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New Ligands Beyond N-Heterocyclic Carbenes for Application in Homogeneous Catalysis

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Abstract: Building on the success of N-heterocyclic carbenes, extended versions comprised of an exocyclic metal bonding site have become increasingly popular. Pyridinium amidates (PYAs) belong to these ligand systems, as they contain a N-donor site that is formally stabilized by a pyridine-derived carbene. These PYAs are characterized by a unique donor flexibility, which imparts in some settings extraordinarily high catalytic activity, and in other settings remarkable stability of (catalytic) intermediates, which allows for deciphering mechanistic pathways.

Keywords: High turnover catalysis · N-heterocyclic carbene · Pyridinium amidate · Stable hydrides

1. N-Heterocyclic Carbenes in Organometallic Chemistry

The discovery of N-heterocyclic carbenes (NHCs) as ligands for transition metals has made a marked impact on homogeneous catalysis.[1] This development may be attributed to a combination of several effects, perhaps most notably to: i) the facile access of N,N'-disubstituted imidazolium salts as key ligand precursors, ii) the stability of the free carbene, which allows straightforward metalation in many cases, and iii) the beneficial effect of the NHC ligand upon catalytic activity, most prominently demonstrated for ruthenium-catalyzed olefin metathesis (Grubbs-II catalysts)[2] and palladium-catalyzed cross-coupling reactions (PEPPSI-type catalysts).[3] While initial work focused on comparison of imidazole-derived NHC ligands (**A**, Fig. 1) with analogous phosphine complexes, very rapidly the unique characteristics of NHCs became apparent, including an often orthogonal behavior compared to phosphines.[4] The most popular characteristics associated with NHCs pertain to their fan-like sterics (as opposed to the cone-like properties of phosphines), and their strong σ donor properties (whereas phosphines impart considerable π acceptor properties).

Both aspects are amenable to tailoring. For example, ring-expanded NHCs (**B**) exert a higher steric pressure on the metal coordination sphere, as the N-substituents in a 6- (or 7-) membered heterocycle point much more directly towards the metal coordination sphere compared to Arduengo-type imidazole-derived NHCs.[5] Likewise, the σ donor properties decrease with carbonyl groups in the ligand backbone, or increase, when one of the nitrogen atoms is displaced to a remote position as in mesoionic NHCs (**C**), that is, NHCs which do not feature any uncharged Lewis structure and with positive and negative charges mutually conjugated (*e.g.* 4-imidazolylidene, Fig. 1).[6]

The most common benefits of NHCs, cited in countless introductions, refer to their strong donor ability and covalent bonding. The strong donor properties promote oxidative additions (*e.g.* in cross-coupling reactions), and labilize *trans*-positioned ligands (for example preventing the re-coordination of phosphine in the activated Grubbs-II catalyst).[7] The covalent bonding, in contrast, is often associated with a highly robust metal-carbon bond, which entails enhanced catalyst integrity and thus high turnover numbers. A further aspect of NHCs, even though only rarely discussed in literature, relates to the ambiguity of the donor as an anionic (X-type) or neutral (L-type) ligating site. This ambiguity is illustrated with the different resonance structures available for an NHC-metal complex (Fig. 2), comprised in one limiting case of a neutral ligand with a Fischer carbene-type metal coordination. The other limiting resonance structure features a dipolar ylid, with a carbanionic metal bonding site that is charge-neutralized by the adjacent iminium nitrogen.

Ground-state analyses all converge to a high predominance of the ylid resonance structure in metal complexes,[4] and such

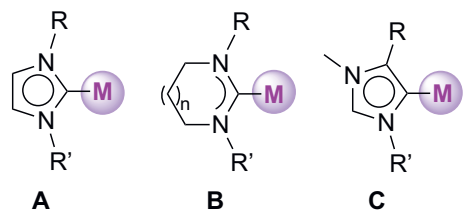

Fig. 1. Arduengo-type imidazole-derived N-heterocyclic carbene **A**, ring-expanded NHC **B**, and mesoionic imidazole-derived NHC **C**.

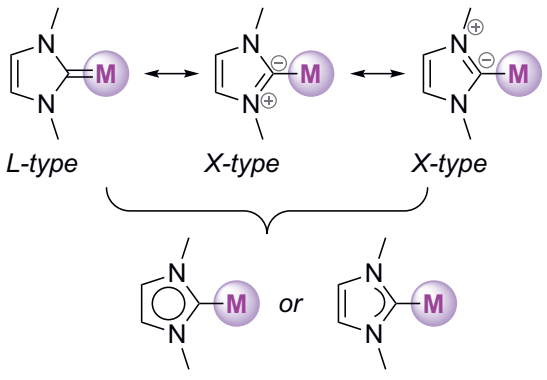

Fig. 2. Most relevant resonance structures of Arduengo-type NHCs with L- and X-type (neutral and anionic, respectively) bonding sites, as well as the most common schematic representation of NHC complexes.

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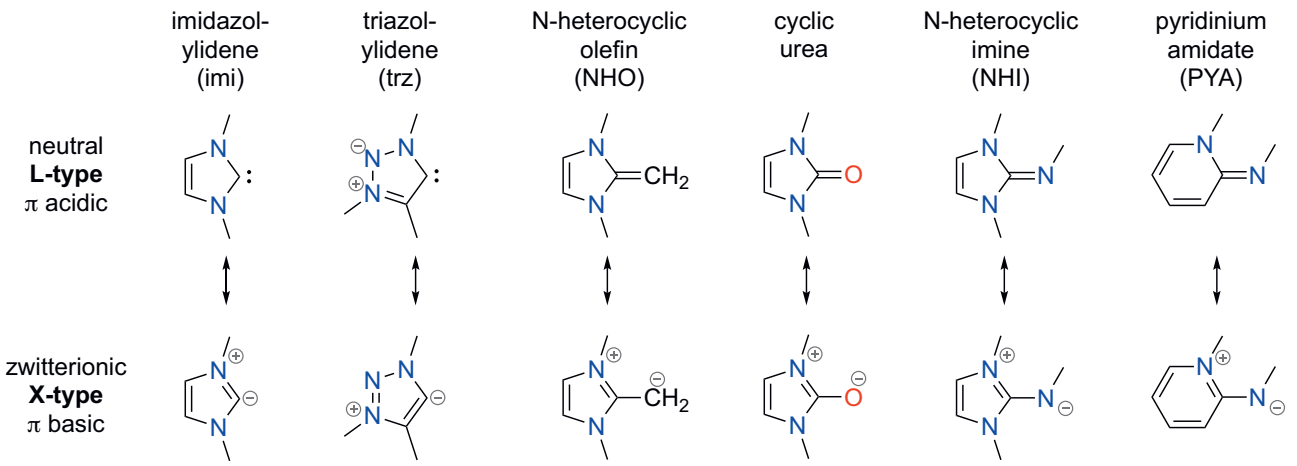


Fig. 3. Imidazole- and triazole-derived NHCs, as well as examples of expanded versions that contain an exocyclic metal coordination site, including N-heterocyclic olefins, cyclic urea, N-heterocyclic imines, and pyridinium amidates as a subclass of N-heterocyclic imines with a pyridine- rather than an imidazole-derived carbene as the stabilizing backbone.

a model is also rationalizing the strong donor properties of the ligand. Scattered evidence supports, however, also the relevance of π bonding between the metal and the carbon, and thus a carbene-type behavior.[8] Obviously, however, any change in ligand properties is difficult to identify due to the conjugation of the formally positive and negative centers in the NHC, and the lack of efficient probes.

2. Expansion of the N-Heterocyclic Carbene Manifold

One approach to exploit this ligand dichotomy involves the introduction of an exocyclic donor site. When stabilized by a carbene, the donor site is formally neutral (L-type), though when stabilized by the ylidic form, the donor site becomes anionic (X-type). For example, introducing an exocyclic methylene unit affords the so-called N-heterocyclic olefins (NHO),[9] and introducing a nitrene unit produces N-heterocyclic imines (NHI, Fig. 3).[10] A synthetically very versatile sub-group of N-heterocyclic imines are systems based on a pyridine- rather than imidazole-derived NHCs, termed pyridinium amidates (PYA).[11]

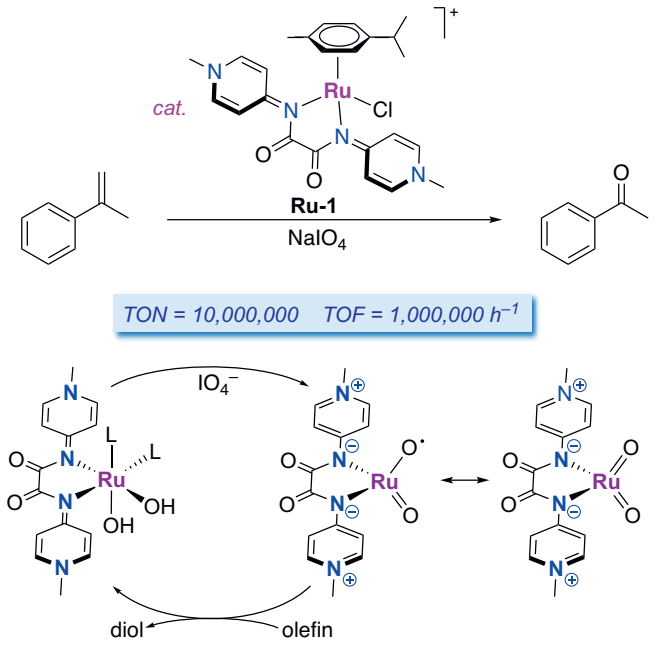
Pyridinium amidates were first introduced in 2009[12] and are readily available from the corresponding aminopyridine upon sequential functionalization of both nitrogens. Alternatively, pyridinium chlorides are functionalized by a nucleophilic aromatic substitution, *e.g.* by an aniline derivative. Subsequent deprotonation of the exocyclic amine or amide provides the free PYA ligand and takes place under considerably milder conditions than C–H bond breaking to form N-heterocyclic carbenes. The free PYA coordinates to a wide range of transition metals in different oxidation states.[11] Their donor flexibility has been established using various read-outs, including polarity- and charge-induced modulation of charge transfer bands in UV-vis spectra, redox-properties by electrochemistry, and NMR spectroscopically by toggling between the quinoidal (L-type) and aromatic (X-type) preponderance of the limiting resonance structures.[13]

3. Catalytic Application of PYA Complexes

The synthetic versatility offers direct access to a range of different ligand structures, with variation of the ligand denticity, chelating sites, and also donor strength, which strongly depends on the location of the amino substituent on the pyridine ring (*ortho*, *meta*, *para*). This variability has led to highly active complexes that are very useful for catalysis, and in some cases also extremely unreactive complexes, which provide insights into fundamental steps of organometallic chemistry, with examples for both extremes highlighted below.

3.1 *Ru PYA-Catalyzed Olefin Oxidation*

Ruthenium complex **Ru-1** is an extremely active catalyst in the Lemieux-Johnson oxidation of olefins (Scheme 1), leading to the formation of the corresponding aldehydes and ketones (Scheme 2).[14] The complex achieves extraordinarily high turnover numbers in the range of 10,000,000 and also high turnover frequencies (*ca.* 10^6 h^{-1}). Even though the catalyst is based on ruthenium as a precious metal, the ultra-high performance minimizes the costs associated with the catalyst. The high performance has been attributed to a ligand effect, as analogous systems with bipyridine are relatively poor catalysts and not competitive with **Ru-1**. The current working model for the high activity is based on an efficient reduction of the energies related to the formation of the high valent ruthenium oxo or ruthenium oxyl intermediate that triggers the oxygen transfer to the olefin, and simultaneously, a low barrier for the formation of the low-valent ruthenium aqua complex that then reacts with the sacrificial oxygen donor. This stabilization of both the oxidative and the reductive processes may be a direct

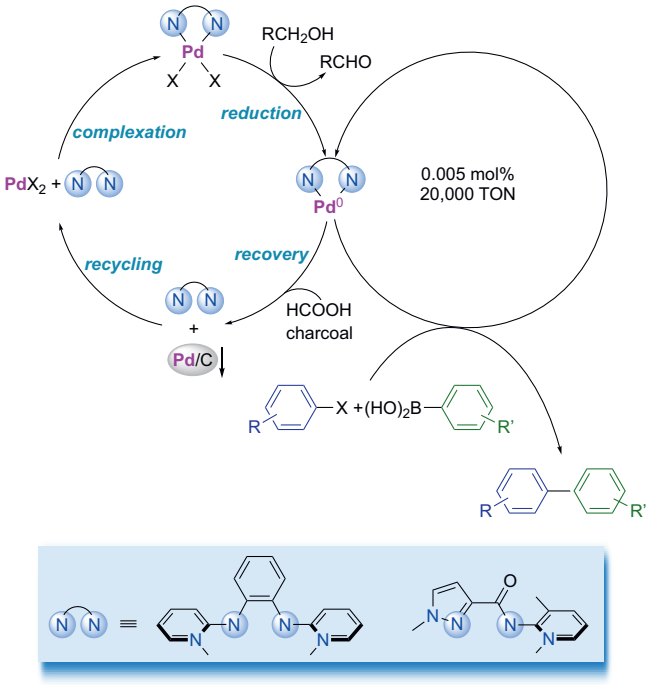


Scheme 1. Catalytic olefin oxidation with **Ru-1** as a catalyst precursor and postulated PYA donor-flexibility as key for lowering key energy barriers in the catalytic cycle.

consequence of the donor-flexibility of the PYA ligands, as the X-type anionic bonding will stabilize ruthenium in high oxidation states, while the L-type bonding facilitates the reductive step.

3.2 *Pd PYA-Catalyzed Cross-Coupling Reactions*

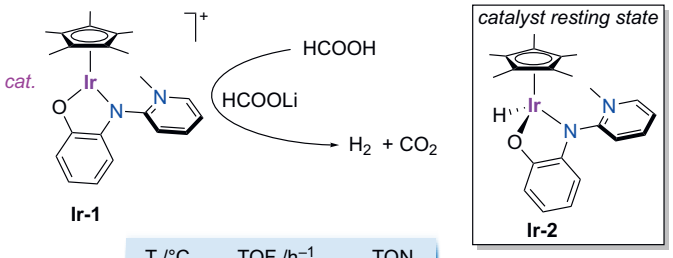
Considering the toggling of palladium from oxidation state 0 to +2 and back on the catalytic cycle of cross-coupling reactions, it appeared to be a logical choice to evaluate PYA ligands for these transformations. Indeed, appropriate tailoring of these ligands affords catalytic systems with very high (*ca.* 20,000) turnover numbers in ketone α-arylation reactions, thus allowing the reduction of palladium loadings substantially.[15] Moreover, the weaker bonding of PYA ligands to palladium as compared to NHCs or phosphines provides access to a clean separation of the catalyst from the product stream.[16] For example, treatment of the post-catalytic mixture with formic acid induces ligand protonation and precipitation of palladium, which can be collected and recycled (Scheme 2). The product stream is essentially palladium-free (<5 ppm), while a similar purification with phosphine-ligated palladium catalysts leaves some 80 ppm palladium in the product fraction as a direct consequence of the stronger bonding of phosphines to palladium.



Scheme 2. Catalytic Suzuki-Miyaura cross-coupling with Pd PYA complexes at low loading and recovery of palladium from the product stream for recycling.

3.3 *Ir-PYA-Catalyzed Formic Acid Dehydrogenation*

The iridium PYA complex **Ir-1** is an excellent catalyst for formic acid dehydrogenation (Scheme 3),[17] one of the key steps in the reversible storage of dihydrogen on CO_2, and thus an elemental process towards a hydrogen economy.[18] The complex is remarkable as it does not feature the classic three-legged piano-stool geometry and does not form stable bonds with exogeneous ligands apart from hydrides. In the presence of formate and formic acid, it catalyzes hydrogen evolution with rates that are directly correlated to the reaction temperature, thus providing an easy means to tailor fuel release according to demand. The catalyst is very resilient and achieves millions of turnover numbers. Notably, isotope labeling experiments indicate that the rate limiting step is the cleavage of the O–H bond, associated with protonation of the iridium hydride



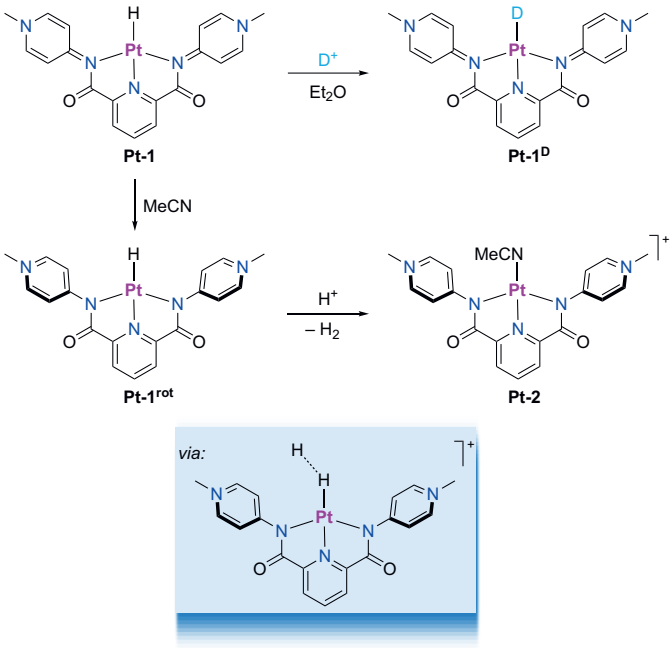
T /°C	TOF /h^{-1}	TON
60	22,000	1,300,000
80	77,000	2,100,000
100	260,000	3,000,000

Scheme 3. Catalytic formic acid dehydrogenation with **Ir-1** together with temperature-dependent activity and hydride complex **Ir-2** identified as catalyst resting state.

Ir-2. In contrast, most other dehydrogenation catalysts feature the cleavage of the much stronger C–H bond as the rate limiting step.

3.4 *Deciphering Elemental Steps of Hydride Protonation Through a Stable Pt PYA Hydride Complex*

While the hydride in **Ir-2** is very reactive, it is remarkably stable in **Pt-1** (Scheme 4). In fact, in ether solution, it resists protonation even when using very strong acids such as Brookhart's acid, $[(Et_2O)_2H][BArF_4]$.[19] However, when using MeCN as the solvent, protonation is instantaneous. Spiking the ether solution with defined amounts of MeCN or using a weaker acid such as HCOOH leads to hydride protonation and dihydrogen evolution in the time span of 30 min to 10 h, which allows for detailed monitoring of the reaction. Kinetic fitting unambiguously reveals a slow adduct formation prior to H–H bonding and release of dihydrogen, indicating that hydride protonation, even though thought to be a simple process, is stepwise even with strong acids. In **Pt-1**, the protonation is proposed to be induced by a change in PYA coordination from L- to X-type, which in turn is



Scheme 4. Protonation of a highly robust platinum hydride. With L-type PYA bonding in **Pt-1**, only H/D exchange is taking place, while with X-type PYA bonding in **Pt-1^{rot}**, induced by a polarity change, protonation leads to H_2 evolution and yields **Pt-2**.

induced by the polarity change of the medium upon addition of MeCN. This change in PYA bonding in **Pt-1^{rot}** transfers electron density from the platinum center to the hydride and renders the hydride amenable to protonation and displacement of dihydrogen by MeCN to give **Pt-2**. In the absence of a change in PYA coordination mode, only H/D isotope exchange was detected, rationalized by proton bonding by the platinum center rather than the hydride.

4. Conclusions

Donor-flexible ligands such as PYAs offer interesting opportunities for catalytic application. This is demonstrated in several processes with high turnover numbers and frequencies, some setting a new benchmark for the corresponding transformation. In the other extreme, they impart very high stability to species that are often considered fleeting intermediates, thus allowing for mechanistic interrogation. Many areas remain still underexplored, as may be appreciated by the countless options to couple NHCs with other more extended donor systems such as diazoolefins[20] or triazenes,[21] and to vary the NHC scaffold. Moreover, only little work has focussed so far on early transition metals, even though some recent catalytic applications may obviously benefit from elasticity in the ligand donor properties.

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Author Contributions

K. S., E. R., N. L., and A. B. performed the experimental work under the supervision of M. A., M. A wrote the manuscript.

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