N-Heterocyclic carbenes as ligands for metal complexes – challenging phosphane ligands in homogeneous catalysis
1. Introduction

Since the first report by Ófele in 1968,[1a] the metal coordination chemistry of N-heterocyclic carbenes (NHCs), derived from imidazole, pyrazole, and triazole, has had a long, steady history in our laboratory. Numerous metal compounds were synthesized and characterized before the free carbene ligands became available through the important work of Arduengo et al.[2] A series of Ph.D. theses[3, 4] yielded a large number of publications. The related C–C-saturated carbenes (e.g., R = neopentyl) resulting from “Wanzlick dimers”[5] were investigated in terms of their organometallic chemistry by Lappert and his associates.[6]

The ylidenes A–D are nucleophilic singlet carbenes. They have been attached to metals either from the corresponding azolium salts (A–D) or from “Wanzlick dimers” (D), ever since the pioneering work of Ófele[1a] and Wanzlick[1b] appeared in the literature. Since N-heterocyclic carbenes are now available as “bottle-able compounds” (a phenyl-substituted triazole-derived ylidene of type C[21] is the first carbene to be commercially available[**]), their inorganic and organometallic chemistry has gained enormously in versatility and depth.[7]

2. Early Breakthroughs

In 1992/93, we noted the striking similarity of electron-rich organophosphanes PR₃ and N-heterocyclic carbenes (NHCs) in terms of their metal coordination chemistry, particularly the ligand properties and metal complex synthesis.[8–10] It was pointed out that both low- and high-oxidation-state transition metals are compatible with the “Wanzlick–Ófele carbenes,”[***] with typical examples being represented by the well characterized species 1–4.

Keywords: carbone ligands • carbenes • heterocycles • homogeneous catalysis

N-Heterocyclic carbenes have become universal ligands in organometallic and inorganic coordination chemistry. They not only bind to any transition metal, be it in low or high oxidation states, but also to main group elements such as beryllium, sulfur, and iodine. Because of their specific coordination chemistry, N-heterocyclic carbenes both stabilize and activate metal centers in quite different key catalytic steps of organic syntheses, for example, C–H activation, C–C, C–H, C–O, and C–N bond formation. There is now ample evidence that in the new generation of organometallic catalysts the established ligand class of organophosphanes will be supplemented and, in part, replaced by N-heterocyclic carbenes. Over the past few years, this chemistry has been the field of vivid scientific competition, and yielded previously unexpected successes in key areas of homogeneous catalysis. From the work in numerous academic laboratories and in industry, a revolutionary turning point in organometallic catalysis is emerging.
Spectroscopic studies revealed the close relationship of NHCs and organophosphanes. They are both pronounced \(\sigma\)-donor ligands with only little backbonding character. Regarding the theory of their bonding, the NHCs are best treated as “diaza-allyl systems”, with little \(\pi\) aromaticity being present in the C–C and CN unsaturated species A–C.

Four initial key patents were filed with priority of December 29, 1994. They cover transition metal complexes of Group 8–10 elements exhibiting N-heterocyclic carbenes including imidazole- and pyrazole-derived carbenes as well as chelating dicarbenes ligands. A catalytic procedure to generate aldehydes by hydroformylation with catalysts containing N-heterocyclic carbenes was disclosed in the second patent. The catalytic C–C coupling to make aromatic aldehydes with the same catalysts (e.g., hydroformylation and related coupling reactions) is covered by the third patent, and the fourth reports novel complexes of the lanthanoid metals including scandium and yttrium.

Somewhat later, the generation and large-scale synthesis of pure N-heterocyclic carbenes was described (“ammonia method”):

- Liquid ammonia or mixtures of liquid ammonia with organic amines or polar-aprotic solvents were used as solvents,
- to smoothly and quantitatively deprotonate the corresponding azolium salts
- with reagents such as metal hydrides, -amides, -alkoxides,
- and -carboxylates
- at temperatures between –75 and 0 °C

This technique following Equation (1) also applies to large-scale syntheses. It includes deprotonation agents such as the commercial K\([\{(CH_3)SiNSi(CH_3)\}_2\] and Li\([N(C_3H_7)_2]\] that, for example, selectively generate chelating dicarbenes but leave methylene and other hydrocarbon bridges intact [Eq. (2)]. The high-yielding synthesis of novel, functionalized N-heterocyclic carbenes in liquid ammonia was described in detail as the standard literature technique in 1996. Other techniques include the use of potassium hydride or potassium tert-butyllithium in THF to deprotonate the azolium precursor cations. Care has to be taken with the choice of the deprotonating agent, because certain hydrides yield imidazolidines \((+H^-)\) instead of the carbene.

3. Easy Access

Most easily available are stable carbenes derived from imidazole, not least because numerous imidazolium precursor compounds can be made along various reliable routes. The one-pot synthesis starting from glyoxal, primary amine, and formaldehyde is straightforward (Scheme 1a), its variation (Scheme 1b) allows unsymmetrically N-substituted derivatives \((R^1, R^2)\) to be made, while in another route (Scheme 1c) the imidazolide anion is alkylated by reactive alkyl-/aryl halides (or -triflate derivatives). The orthoformiate route (Scheme 1d) converts the easily accessible 1,2-diamines (e.g. from Pd-catalyzed Buchwald coupling) into the aryl-substituted imidazolium salts. The heterocycle synthesis according to Scheme 1a and b was previously mentioned in the literature. The desulfurization of the cyclic thiourea derivatives (Scheme 1e) depends on relatively drastic conditions but works well in many cases, for example, benzimidazolin-2-yldienes from the corresponding 2-thiones. Vacuum ther-
mols of methoxy derivatives (Scheme 1f) yields carbenes in good yields, as well, for example, 4,5-dihydro-1H-1,2,4-triazol-5-yldienes.\(^{[21]}\)

The free carbenes A and D are stable to air. Their “air sensitivity” is in fact hydrolysis. It is reported that D hydrolyzes instantaneously, while A is much more robust because of “aromatic stabilization”.\(^{[22]}\) Hydrolysis yields acyclic products by C–N bond cleavage.\(^{[22]}\)

4. Metal Coordination Chemistry

N-heterocyclic carbenes in fact behave like typical \(\sigma\)-donor ligands that can substitute classical 2\(\pi\)-donor ligands such as amines, ethers, and phosphines in metal coordination chemistry.\(^{[23–32]}\) It was determined in 1993 that “heterocarbenes show bonding properties similar to those of trialkyphosphines and alkylphosphinates”.\(^{[9]}\) Nolan et al. concluded from structural and thermochemical studies that “in general these ligands behave as better donors than the best phosphane donor ligands with the exception of the sterically demanding (adamantyl) carbene”.\(^{[118]}\)

Examples are the “titration” of TiCl\(_4\)·2PR\(_3\), with two NHC equivalents to give TiCl\(_4\)·2NHC, or of VCl\(_2\)·4NR, with four equivalents to yield VCl\(_2\)·4NHC.\(^{[26]}\) The typical examples 1–4 result from the free carbenes. The complexation to beryllium chloride\(^{[11]}\) is typical in that the analogy to other \(\sigma\)-donor ligands is evident (Eq. (3)).

Metal complexes of alkylidene-bridged dicarbenes followed soon.\(^{[21]}\) Also, the first chemistry occurring at the five-membered heterocycles was reported, for example, the OsO\(_4\)-addition to the C–C unsaturation (Eq. (4)).\(^{[23]}\) This latter reaction once again indicates that there is little to no \(\pi\)-aromaticity in the five-membered ring, quite consistent with recent charge-density studies.\(^{[34]}\)

Numerous molecular structures were determined by single-crystal X-ray diffraction. It was shown that there is little or no variation in the geometrical details of the NHC ligands from case to case. The metal–carbene bonds are rather long (\(>210\) pm), while in Fischer- and Schrock-type complexes these distances are significantly below 200 pm because of pronounced backbonding (“double bond”). An excellent benchmark structure is the olefin metathesis catalyst 5 which exhibits both types of carbenes (Figure 1). As a result of this particular bonding situation, nucleophilic NHCs can, depending on the steric situation, rotate around the metal–carbon axis.
Figure 1. ORTEP representation of the molecular structure of the olefin metathesis catalyst 5. Selected bond lengths [pm]: Ru-C(11) 210.7(3), Ru-C(31) 211.5(3), Ru-C(1) 182.1(3).

Full reports on the synthesis of metal complexes that are relevant to catalysis appeared in 1996 and the following year. While in most cases imidazolin-2-ylidene complexes were described, several triazol-derived systems were reported, too. Salt metathesis and elimination reactions represent the prevailing synthetic access to NHC and related metal complexes. Regitz gave a first review in 1996. A recent exploitation of the azolium route now covers metallocenes, such as 6 [Eq. (5)], and works for both nickelocene and chromocene. Another field of application has thus been opened.

The first carbene-linked cyclophane 8 was made by Youngs et al. from the ionic bis(imidazolium) precursor compound 7, which results from a straightforward alkylation reaction of 2,6-bis(imidazolemethyl)pyridine [Eq. (6)]. Silver oxide was used to deprotonate 7 and, at the same time, introduce the metal center which adopts a linear coordination environment in the binuclear complex 9a (X-ray diffraction study). Monomeric and dimeric silver halide complexes 9b and 9c, respectively, are obtained in the same way while the existence of NHC–copper(Ⅰ) complexes, such as 9d, seems to depend on chelating properties of the ligands. A tetranuclear, ionic complex of formula [Ag₄L₂][PF₆]₄ is derived from the N,N,C,C-macrocycle 8.

Special NHC-transfer reagents are the silver(Ⅰ) complexes of type 9e. They are formed in a simple way by treatment of Ag₂O with imidazolium salts and transfer their NHC ligands to other metals, for example, palladium. This technique seems to be particularly effective in the case of functionalized NHCS with “dangling” substituents. Related nickel and palladium cyclophane-type complexes of the NHC series have recently been made.

5. Catalytic Properties

After the initial patent reports, catalytic data were released in a series of publications, the first of which appeared in 1995.

5.1. Heck and Suzuki Coupling

First, the Heck coupling of aryl bromides and aryl chlorides was communicated: Complexes 10 and 11 are active upon
smooth reduction with formiate or hydrazine, thus generating the active Pd⁰ species. Unexpected were the low catalyst loadings (ca. 10⁻³ mol%) necessary to obtain yields > 99% in the case of bromides, and 0.1–1 mol% for aryl chlorides.⁴⁴ The advantageous properties of the “New structural principle for catalysts in homogeneous catalysis”⁴⁴ was stated as follows: “The new catalyst type described here has a series of advantageous properties and potential for development: a) high thermal and hydrolytic durability resulting from exceptionally stable M–C bonds (long shelf-life, stability to oxidation); b) easy accessibility, and c) no need for an excess of the ligand. The prospects for derivatization to water-soluble catalysts (two-phase catalysis), immobilization, and chiral modification seem promising because of the constitution of the ligands.”⁴⁴ These predictions have since been shown to be correct.

The phosphane-free NHC catalyst 12a, either as the isolated complex or generated in situ, represents the most active coupling agent for aryl chlorides to form (substituted) biphenyls in the Suzuki cross-coupling. Reaction times between two and 48 h are sufficient at room temperature, while at 80°C the productivity is approximately six times better.⁴⁵ The stability of the active catalyst 12b is a result of the “pincer-type” tridentate C,N,C-ligand.⁴²⁶

Highly active and very stable catalysts for Heck, Suzuki, and Sonogashira coupling reactions were discovered in certain palladium(II) complexes of NHCs with “dangling” N-substituents: Catalyst 13a performed particularly well, giving turnover numbers (TONs) of 1.7 × 10⁶ (Heck) and 1.1 × 10⁵ (Suzuki) at > 85% conversion of 4-bromoacetophenone with butyl acrylate and phenylboronic acid, respectively.⁴⁵ After first reports on the Suzuki cross-coupling activity of carbene ancillary ligands involving aryl bromides and activated aryl chlorides,⁴⁷ non-activated, functionalized aryl chlorides were coupled successfully.⁴⁸ Typical examples are shown in Equation (8); dba = trans,trans-dibenzylidenaceton. The sterically demanding 1,3-bis(mesityl)imidazolinylidene (generated in situ from the imidazolium chloride 14b) proved to be the best choice of ligand at palladium(II) centers. The C–C saturated azolium salt 14d is now commercially available.⁴⁸

* Strem Chemicals, Inc. (Kehl, Germany).

A general and user-friendly procedure for Suzuki reactions with aryl chlorides is now based on easy-to-make NHC–palladium catalysts. As shown by Fürstner et al.,⁴⁶ subtle steric effects in the NHC ligands govern the B-alkyl Suzuki–Miyaura coupling,⁴²⁹ with the best results being obtained from the 1,3-di-2-propyl derivative [Eq. (7)], as “imidazolium additive”. In several cases, the in situ technique is more efficient than the use of the preformed palladium catalyst. Other borate complexes with c-C₃H₇, C≡C-C₃H₇, and CH₂CH₃–CH₃ in place of (CH₂)₃CH₃, perform similarly well.
High efficiencies in Heck reactions of aryl bromides were reported by the Nolan group[49] who used palladium in the presence of CP-chelating NHC ligands derived from the sterically demanding imidazolium salt 14a. A catalyst loading of 0.5 mol% based on palladium was sufficient to obtain good yields. Cesium carbonate turned out to be the most efficient base, much better than KO\(_2\)C\(_4\)H\(_9\), NaOAc, and K\(_2\)CO\(_3\).[49]

Exceptionally stable nickel and palladium complexes derive from imidazolium-linked ortho-cyclophanes.[43] They catalyze Heck and Suzuki coupling reactions of aryl bromides and iodides with remarkable activities (TONs 7.1 \(\times\) 10\(^6\) for iodobenzene/\(\text{n- butylacrylate}\) at 140°C; 6.8 \(\times\) 10\(^5\) for 4-bromo-nitrobenzene/\text{n- butylacrylate} at 140°C).

Mixed NHC-phosphane complexes of palladium provide an excellent means of increasing both the activity and stability of the active species in C–C coupling reactions of this type. An important feature seems to be the necessity of bulky NHC ligands, whereas the phosphane has to be optimized for each type of reaction.[119]

Numerous papers confirm the extraordinarily high thermal robustness of NHC catalysts. For example, the bis(carbene)-palladium(ii) catalyst 13c (X-ray diffraction study) maintains activity in the Heck coupling at least of aryl bromides at 184°C (!) in air.[124]

5.2. Aryl Amination

Through the use of NHC catalysts the palladium-catalyzed amination of aryl halides has experienced remarkable advances in substrate scope and reaction rates. Aryl chlorides are the most desired starting materials, simply for economic reasons. Nolan et al. have introduced a sterically hindered version of imidazolylidene in the presence of palladium(0) complexes, albeit elevated temperatures are necessary to achieve good results.[50] Instead, Hartwig’s group used the dihydroimidazolylidene, see Equation (9), and obtained yields near quantitative at room temperature when strong bases such as NaO\(_2\)C\(_6\)H\(_5\) were used to deprotonate the ligand precursor [Eq. (9)].[51] TONs as high as 5 \(\times\) 10\(^3\) were obtained at elevated temperatures for the reaction of morpholine with an unactivated aryl chloride, for example, chlorotoluene (7 h, 100°C). Catalyst precursor ligands of type 14d were used (2,6-diisopropyl instead of mesityl).

Readily available heteroaryl halides were used in the catalytic coupling with 7-azabicyclo[2.2.1]heptane. This useful type of cross-coupling amination once again employs NHC-based catalysts.[52] A typical example is given in Equation (10).

This reaction also works with heteroaryl chloride, albeit less efficiently. Any other ligand system tested so far (e.g., P(C\(_6\)H\(_5\))\(_3\), diphosphane ligands) is inferior under comparable conditions. Yields around 70% were achieved.[52] The synthetic utility of the catalyst system seems to be broad and useful for the synthesis of \(N\)-arylaminines. Also [Ni(acac)\(_2\)] in combination with sterically hindered NHC ligands catalyzes the amination of aryl chlorides.[53] Future work must be aimed at avoiding the use of sodium hydride to regenerate the catalytically active nickel species.

5.3. Amide \(\alpha\)-Arylation

Sterically hindered N-heterocyclic carbenes have become the ligands of choice for the palladium-catalyzed \(\alpha\)-arylation of amides.[54] The Hartwig group showed in an extensive study that cyclization reactions following Equation (11) give an excellent performance—conversions and yields up to quantitative—when the bulky ligand precursor 14b was employed in the presence of palladium(ii) acetate. Enantiomeric excesses up to 67% were obtained when the chiral imidazolium salt 15 was used as a ligand precursor in the
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cyclization of amides where \( R^1 + R^2 \). Chiral oxindoles, important substructures in numerous biologically active molecules, are thus catalytically accessible by easy means.\[54\]

In an extension of common cross-coupling reactions, Nolan et al. have found that methoxysilanes \( R_2Si(OCH_3)_3 \) (\( R = \text{vinyl, phenyl} \)) react with aryl bromides and electron-deficient aryl chlorides according to Equation (12). Also, 2-halopyridines can be coupled to give 2-aryl pyridines.\[55\] The catalyst is formed in situ from \( \text{Pd(OAc)}_2 \) (3 mol%) and the equimolar amount of bulky imidazolium salt \( 14b \) (also \( 14c \), isopropyl in place of mesityl). The new catalysts seem to work in reactions of vinyltrimethoxysilane.\[55\] As in the majority of papers in this field, no turnover numbers and frequencies (TONs and TOFs) are reported, so comparison with other catalysts is not easily possible.

5.4. Hydrosilylation

Chiral N-heterocyclic carbenes, their metal complexes, and their successful applications in catalysis appeared in 1996.\[56a\] As an example, the hydrosilylation of acetophenone with rhodium catalysts (16) was used. The enantiomeric excesses reported at that time (>30%) were subsequently raised

\[
\begin{align*}
16 & \\
17 & 
\end{align*}
\]

in the Ph.D. thesis work of M. Steinbeck to >70%.\[40\] Simple chiral N-substituents, such as \( C^*H(CH_3)_2C_6H_5 \), were sufficient to generate significant optical induction into the prochiral substrates. Chelate complexes 17 exhibiting chiral oxazoline building blocks became available in 1998.\[56b\] They are made from the free imidazole \( C_2N_2H_2R \) by stepwise treatment with \( ClCH_2C=\text{N} \), \( C_6H_5OH \), and chiral \( \beta \)-aminoalcohols \( HOCH_2C^*HRNH_2 \).

5.5. Olefin Metathesis

Catalytic Heck-type reactions\[44, 47, 57a±e\] and a new generation of olefin metathesis catalysts\[57f±n\] were reported in 1998/99. On both topics, NHC ligands amply demonstrated their excellence over standard phosphane ligands in homogeneous catalysis. Therefore, these subjects became a major focus of our research.\[5\] Typical catalysts with N-heterocyclic ligands for the olefin metathesis are 18–21, for the Heck coupling 22 and 23. Catalysts of type 21 (mixed-metal systems) are described in ref. [56].

Ring-opening polymerization (ROMP), acyclic diene metathesis (ADMET), and ring-closing metathesis (RCM) are the best understood metathesis varieties as yet. Overviews on the rapid development in this area were given by Grubbs\[58\] and Fürstner.\[59\] It is clear by now that N-heterocyclic carbenes have made ruthenium the most promising “olefin-metathesis metal”, predominantly because of the high tolerance to functional groups and the mild reaction conditions (normally room temperature).

In an extensive comparative study, Fürstner et al. have adjusted the metathesis catalysts of types 19 and 20 by changing the electronic and steric properties of the NHC ligands.\[59b\] They made a comprehensive series of new derivatives, which included those with Ru=CHR entities tethered to form a metallacycle, for example, the structurally investigated compound 21. It was concluded that “No single catalyst outperforms all others in all possible applications.”\[59b\] We conclude that the great structural versatility of the catalysts of types 19 and 20 is thus all the more important.

The mixed-ligand olefin metathesis catalysts such as those of types 19 and 20 were first patented\[57k\] and then communicated at the XVIIIth International Conference on Organometallic Chemistry in Munich,\[60\] before appearing in the journals in 1999.\[57i\] Papers by Grubbs\[61\] and Nolan’s groups\[62\] on the same subject followed a little later.\[63\]
series of patents by Grubbs et al. covers some of this work including the synthesis of the corresponding ruthenium NHC catalysts.[64a–e]

The mixed carbene/phosphane ruthenium catalysts 24 and 25 were subjected to density functional theory (DFT) calculations. They showed low dissociation barriers of the NHC ligands compared to the phosphanes.[57i] The same overall picture was obtained from palladium(0) species of the type [(NHC)Pd0(PR3)].[65]

Ligand-exchange studies, however, revealed that the π-bonding of the olefin (associative mechanism) may be the decisive factor.[66] Phosphane dissociation is facilitated in [Ru(PR3)2Cl2(CHC6H5)] but the resulting 14e-intermediate binds the olefin better in 20. As seen in Scheme 2, the carbene strengths the olefin binding to the metal, a fact which is thought to account for the excellent activities of catalysts 19–21.[66] Better olefin association may explain why the bis(NHC) complex 18 is more active than the corresponding bis(phosphane) catalyst [Ru(PCy3)2Cl2(CHC6H5)]. In the bis(NHC) case, the associated olefin (step 1) could strongly labilize one of the NHC ligands for subsequent dissociation. The mixed-metal catalyst 21 is more ROMP-active than its mononuclear counterpart 19 by an order of magnitude.

The C–C saturated derivatives 20 were published later in the year 1999.[67–69] Catalysts 20 exhibit excellent activities, working at monomer:catalyst ratios of up to 1000000:1 for ROMP. However, the stability of type 20 catalysts is clearly lower than that of their C–C unsaturated counterparts. Various applications in the ring-closing metathesis of olefins were reported recently, thus showing the great interest in this field.[66–71]

As a further exploitation of the outstanding carbene effects, the ruthenium complex 28 was recently generated in situ by Grubbs et al.[72] and successfully employed in the olefin metathesis. For this purpose, a η1-vinylidene precatalyst 27 was generated by a standard method from the p-cymene complex 26 and converted into the active catalyst by a olefin metathesis reaction itself (Scheme 3). The major advantages of these catalysts are that they are compatible with functional groups (heteroatoms) and protic solvent systems, and that they work under mild conditions, normally at room temperature. Contributions in the area of olefin metathesis came also from Blechert’s group.[73] In a joint effort, the stereoselective ring-closing metathesis (RCM) following Equation (13) was developed with catalysts 18 and 19, with the latter (R = CH(CH3)C6H5; R’ = cyclo-C6H11) yielding 40% enantiomeric excess.[4k, 4n, 73] This results holds promise for an improvement of the desymmetrization of prochiral olefins.

In a similar approach, methylene complexes of type 25 were treated with 1,1-difluoroethylene, with the result that the metathesis exchange reaction \( L_x Ru=CH_2 + F_2C=CH_2 \rightarrow L_x Ru=CF_2 + H_2C=CH_2 \) occurred.[74] This method is an easy means to generate dihalocarbene metal complexes that are rare in organometallic chemistry.

5.6. Metathesis Cross-Coupling

Not only has the synthesis of trisubstituted and functionalized olefins become possible through the catalyst 29a,[75] there is also the cross-metathesis of α,β-saturated amides with terminal olefins, for example, styrene, is also catalyzed by this
compound.[70] Equation (14) shows one out of numerous examples (THP = tetrahydropyranyl). More electron-rich amides give poorer yields because of carbonyl chelation at the catalytic center. Nevertheless, this is at present the most promising approach to a difficult reaction. The chelate congener 29b of type 19 catalysts combines the steric bulk (N-mesityl) with enhanced thermal stability and steric constraints.[106]

This type of catalyst was recently used to cyclize N-allyl-N-isopropyl acrylamide by ethylene release (α, ω) in a metathetical approach.[120] The first product is N-isopropyl-3-pyrrolin-2-one. Upon warming, a radical reaction with the same catalyst leads to a chlorinated product.[120]

5.7. Sonogashira Coupling

The palladium(0) species 30, which is active in the Heck and Suzuki C–C-coupling,[76] can also be employed to furnish a Sonogashira-type coupling to make the bromo-eneyne 31, a common building block of natural products [Eq. (16)]. The analogy with the standard catalyst [Pd[P(C6H5)3]3] was noted by the authors who, at the same time, presented a new, simple synthesis of PdP bis(carbene) complexes: (π-allyl)palladium(II) chloride is treated with the free carbene under reducing conditions [Eq. (15)]. Copper-free conditions were reported for the Sonogashira coupling of aryl bromides with alkyllsilanes on Pd(OAc)2 or 14d.[121]

5.8. Ethylene/Carbon Monoxide Copolymerization

Yet another catalytic application was found in 1999: dicationic palladium(II) NHC complexes such as 32 catalyze the copolymerization of C2H4 and CO to give high molecular weight, strictly alternating poly(C2H4-alt-CO) under mild conditions and low pressure.[77] Polyketones play a considerable role in numerous technical applications, particularly in the car industries.

5.9. Kumada Coupling (Grignard Cross-Coupling)

A promising entry into the Grignard cross-coupling of aryl chlorides as sketched in Equation (17) was opened by NHC catalysts of nickel.[78] Generated in situ from [Ni(acac)2] and imidazolium salts, the catalysts—very likely zero-valent nickel species such as 33a,b—effect the C–C coupling even at room temperature (3 mol% Ni). All previous catalysts required much higher temperatures, with the result that they suffer from insufficient selectivity because of the formation of numerous side products. The related palladium(0) catalysts mentioned by Nolan et al.[79] are less active than the nickel(0)
systems; they require higher temperatures, typically around 80°C.

The first case of catalytic C–F bond activation in conjunction with selective C–C bond formation was observed with NHC–nickel catalysts.[80] Once again, a sterically demanding carbene 14c, was successful and simply generated in situ from [Ni(acac)2] and the azolium salt [Eq. (18)]. The yields of the desired heterocoupling products were as high as 97% (R1 = CF3). Both the product selectivity and the Hammett correlation suggest a polar reaction and disfavor the radical pathways seen to participate when NiCl2 alone is used as a coupling reagent.[80]

$$\begin{align*}
\text{R}^1 &= \text{H, CF}_3, \text{OCH}_3 \\
\text{R}^2 &= \text{H, 4-t-C}_6\text{H}_4, 2,4,6-(\text{CH}_3) \\
\text{cat} &= [\text{Ni(acac)}_2] + 14c
\end{align*}$$

(18)

5.10. Stille Coupling

Another common type of C–C coupling, named after John Stille, works with catalysts that were generated from Pd(OAc)2 and imidazolium salts.[81] Equation (19) shows a typical example, which works well in 1,4-dioxane at 100°C (12 h) in the presence of tetrabutylammonium chloride.

$$\begin{align*}
\text{Cl} + \text{Sn(CH}_3)_2 &\xrightarrow{\text{cat.}} \text{SnCl}_2 + \text{PhCH}_2
\end{align*}$$

(19)

5.11. C–H Activation

Certain NHC complexes of iridium have a strong tendency to undergo C–H activation. For example, the dimethyl iridium(0) species 34 undergoes loss of methane under protolytic conditions, and forms the internal π-olefin complex 35 in a stepwise manner and in high yields by β-H migration [Eq. (20)].[82] The related process occurs with the isopropyl derivative 36 [Eq. (21)].[82] However, the stable dicationic 39 can be generated without CH activation from the dichloro complex (38) instead of the dimethyl precursor compound [Eq. (22)].[82] This story tells us that 1) chelate structures of NHC–metal complexes can spontaneously occur by C–H activation, and 2) the latter reaction is principally feasible with NHC–metal catalysts.

As a matter of fact, a new approach to the activation of the greenhouse gas methane was opened by virtue of the NHC–palladium complex 11b ([C6H5 in place of CH3]: Trifluoracetic anhydride yielded the methyl ester upon treatment with methane in the presence of potassium peroxodisulfate according to Equations (23a) and (23b). Remarkable are the relatively mild reaction conditions: 20–30 bar CH4, 80–90°C. The peroxodisulfate provides the redox equivalents necessary to balance the conversion CH4 → H+ + CH3+ + 2 e− / O2− + 2 e− → 2O2−. Neither the Periana (Pt) nor the Sheldon system (Pd) gives any methane activation under such conditions.

5.12. Hydrogenation, Hydroformylation

These olefin functionalization reactions work with rhodium(0) catalysts of type 16, as mentioned in previous reviews[7, 56] based on the Ph.D. theses of M. Steinbeck,[4h] J. Fischer,[4d] and C. Köcher.[4g, 29] Detailed investigations are
required in this promising, industrially relevant area. The concept of two-phase catalysis has plenty of potential here, especially since successes were achieved with this principle in the industrial Ruhrchemie/Rhône-Poulenc process.[85, 86] Watertable NHC–metal complexes are known, too.[30]

Recent reports predict a great future of NHC catalysts in alkene hydrogenation: Using sterically hindered ligands, the Nolan group achieved TONs up to \(2.4 \times 10^5\) at only 4 bar hydrogen pressure at 100 °C for the substrate 1-hexene.[87] However, the ruthenium(l) catalysts tested work well only at elevated temperatures but not under the mild conditions typical of the classical Wilkinson (Rh) catalyst. Also, the replacement of phosphane by the carbene [Eq. (24)] does not dramatically improve the catalyst’s activity. The 14e intermediate \([\text{HRu(CO)}(\text{Cl})L]\) is thought to be the active species, the formation of which is enhanced by addition of \(\text{HBF}_4 \cdot \text{O(C}_2\text{H}_5)^2\).[87] Catalyst \(40\) has a distorted trigonal-pyramidal structure in the solid state.[87]

Based on our results,[29] vinyllarenes were subjected to hydroformylation with NHC-rhodium catalysts. High selectivities were obtained for the branched isomer,[88] possible candidates in the synthesis of important pharmaceuticals, such as ibuprofen. Branched-to-linear ratios of up to 97:3 were obtained with styrene and some of its derivatives in the presence of square-planar catalysts \(41a\) or \(41b\) made by ligand exchange from Wilkinson’s catalyst \([\text{RhCl}(\text{P(C}_6\text{H}_5)_3])_3\]. Unfortunately, the catalytic activities are still low (TOF < 10 h\(^{-1}\)), in accord with earlier reports on catalyst \(16\).[4g, 29]

Cationic NHC–iridium(l) catalysts of type \(41c\) were used in olefin hydrogenation[90] and in transfer hydrogenation with ketones.[90] The catalyst stability is at the expense of activity in these cases. However, increased hydrogen pressure at 50 °C gives acceptable results.[90]

5.13. Furan Synthesis and Alkyne Coupling

A quasi-catalytic furan synthesis by the rearrangement reaction following Equation (25) was reported by Dixneuf et al.[91] The catalyst \(42\) is a benzimidazolin-2-ylidene complex of ruthenium.[91a] Yields of around 80% were reported (1 mol% cat., 80 °C, 25 h). In a subsequent paper, the improved catalyst \(43\) was used.[91b]

An alkyne coupling reaction following Equation (26a) was described by Herrmann and Baratta.[27a] Once again, ruthenium is required as the mediating metal. The NHC complex \(45\) used for this purpose[27b] associates 2e ligands such as phosphanes and carbenes to form tetracoordinate adducts \(46\) [Eq. (26b)]. The \(\pi\) addition of alkynes clearly facilitates the consecutive C–C-coupling. Conversions as high as quantitative were achieved with \(R = \text{C}_3\text{H}_7\), \(\text{C}_3\text{H}_7p-\text{CH}_3\), \(\text{SiMe}_3\) within 5–10 min. In most cases, the \(\text{trans}\)-coupling product \(44a\) dominated, with the exception of \(R = \text{SiMe}_3\) where the \(\alpha\)-olefin \(44c\) was formed >92%. Maximum turnovers of TOF = 10320 (TON = 860) were reported so far.[27a]

Highly functionalized enones are accessible from readily available acyclic precursor compounds when NHC–ruthenium metathesis catalysts such as \(20\) (\(R = \text{mesityl}\)) are applied. Combined with efficient protodesilylations, this process gives conversions up to 98% at 60 °C, starting from appropriate siloxyalkynes.[126] Equation (27) represents an excellent example of an alkene–siloxyalkyne metathesis.

5.14. Olefin Cyclopropanation

Rhodium(i) and ruthenium(ii) complexes 47 containing NHCs with hemilabile, dangling ether moieties were successfully used as catalysts for the cyclopropanation of olefins with diazooalkanes, [Eq. (28)]. This reaction is of industrial use in the synthesis of insecticides.

\[
\begin{align*}
\text{H} & \quad \overset{\text{cat. 20}}{\text{H}} \\
\text{CH}_2=\text{CH}_2 & \quad \text{H} \\
\text{H} & \quad \text{H}
\end{align*}
\]

5.15. Arylation and Alkenylation of Aldehydes

A convenient, user-friendly method for the addition of aryl or alkenyl boronic acids to aldehydes employs a catalyst formed in situ from RhCl₃·3H₂O, the bulky imidazolium salt 14b, and inexpensive aqueous bases. The addition is chemoselective for aldehydes and compatible with many functional groups in both reaction partners. Secondary aldehydes—possibly asymmetric varieties in the future—are thus formed according to Equation (29) in good to excellent yields.

\[
\begin{align*}
\text{R}=\text{alkyl, } \text{L}=\text{P(C}_6\text{H}_5)_3
\end{align*}
\]

5.16. Reduction of Aryl Halides

Dehalogenation of aryl halides was performed when nickel(0) catalysts (3 mol%) of bulky N-heterocyclic carbenes were used in the presence of β-hydrogen containing alkoxides, with the latter acting as reducing agents. Most efficient once again was the carbene derived from the imidazolium salt 14b by in situ deprotonation by the alkoxide (normally NaO(C₂H₅). Mild reaction conditions (THF, 65 °C, 1–3 h) are convincing indications that this new way of replacing halides (F, Cl, Br, I) by hydrogen can find practical use through further improvement.

5.17. Atom-Transfer Radical Polymerization

Styrene and methyl methacrylate undergo atom transfer radical polymerization (ATRP) in the presence of catalysts possessing donating NHC ligands. Thus, the tetrahedral iron(ii) complex 48, reported by Grubbs et al., works at 85 °C for styrene to provide a polymer with low polydispersities ($M_w/M_n \approx 1.1$). ATRP is a method to control free-radical polymerizations. Compound 48 gives the highest polymerization rates seen for ATRP in organic solvents to date.

5.18. Asymmetric Catalysis

Apart from a few examples, stereoselective synthesis has to date not been generally investigated with NHC catalysts. The number of reported successes is correspondingly small. In the Enders’ group in particular, however, triazolinylidene ligands have developed a convincing potential. Chiral catalysts such as 49 and 50 (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) gave moderate optical inductions up to 44%.
compounds. For example the asymmetric catalyst effects the conversion of 4-allyloxy-3,5-dimethyl-2,5-heptadiene into (2S)-((2Z)-buten-2-yl)-3-methyl-2,5-dihydrofuran in 90% enantiomeric excess.[120]

Good to excellent stereoselectivities in the hydrogenation especially of trisubstituted alkenes (25°C, 50 bar H2) were obtained by virtue of the NHC-chelate iridium(0) catalyst 50.[123] The cationic catalyst is modeled after the basic structure of 41c.[90] This was the first report of high optical induction using electron-rich carbene ligands in catalytic processes.

Chiral silver(0) dianimocarbenes act as carbene transfer agents to copper salts. The products catalyze the addition of diethylzinc to cyclohexanone[97] according to Equation (30).

The optical yields are certainly subject to further improvement but the easy generation of the catalyst is striking indeed.

6. Ionic Liquid Effects

Great progress in catalytic C–C coupling reactions was recently made with non-aqueous ionic liquids (“NAIL”).[98] As demonstrated for the Heck coupling of aryl halides, molten tetraalkylammonium halides (particularly [N(C4H9)4]Br) improved both the stability and activity of almost every known palladium catalyst system compared to standard solvents such as DMF, N,N-dimethyl acetamide, or 1-methyl 2-pyrrolidone.[98b] Remarkably, the yield with the NHC catalysts 10 improves from 20% to >99% for the coupling of bromobenzene with styrene. Effects of similar magnitude were reported for low reactive chloroarenes.[98b]

Ionic solvents are relatively expensive. However, they can be recycled, without loss of catalyst. In the mechanistic considerations, anionic catalyst species of type [Br–PdII–Ligand]− are invoked, at least for the NHC- and palladacycle catalyst systems PdII, albeit PdII/PdIV equilibria cannot be ruled out.[98b]

The ionic-liquid concept[98] was taken up by the Italian group of Calò.[99, 100] They used related palladium complexes of benzothiazole carbene ligands 52[99b] in a melt of tetra(n-butyl)ammonium salts to carry out the coupling of aryl bromides with 3-hydroxy-2-methylene alkanooxetanes. β-Arylketones are thus formed in good yields.

Imidazolium salts are among the best investigated ionic liquids. Their beneficial effects in catalytic processes may in part originate from their easy conversion into NHC-metal complexes, since coligands of reasonable basicity are known to induce deprotonation.[24, 29] Reactions following Equation (31) to convert the imidazolium metalloc 53a into the NHC complex 53b may then occur under a pseudo “ionic liquid effect”. A Russian report is indicative of the chemistry following Equation (31) but the product was not unambiguously characterized because of concomitant decomposition reactions.[101] Similarly, the alkoxy rhodium complex 54a undergoes spontaneous formation of the NHC derivative 54b [Eq. (32)] a reaction which is now a standard synthesis[19].

7. Avoiding Catalyst Leaching

Polymer-supported NHC catalysts were published in 2000: Good results in the Heck coupling reactions were achieved with polymers on the basis of the Wang resin (4-bromomethyl)phenoxymethylpolystyrene. Hardly any catalyst leaching was observed, which supported earlier proposals that the NHCs are strongly bound to the catalyst metal center.[7] The methodology is outlined in Scheme 4 and described in full detail in refs.[4l, 65]

An alternative strategy was pursued by Blechert et al. to obtain a polymer-supported olefin metathesis catalyst. In this case, the polymer-anchored ligand precursor was built up first and then treated with the catalyst metal compound. Scheme 5 outlines this straightforward methodology.[102] Excellent results were obtained in the ring-closing metathesis and the cross-metathesis, for example, yne–ene metathesis.[102] Yao developed a soluble poly(ethylene glycol) (PEG) bound polymer catalyst of type 18 which is immobilized through the phenylalkylidene moiety to a PEG support.[100]

Four consecutive ring-closing metathesis steps were achieved by Barrett et al. with the help of recyclable catalysts of type 55.[104] Here, the classical carbene that initiates the metathesis is itself anchored to the vinylated polystyrene resin by a metathetical step as shown in Equation (33). This catalyst is more efficient in olefin metathesis, especially in RCM, than the congener derived from the bis(phosphane) ruthenium complex [{(PR3)2RuCl2(=CHR)}]. The working principle of
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An elegant approach to immobilized olefin-metathesis catalysts was reported by Buchmeister et al. \cite{125} They prepared monolithic materials exhibiting a particle diameter of $1.5 \pm 0.5 \mu m$, by the metathetic copolymerization of appropriate olefins. The monolithic carrier is then functionalized by “living” NHC-ruthenium termini (from amidazolium precursor and $[\text{Cl}_2\text{Ru(PCy}_3)_2\text{CHC}_6\text{H}_5]$). The catalyst 55b (Ad = adamantanyl) thus formed shows high activities in both the ring-closing and ring-opening metathesis, with cis/trans ratios in the polymeric products that correspond exactly to what has been seen in homogeneous catalysis. The lack of any microporosity in the catalysts 55b minimizes diffusion effects to a large extent, thus giving high turnover frequencies often beyond those of homogeneous catalysts.

An alternative concept—immobilization of olefin metathesis NHC-catalysts on a monolithic material prepared by a sol–gel technique—was presented by Hoveyda et al. \cite{127} They made ruthenium-containing glass pellets that efficiently promote olefin metathesis reactions. The catalysts are robust and stable in air.

8. 2,3-Dihydro-1H-imidazol-2-ylidenes

C–C saturated N-heterocyclic carbenes are expected to be yet stronger α-donor ligands than their C–C unsaturated counterparts. While the five- and six-membered compounds 56 and 57, respectively, have been documented in metal complexes for quite some time, \cite{105} Thus, the examples 58 were independently reported by the research groups of Grubbs \cite{68} and Herrmann \cite{67} and showed that the activity for the olefin metathesis is—with the reactions investigated—higher than that of the C–C unsaturated analogues. However, the catalyst stability seems generally lower.
9. Acyclic Bis(amino)carbenes

A new approach in catalysis is the use of the “open-chained” bis(amino)carbenes $59 - 61$. They are accessible from the corresponding formamidinium salts according to

$$R^{1}, R^{2} = \text{alkyl}, \text{aryl}; R^{3} = \text{aryl}; X = O, S$$

Equation (34), as shown by Alder et al.$[107]$ It was found that the free carbenes are stable for a number of substituents $R^{1}$ and $R^{2}$, with the most investigated members of $59$ carrying two diisopropylamino or two piperidyl substituents.$[108]$ Neutral and anionic deprotonation agents can be used, preferentially Li[$N(C_{3}H_{7})_{2}$] or K[$N(SiMe_{3})_{2}$] in liquid ammonia, to generate this specific subgroup of N-functionalized carbenes. Several metal complexes were synthesized with these ligands, for example $62$.$[108a]$ The stable aminooxy- and aminothiocarbenes such as $60$ described recently by Alder et al.$[107b]$ are close to the classical Fischer-type carbene complexes.

It is worth of mention that bis(amino)carbenes can (side-on) coordinate to transition metals. For example, the tetracarbonylchromium(0) complex $63$ has a $p^{2}(CN)$-coordination, with bond lengths of 192.0(1) pm for the carbone−chromium bond and 220.7(1) pm for the nitrogen−chromium bond. Accordingly, the respective C−N bonds differ by around 15 pm.$[34]$ This effect may very well stabilize the undercoordinated “resting state” of N-heterocyclic carbene catalysts.

10. Theoretical Studies

The bonding theory of N-heterocyclic carbenes with regard to their cyclic structure and their metal bonding has been the subject of theoretical studies that are covered in previous review articles.$[7]$ Experimental and theoretical charge-density studies revealed that free NHCs have somewhat less $\pi$-electron delocalization than in their metal complexes.$[34]$ Acyclic bis(amino)carbenes (e.g., $59$) donate significantly more electron density to metals than their cyclic counterparts.$[108a]$ Here, the nitrogen lone pairs can participate in intramolecular coordination to the metal.$[34]$ Recent density functional theory (DFT) studies predict that oxidative addition of imidazolium salts to platinum(0) is an exothermic process.$[109]$ This result is consistent with the experimental finding that a hydridoplatinum(0) NHC complex is thus formed.

Kinetic and DFT studies on alkyl-carbene elimination from NHC−palladium(0) complexes revealed a new type of reductive elimination with implications for catalysis.$[310]$ Elimination of methylimidazolium cations from $64$ [Eq. (35)] proceeds in a concerted way and suggests similarities in the reactivity of $M−R$ and $M−N$(NHC) bonds. This finding once again highlights the principal differences between conventional metal−carbenes [L,$M$,$R_{1}$,$R_{2}$] and N-heterocyclic carbenes.$[110]$
Structural versatility is a great strength of N-heterocyclic carbenes (Scheme 6): chirality (a), functionalization (b), immobilization (c), water solubility (d), and chelate effects (e) can be achieved by easy means. All these varieties have principally been verified, and stable transition metal complexes were described in all cases.\[4, 7\]

Scheme 6. The versatility of ylidenes derived from imidazolium compounds.

Numerous new varieties of NHC-metal complexes were reported within a short period of time, among them the first alkaline earth complexes,\[33\] the silver salt 65 with its strained structure,\[111\] the pyridyl–NHC palladium chelate 66,\[112\] the nine-membered rhodium complex 68\[29\] and the eleven-membered chiral palladium complex 69.\[113\] The electronic effects in chelating NHC–metal complexes may also be adjusted for certain purposes by changing the bridging groups.

For example, the formally anionic BH\(_2\) group in complex 67 can replace the isoelectronic standard CH\(_3\) moiety, thus changing the charge of the metal.

Some of the ionic-liquid effects in organometallic catalysis are likely to arise from NHC catalysts, be it as free carbenes or as their metal complexes; both can be readily formed in situ from azolium salts. It is also reasonable to assume in biological systems similar phenomena occur when the ubiquitous imidazolium groups interact with metal ions. We know from the foregoing discussion that NHC ligands are compatible with literally any kind of metal in low and high oxidation states. The naturally occurring thiazolium salt thiamine 70, the coenzyme of vitamin B\(_1\), catalyzes the decarboxylation of pyruvate, with the deprotonated ylide form of 70 known to be the active catalyst.\[114\] The biochemistry of NHC–metal complexation lies ahead of us like an uncharted sea.\[131\] This is also true for the chemistry of the homologous and isoelectronic congeners E, F, and G metal compounds of which have been described in some detail,\[22, 115\] including the C–C saturated derivatives of the silylenes and germynes. Now that the heavier congeners of carbenes are available, this field is also ready to be developed in organometallic catalysis. As a matter of fact, the µ-silylene palladium complex 71 has just been made and structurally characterized.\[116a\] It dissociates in solution to form low-coordinate mononuclear palladium species. The analogous compound of the C–C unsaturated silylene was reported, and has moderate activity in the Suzuki coupling (aryl bromides).\[116b\]

Beyond catalysis, N-heterocyclic carbenes are going to gain relevance in materials science. For example, Liu et al. just reported on the first thermally stable liquid crystals based on NHC–palladium complexes such as 72.\[117\] The arrangement of this type of rodlike molecule results in

\[
R = \text{C}_n\text{H}_{2n+1} \quad (n \geq 10) \\
X = \text{Cl, Br}
\]
the preferential formation of a monolayered lamellar structure. The mesophases of 72 and related compounds have a mosaic texture. The new liquid crystalline phases are thermally stable up to the isotropic temperatures without decomposition. Once again, the ease of preparation, the thermal stability, and the structural versatility are unique features, as in catalysis.

Addendum: Dinitroxide Carbenes

A peculiar class of N-heterocyclic carbenes was recently described by Weiss et al.[130] Although unstable in the free state, the nitroxide carbene 73 could coordinate to a palladium(II) center, to form the cationic, dinuclear complex 74 [Eq. (36)]. These carbenes can be regarded as nitronyl–nitrosonium systems. A reversed-polarity singlet structure is stabilized here, with the carbene acting as σ-donor and as σ-acceptor ligand at the same time (“Autoumpolung” concept). The Pd–C bond of 197(7) pm (X-ray diffraction study) is in the typical range as in related NHC complexes. The variable electronic nature of the dinitroxide carbenes predisposes them as electronically flexible ligands. Complexes of Ag(I), Au(I), and Hg(II) were also obtained.[130]

The work in my research group is performed by many skillful and innovative Diploma, Ph.D., and Postdoctoral students. Their dedication and spirit has opened a new, fascinating area of organometallic chemistry and catalysis. The results once again demonstrate that science is an undertaking for our young generation. I am grateful that I could always rely on my research students who organized their work so efficiently that I was able to serve to my university as President at the same time. Jörg Fridgen is acknowledged for the flawless preparation of the formulae, equations, and schemes presented in the above text. I thank Dr. Karl Öfele, our pioneer of NHC coordination chemistry, for excellent advice over the many years we shared common research interests in the Anorganisch-chemisches Institut of Technische Universität München.

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