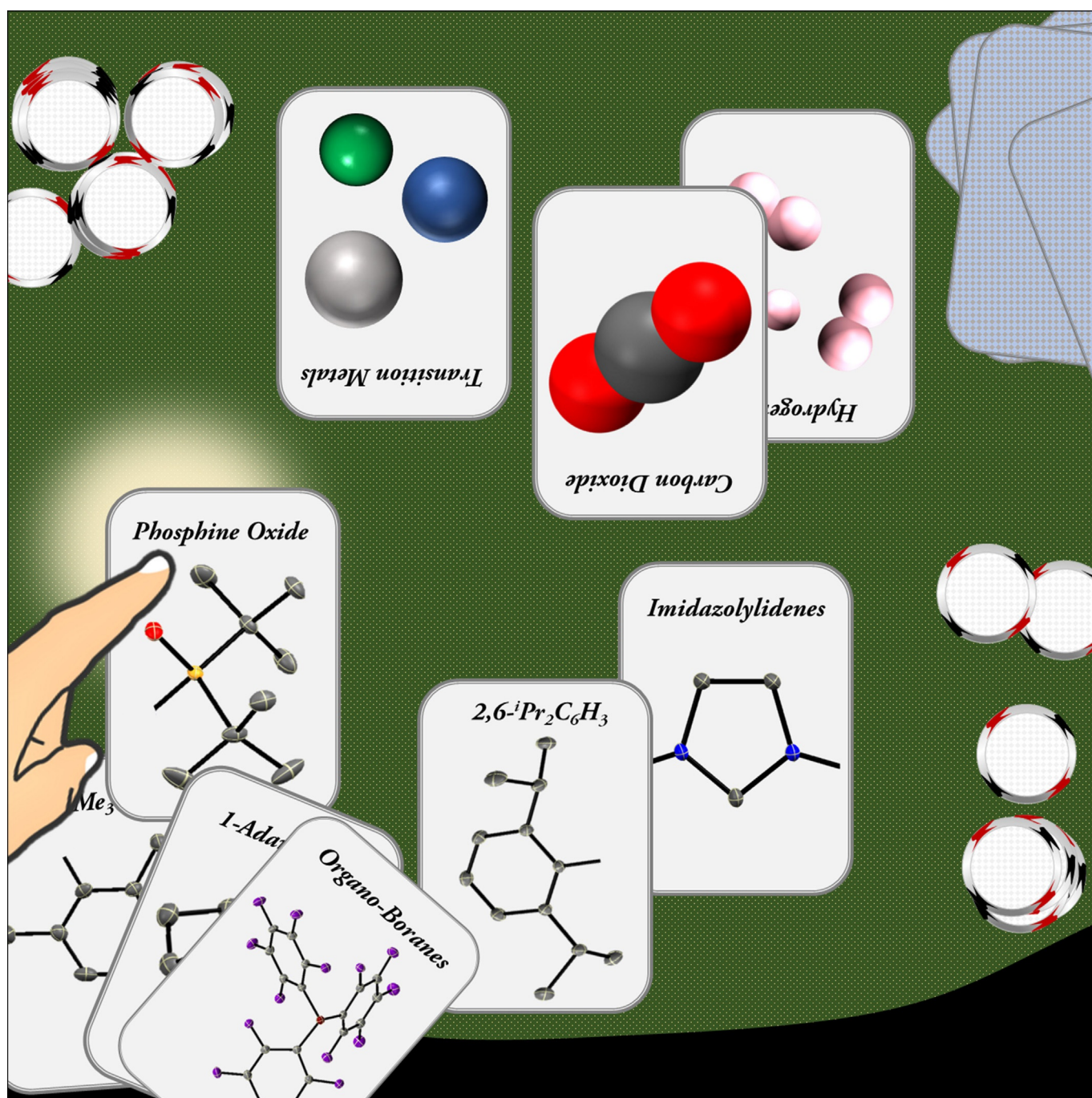■ N-Heterocyclic Carbenes

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

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Abstract: This article discusses the concept of N-heterocyclic carbenes (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 imidazolylidenes (PoxIms), and their synthesis and strategic use are highlighted. The utility of PoxIms by far exceeds the conventional use as multidentate ligands for metal complexes on account of the synergetic functions 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 carbenes (NHCs) have received considerable attention since the first report on the isolable and crystalline NHC (Figure 1).[1, 2e] Much effort was devoted to understand their electronic and steric natures,[2b, g] which contributed to the design of other types of stable carbenes,[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]
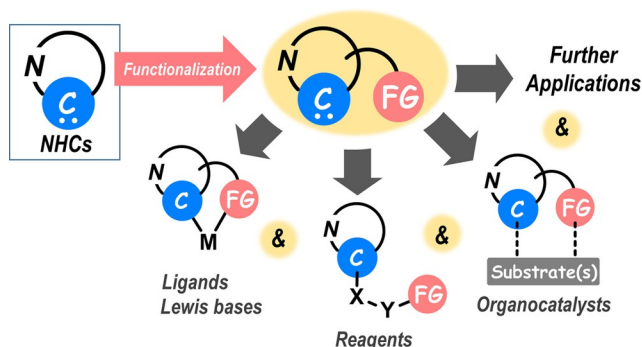

Figure 1. A conceptual illustration of multifunctional multipurpose NHCs.

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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 carbenes 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 imidazolylidenes (PoxIms) 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 bases[7a, d, e] and organocatalysts.[7b, c] 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,[8b, 5c] as well as an electron-withdrawing substituent.[8a] Nevertheless, the multipurpose use of such carbenes remains scarce.

Recently, we have developed PoxIms through the direct introduction of a phosphine oxide moiety onto the nitrogen atom of the imidazolylidene ring (Figure 2c). Intriguingly,
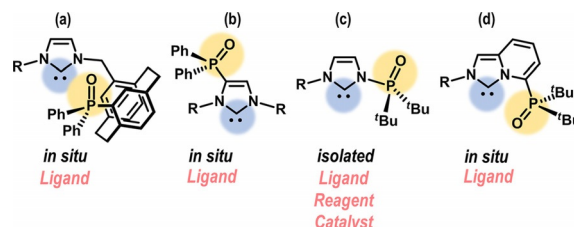

Figure 2. Reported examples on phosphine oxide-substituted NHCs. a) Reported by Bolm et al. (ref. [8a]). b) Reported by Arduengo and Streubel et al. (ref. [8b]). c) PoxIms, reported by our group (ref. [5]). d) Reported by Nozaki et al. (ref. [5c]).

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.[5a] The isolable and shelf-stable precursors PoxIm·HOTf
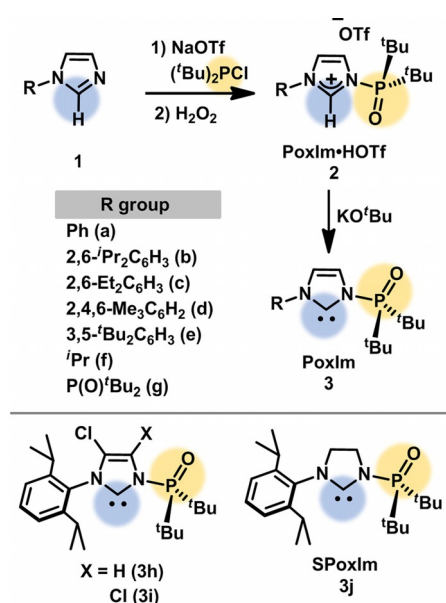

Figure 3. Simplified synthetic Scheme to selected examples for PoxIms (**3**).

(**2**) were obtained from the reaction of imidazoles (**1**) and *t*Bu₂PCl, followed by oxidation with H_2O_2. A subsequent treatment of **2** with KO*t*Bu furnished PoxIms (**3**). The bis-phosphine oxide-substituted imidazolylidene **3 g** was also synthesized through this route. Further derivatization of **3 b** with CCl_4 afforded either mono- or bis-chlorine-substituted PoxIms (**3 h** and **3 i**), whereby either could be synthesized selectively by varying the reaction time. *N*-Phosphine oxide-substituted imidazolinylidene (SPoxIm) **3 j** 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.

Strategic Use of PoxIms as External Stimuli-Responsive Lewis Bases in Frustrated Lewis Pair Chemistry

Recent developments on the chemistry of frustrated Lewis pairs (FLPs, [LA···LB]; Figure 4b) are remarkable in organic synthesis,[9] as illustrated by the catalytic hydrogenation of unsaturated compounds with earth-abundant and harmless main-group elements.[10] 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 (H_2). However, this reactivity of FLPs eventually inhibits their isolation and makes them unstable for shelf storage, which somewhat limits their utility in organic synthesis.[11]

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).[12] In order to achieve this "frustration revival strategy", we designed PoxIms that undergo significant changes to the spatial environment surrounding their carbene center through rotation of the *N*-phosphine oxide moiety.

Treatment of **3 b** with $B(C_6F_5)_3$ in toluene at room temperature (rt) resulted in the formation of **4 b** as a classical carbene–borane adduct, which was isolated in 95% yield (Figure 5a). The structures of **3 b** and **4 b** were determined by single-crystal X-ray diffraction analysis, which confirmed the rotation of the phosphine oxide through the formation of **4 b** from **3 b** (Figure 5b). For the PoxIm moiety in **4 b**, a percent buried volume ($\%V_{bur}$)[13] of 30.3 was calculated, which is a significant decrease relative to the $\%V_{bur}$ value of free **3 b** (53.0). When the reaction of **3 b** with $B(C_6F_5)_3$ was monitored at −90 °C by NMR spectroscopy, the quantitative formation of **5 b**, that is, a classical phosphine oxide–borane adduct, was observed (Figure 5a). Upon
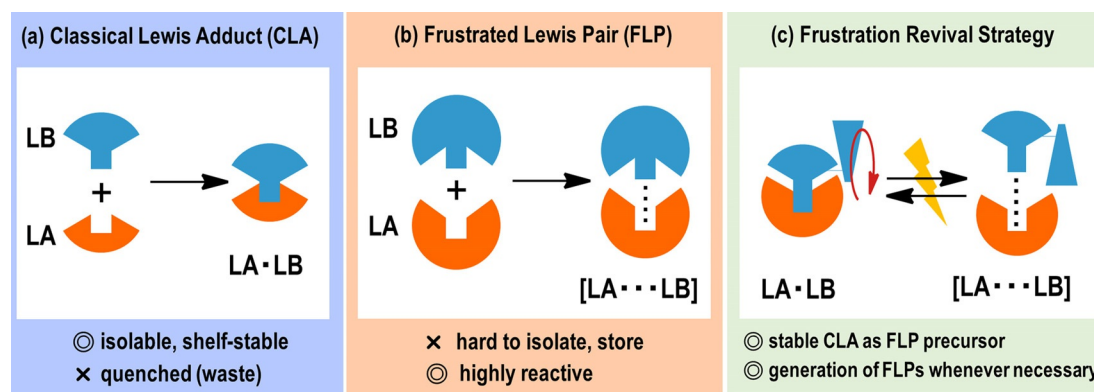

Figure 4. Reactions between Lewis acids (LAs) and Lewis bases (LBs) to afford a) classical Lewis adducts (CLAs) and b) frustrated Lewis pairs (FLPs). c) The concept of the "frustration revival strategy".
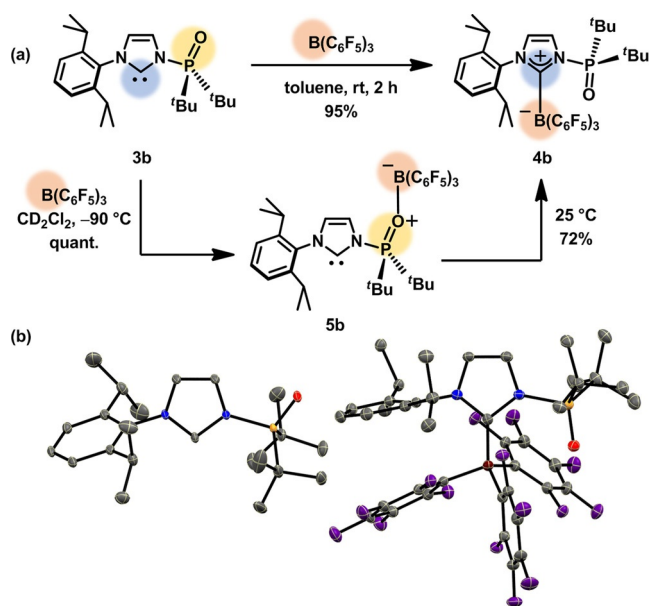
Figure 5. a) Reactions between **3 b** and B(C₆F₅)₃. b) Molecular structures of **3 b** (left) and **4 b** (right); ellipsoids are set at 30% probability. Hydrogen atoms are omitted. Colors for the atoms: B (brown), C (gray), N (blue), O (red), F (purple), P (yellow).

was formed in only 6% at 60 °C after 3 h. In the case of **4 e**, the heterolytic cleavage of H_2 proceeded efficiently at 120 °C to quantitatively yield **6 e**, whereas only 3% and 7% of **6 e** 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 H_2 than complexes that exhibit lesser degrees of strain. Detailed studies on this revival mechanism are currently ongoing in our laboratory.

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

In the previous topic, two distinct Lewis basic moieties in PoxIms, 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 PoxIms and carbon dioxide (CO_2) could afford an imidazolium-2-carboxylate.[14] A subsequent intramolecular nucleophilic addition of the carboxylate to the phosphine oxide could then yield a novel type of carboxylic–phosphinic mixed anhydride (Figure 7).[5b]

Figure 7. Strategic use of multifunctional PoxIms for the direct phosphorylation of CO_2.

elevating the temperature to 25 °C, **5 b** was converted into **4 b** in 72% yield. These results demonstrate a versatile aspect of PoxIms, that is, PoxIms drastically change their spatial environment ($\Delta\%V_{bur} > 20\%$) 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 (**5 b**), and one that is thermodynamically formed (**4 b**).

In the solid state, **4 b** was stable at 20–30 °C for several weeks, even in the presence of air and moisture. Although this stability of **4 b** suggests the reactivity of a quenched CLA, typical FLP reactivity to activate H_2 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 PoxIm moiety. As shown in Figure 6, the complex **4 d** reacted with H_2 affording **6 d** quantitatively at 80 °C, whereas **6 d**
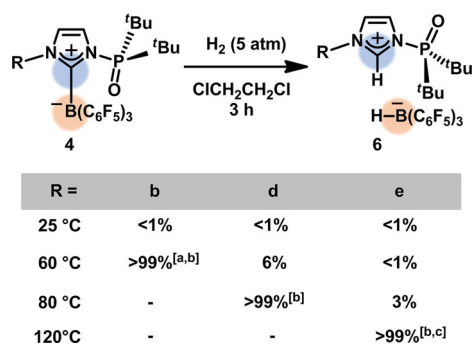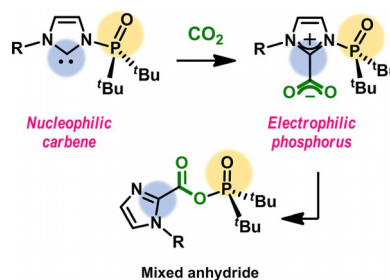
As anticipated, CO_2 was quantitatively phosphorylated by PoxIm **3 f** to afford carboxylic–phosphinic mixed anhydride **8**, which was isolated in 99% yield (Figure 8). This reaction is attractive, especially with respect to its atom-economy, as by-products such as those inevitably generated by the previously reported procedures were not observed. The formation of key
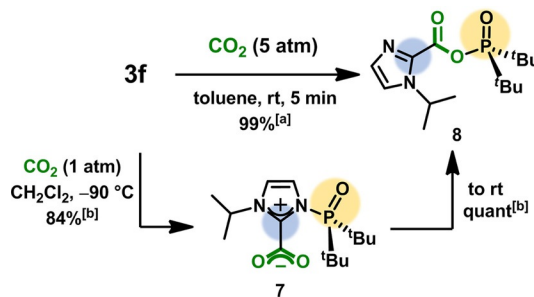

R =	b	d	e
25 °C	<1%	<1%	<1%
60 °C	>99%[a,b]	6%	<1%
80 °C	-	>99%[b]	3%
120°C	-	-	>99%[b,c]

Figure 6. Reaction of **4** with H_2. Yields of **6** were determined by NMR analysis. For the structure of the R groups, see Figure 3. a) CH₂Cl₂ was used as the solvent. b) Yields of the isolated products. c) C₆H₅Br was used as the solvent.

Figure 8. Reaction of **3 f** and CO_2 to afford **7** at −90 °C and **8** at rt. a) The yield of the isolated product. b) NMR yields.

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 CO_2 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).
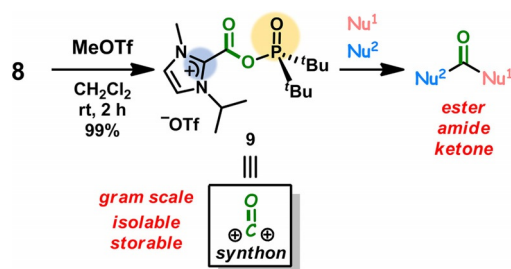

Figure 9. A novel synthon for unsymmetrical carbonyls derived from mixed anhydride **8**.

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 CO_2 by PoxIm **3 f** was also demonstrated by a straightforward one pot conversion of CO_2 to unsymmetrical ketone **10** in 75 % overall yield (Figure 10).
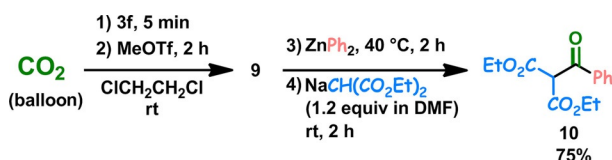

Figure 10. A straightforward one-pot transformation of CO_2 into **10**. The isolated yield of a mixture of keto/enol (8:1) isomers is given.

In the succeeding study on the phosphorylation of isocyanates and aldehydes,[5d] bis-phosphine oxide-substituted **3 g** was found to catalyze the cyclotrimerization of phenyl isocyanate, whereas phenyl isocyanate was efficiently phosphorylated by PoxIm **3 c** (Figure 11).[15] 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).[5c]
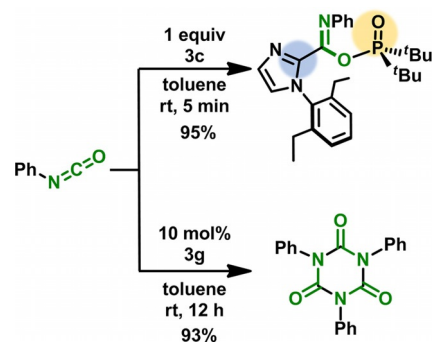

Figure 11. Reaction of phenyl isocyanate with PoxIms **3 c** and **3 g**. The isolated yields are given.
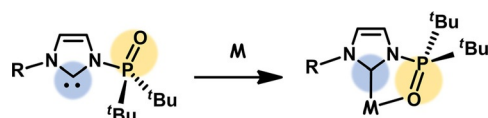

Figure 12. PoxIms as bidentate ligands in transition-metal (M) complexes.

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 phosphine 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 imidazolylidenes (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 CO_2 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 phosphine 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.

[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, *Chem. Rev.* **2015**, *115*, 9307–9387; g) A. Gómez-Suárez, D. J. Nelson, S. P. Nolan, *Chem. Commun.* **2017**, *53*, 2650–2660; h) S. Yao, Y. Xiong, M. Driess, *Acc. Chem. Res.* **2017**, *50*, 2026–2037.

[3] For selected reviews, see: a) F. E. Hahn, M. C. Jahnke, *Angew. Chem. Int. Ed.* **2008**, *47*, 3122–3172; *Angew. Chem.* **2008**, *120*, 3166–3216; b) M. Melaimi, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2010**, *49*, 8810–8849; *Angew. Chem.* **2010**, *122*, 8992–9032.

[4] For selected reviews on functionalized NHCs, see: a) D. Pugh, A. A. Danopoulos, *Coord. Chem. Rev.* **2007**, *251*, 610–641; b) O. Kühl, *Chem. Soc. Rev.* **2007**, *36*, 592–607; c) S. T. Liddle, l. S. Edworthy, P. L. Arnold, *Chem. Soc. Rev.* **2007**, *36*, 1732–1744; d) A. T. Normand, K. J. Cavell, *Eur. J. Inorg. Chem.* **2008**, 2781–2800; e) L. Mercs, M. Albrecht, *Chem. Soc. Rev.* **2010**, *39*, 1903–1912; f) S. Gaillard, J.-L. Renaud, *Dalton Trans.* **2013**, *42*, 7255–7270; g) C. Fliedel, P. Braunstein, *J. Organomet. Chem.* **2014**, *751*, 286–300; h) M. C. Jahnke, F. E. Hahn, *Chem. Lett.* **2015**, *44*, 226–237; i) R. E. Andrew, L. G. -Sebastián, A. B. Chaplin, *Dalton Trans.* **2016**, *45*, 1299–1305; j) S. Hameury, P. de Frémont, P. Braunstein, *Chem. Soc. Rev.* **2017**, *46*, 632–733.

[5] a) Y. Hoshimoto, T. Kinoshita, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2015**, *54*, 11666–11671; *Angew. Chem.* **2015**, *127*, 11832–11837; b) Y. Hoshimoto, T. Asada, S. Hazra, T. Kinoshita, P. Sombut, R. Kumar, M. Ohashi, S. Ogoshi, *Angew. Chem. Int. Ed.* **2016**, *55*, 16075–16079; c) W. Tao, S. Akita, R. Nakano, S. Ito, Y. Hoshimoto, S. Ogoshi, K. Nozaki, *Chem. Commun.* **2017**, *53*, 2630–2633; d) Y. Hoshimoto, T. Asada, S. Hazra, M. Ohashi, S. Ogoshi, *Chem. Lett.* **2017**, *46*, 1211–1213.

[6] 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. Sugiura, M. Nakajima, *Chem. Rec.* **2013**, *13*, 362–370; d) I. B. Sivaev, 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) P. K. Majhi, S. Sauerbrey, G. Schnakenburg, A. J. Arduengo III, R. Streubel, *Inorg. Chem.* **2012**, *51*, 10408–10416.

[9] For reviews on FLPs, see: a) D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46–76; *Angew. Chem.* **2010**, *122*, 50–81; b) 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. Oestreich, J. Hermeke, 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) Á. Gyömöre, M. Bakos, T. Földes, I. Pápai, A. Domján, T. Soós, *ACS Catal.* **2015**, *5*, 5366–5372; c) M. Bakos, Á. Gyömöre, A. Domján, T. Soós, *Angew. Chem. Int. Ed.* **2017**, *56*, 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. Blacque, H. Berke, *Organometallics* **2009**, *28*, 5233–5239; c) T. J. Herrington, 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. Díez-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. Falivene, R. Credendino, 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.