are potentially crucial parts of unprecedented molecular transformations as well as novel organo- and metal-based catalysts.

Herein, our recent studies on the design, synthesis, and the strategic use of N-phosphine oxide-substituted imidazolylidene (PoxIm)s are highlighted as a model of isolable, multifunctional, and multipurpose NHCs.

NHCs Equipped with Phosphine Oxide Substituents

NHCs have become well-established ligands in organometallic chemistry, similar to amines and phosphines. Their synergetic use as multidentate ligands has also been studied extensively, and various NHCs (or NHC-HX precursors) equipped with additional Lewis basic functions have been synthesized.[4] However, there are only a few examples of phosphine oxide-substituted NHCs, including those generated in situ (Figure 2), even though phosphine oxides have frequently been used as Lewis base[7a, d, 4] and organocatalysts.[7b, d] The reactivity of phosphine oxide-substituted NHCs should be of substantial interest, since the phosphine oxide moiety could function as a hemi-labile coordination ligand,[8h, 5c] as well as an electron-withdrawing substituent.[8d] Nevertheless, the multipurpose use of such carbene remains scarce.

Recently, we have developed PoxIm s through the direct introduction of a phosphine oxide moiety onto the nitrogen atom of the imidazolylidene ring (Figure 2c). Intriguingly,
PoxIms contain the N-phosphine oxide moiety, which can work as a Lewis base and an electrophile, and a nucleophilic/Lewis basic carbene, which should allow multipurpose utility (vide infra). A simplified synthetic scheme to PoxIms is shown in Figure 3. The isolable and shelf-stable precursors PoxIm·HOTf (2) were obtained from the reaction of imidazoles (1) and tBu₂PCl, followed by oxidation with H₂O₂. A subsequent treatment of 2 with KOTBu furnished PoxIms (3). The bis-phosphine oxide-substituted imidazolylidene 3g was also synthesized through this route. Further derivatization of 3b with CCl₄ afforded either mono- or bis-chlorine-substituted PoxIms (3h and 3i), whereby either could be synthesized selectively by varying the reaction time. N-Phosphine oxide-substituted imidazolinylidene (SPoxIm) 3j was also prepared using a similar synthetic route from the corresponding imidazoline. These simple and scalable synthetic procedures should facilitate further derivatization and applications of PoxIms.

Figure 3. Simplified synthetic Scheme to selected examples for PoxIms (3).

Recent developments on the chemistry of frustrated Lewis pairs (FLPs, [LA···LB]; Figure 4b) are remarkable in organic synthesis, as illustrated by the catalytic hydrogenation of unsaturated compounds with earth-abundant and harmless main-group elements. FLPs are recognized as weakly bond noncovalent complexes comprising an electron-acceptor (Lewis acid, LA) and an electron-donor (Lewis base, LB), in which the formation of classical Lewis adducts (CLAs, LA·LB; Figure 4a) is encumbered by steric repulsion between LA and LB. Whereas the typical chemical features of both the LA and the LB are usually quenched through the formation of CLAs, FLPs exhibit a reactivity that is sufficiently high to activate the enthalpically strong H–H bond in molecular hydrogen (H₂). However, this reactivity of FLPs eventually inhibits their isolation and makes them unstable for shelf storage, which somewhat limits their utility in organic synthesis.

We therefore envisioned a strategy to control the interconversion between CLAs and FLPs by using external stimuli, which should offer an opportunity to use isolable and shelf-stable CLAs as precursors for active FLPs under closely controlled reaction conditions rather than under ambient conditions (Figure 4c). In order to achieve this “frustration revival strategy”, we designed PoxIms that undergo significant changes to the spatial environments surrounding their carbene center through rotation of the N-phosphine oxide moiety.

Figure 4. Reactions between Lewis acids (LAs) and Lewis bases (LBs) to afford a) classical Lewis adducts (CLAs) and b) frustrated Lewis pairs (FLPs). c) The concept of the “frustration revival strategy”.
elevating the temperature to 25 °C, 5b was converted into 4b in 72% yield. These results demonstrate a versatile aspect of Poxlms, that is, Poxlms drastically change their spatial environment (Δ%Vbur > 20%) through the rotation of the N-phosphine oxide moiety, which affords two types of CLAs upon reaction with B(C6F5)3: one that is kinetically formed (5b), and one that is thermodynamically formed (4b).

In the solid state, 4b was stable at 20–30 °C for several weeks, even in the presence of air and moisture. Although this stability of 4b suggests the reactivity of a quenched CLA, typical FLP reactivity to activate H2 was revived under thermal conditions (Figure 6). Furthermore, the temperature, which was required to induce the revival of FLPs from CLAs, was controlled by changing the substituent groups on the nitrogen atom in the Poxlm moiety. As shown in Figure 6, the complex 4d reacted with H2 affording 6d quantitatively at 80 °C, whereas 6d was formed in only 6% at 60 °C after 3 h. In the case of 4e, the heterolytic cleavage of H2 proceeded efficiently at 120 °C to quantitatively yield 6e, whereas only 3% and 7% of 6e were obtained after 3 h at 80 °C and 100 °C, respectively. These results suggest that carbene–borane complexes with larger strain can operate at lower reaction temperatures to activate H2 than complexes that exhibit lesser degrees of strain. Detailed studies on this revival mechanism are currently ongoing in our laboratory.

Strategic Use of Poxlms as Reagents for the Transformation of the Carbon–Oxygen Double Bond

In the previous topic, two distinct Lewis basic moieties in Poxlms, that is, the phosphine oxide and the carbene, were used to form two types of CLAs as well as FLP species with B(C6F5)3. Since the phosphine oxide moiety can moreover function as an electrophile, we envisioned that the reaction between Poxlms and carbon dioxide (CO2) could afford an imidazolium-2-carboxylate. A subsequent intramolecular nucleophilic addition of the carboxylate to the phosphate oxide could then yield a novel type of carboxylic-phosphinic mixed anhydride (Figure 7).

As anticipated, CO2 was quantitatively phosphorylated by Poxlm 3f to afford carboxylic-phosphinic mixed anhydride 8, which was isolated in 99% yield (Figure 8). This reaction is attractive, especially with respect to its atom-economy, as by-products such as those inevitably generated by the previously reported procedures were not observed. The formation of key
intermediate 7 was confirmed by NMR analyses at –90°C, and the structure of 7, in which the P=O bond is oriented in an anti fashion with respect to the imidazolium C2 carbon atom, was also supported by theoretical calculations. These results thus offer a different opportunity to employ multifunctional PoxIms.

We further envisioned that this phosphorylation method of CO₂ could be applied to the straightforward synthesis of valuable carbonyl compounds. For that purpose, we treated 8 with MeOTf to obtain 9, which is a versatile precursor for unsymmetrical carbonyl compounds (Figure 9).

Indeed, 9 served as an intermediate in the synthesis of various carbonyl compounds such as an ester, an amide, and an unsymmetrical ketone. Moreover, the synthetic utility of the direct phosphorylation of CO₂ by PoxIm 3f was also demonstrated by a straightforward one-pot conversion of CO₂ to unsymmetrical ketone 10 in 75% overall yield (Figure 10).

In the succeeding study on the phosphorylation of isocyanates and aldehydes, bis-phosphine oxide-substituted 3g was found to catalyze the cyclotrimerization of phenyl isocyanate, whereas phenyl isocyanate was efficiently phosphorylated by PoxIm 3c (Figure 11). These results demonstrate the further utility of PoxIms as an efficient reagent for the transformation of heterocumulenes and carbonyls.

**Strategic Use of PoxIms as Bidentate Ligands in Transition Metal Complexes**

The Nozaki group, in collaboration with our group, have recently reported the first example for the synthesis and use of a transition-metal complex that contains Poxim as a bidentate ligand (Figure 12). The applications of PoxIms in organometallic chemistry are of much interest due to the varied coordination ability of the relatively soft carbene and the hard phosphate oxide, as well as due to their steric flexibility that can drastically change the spatial environment around the carbene center. Further works in this area are ongoing in our group.

**Conclusion and Outlook**

In this article, we have discussed the concept of multifunctional, multipurpose N-heterocyclic carbenes (NHCs). These NHCs contain at least two different functional moieties, which leads to their multipurpose applications beyond the conventional use of coordinating ligands, especially considering the synergistic effects between the carbene moiety and the additional functional substituent(s). N-Phosphine oxide-substituted imidazolidines (PoxIms) and their derivatives represent an example of such NHCs. Indeed, PoxIms have been used as external stimuli-responsive Lewis bases in a “frustration revival strategy” in the context of FLP chemistry, as novel reagents to convert CO₂ into versatile unsymmetrical carbonyl compounds in a straightforward one-pot fashion that is also applicable to isocyanates and aldehydes, and as a bidentate ligand for a cationic Pd complex. These results showcase the multifunctional and multipurpose character of PoxIms.

The present chemistry of PoxIms may contribute to expand the field of multifunctional multipurpose NHCs. A simple alteration of the N-phosphine oxide group in PoxIms to the corresponding phosphate imides, sulphides, or selenides should afford a series of analogous multifunctional and multipurpose NHCs that may exhibit different reactivity relative to that of PoxIms, and accordingly find different applications.
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Conflict of interest

The authors declare no conflict of interest.

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[1] A. J. Arduengo III, R. L. Harlow, M. Kline, J. Am. Chem. Soc. 1991, 113, 361–363.
[2] For a selected book, see: a) C. S. Cazin, N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis, Springer, Heidelberg, 2010; for selected recent reviews, see: b) P. de Frémont, N. Marion, S. P. Nolan, Coord. Chem. Rev. 2009, 253, 862–892; c) Y. Wang, G. H. Robinson, Dalton Trans. 2012, 41, 337–345; d) D. J. Nelson, S. P. Nolan, Chem. Soc. Rev. 2013, 42, 6723–6753; e) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, Nature 2014, 510, 485–496; f) D. M. Flanigan, F. R. -Michailidis, N. A. White, T. Rovis, Angew. Chem. Int. Ed. 2015, 54, 11666–11761; g) M. Sugiura, M. Nakajima, H. Nomura, Organometallics 2015, 34, 11832–11837; h) Y. Hoshimoto, T. Asada, S. Hazra, T. Kinoshita, P. Sombut, R. Kumar, M. Ohashi, S. Ogoshi, Angew. Chem. Int. Ed. 2016, 55, 16075–16079; i) W. Tao, S. Akita, R. Nakano, S. Ito, Y. Hoshimoto, S. Ogoshi, K. Nozaki, Chem. Commun. 2017, 53, 2630–2633; j) Y. Hoshimoto, T. Asada, S. Hazra, M. Ohashi, S. Ogoshi, Chem. Lett. 2017, 46, 1211–1213.
[5] For an example on NHC that can be classified into our defined multifunctional multipurpose NHCS, see: a) Winkler, M. Freytag, P. G. Jones, M. Tamm, Z. Anorg. Allg. Chem. 2016, 642, 1295–1303.
[7] For selected reviews, see: a) V. V. Grushin, Chem. Rev. 2004, 104, 1629–1662; b) M. Benaglia, S. Rossi, Org. Biomol. Chem. 2010, 8, 3824–3830; c) S. Kotani, M. Sugiiura, M. Nakajima, Chem. Rev. 2013, 13, 362–370; d) I. B. Sivas, V. I. Bregadze, Coord. Chem. Rev. 2014, 270–271, 75–88; e) A. W. G. Platt, Coord. Chem. Rev. 2017, 340, 62–78.
[8] a) T. Focken, J. Rudolph, C. Bolm, Synthesis 2005, 429–436; b) F. K. Majhi, S. Sauerbrey, G. Schnakenburg, A. J. Arduengo III, R. Strebuel, Inorg. Chem. 2012, 51, 10408–10416.
[9] For reviews on FLP, see: a) D. W. Stephan, G. Erker, Angew. Chem. Int. Ed. 2010, 49, 46–76; b) Angew. Chem. 2010, 122, 50–81; c) D. W. Stephan, G. Erker, Angew. Chem. Int. Ed. 2015, 54, 6400–6441; Angew. Chem. 2015, 127, 6498–6541; c) S. A. Weicker, D. W. Stephan, Bull. Chem. Soc. Jpn. 2015, 88, 1003–1016.
[10] For reviews on FLP-catalyzed hydrogenations of unsaturated compounds, see: a) J. Paradies, Synlett 2013, 24, 777–780; b) X. Feng, H. Du, Tetrahedron Lett. 2014, 55, 6959–6964; c) M. Oestreicher, J. Hermese, J. Mohr, Chem. Soc. Rev. 2015, 44, 2202–2220; d) D. J. Scott, M. J. Fuchter, A. E. Ashley, Chem. Soc. Rev. 2017, https://doi.org/10.1039/c7cs00154a.
[11] Recently, water-tolerant FLP systems have been developed for the catalytic hydrogenation of unsaturated compounds, see: a) D. J. Scott, T. R. Simmons, E. J. Lawrence, G. G. Wildgoose, M. J. Fuchter, A. E. Ashley, ACS Catal. 2015, 5, 5540–5544; b) A. Góymór, M. Bakos, T. Foldes, I. Pápai, A. Domján, T. Šöös, ACS Catal. 2015, 5, 5366–5372; c) M. Bakos, A. Góymór, A. Domján, T. Šöös, Angew. Chem. Int. Ed. 2016, 55, 5217–5221.
[12] a) T. A. Rokob, A. Hamza, A. Stirling, I. Pápai, J. Am. Chem. Soc. 2009, 131, 2029–2036; For examples on CLAs showing thermally-induced FLP-like reactivity at temperatures higher than ambient, see: b) C. Jiang, O. Blasque, H. Berke, Organometallics 2009, 28, 5233–5239; c) T. J. Her- rington, B. J. Ward, L. R. Doyle, J. McDermott, A. J. P. White, P. A. Hunt, A. E. Ashley, Chem. Commun. 2014, 50, 12753–12756.
[13] a) S. Diez-González, S. P. Nolan, Coord. Chem. Rev. 2007, 251, 874–883; b) A. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano, L. Cavallo, Eur. J. Inorg. Chem. 2009, 1759–1766; c) L. Fallivene, R. Credeni- dino, A. Poater, A. Petta, L. Serra, R. Oliva, V. Scarano, L. Cavallo, Organometallics 2016, 35, 2286–2293.
[14] L. Yang, H. Wang, ChemSusChem 2014, 7, 962–998.
[15] For NHC-catalyzed reactions of isocyanates, see: a) H. A. Duong, M. J. Cross, J. Louie, Org. Lett. 2004, 6, 4679–4681; b) C.-Y. Li, Y.-Y. Kuo, J.-H. Tsai, G. P. A. Yap, T.-G. Ong, Chem. Asian J. 2011, 6, 1520–1524.

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