

Design Concepts for N-Heterocyclic Carbene Ligands

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Abstract

N-heterocyclic carbenes (NHCs) are a widely used class of ligands that have enabled an exciting variety of organometallic chemistry and catalysis. As researchers design and customise these ligands for specific applications, various design concepts have emerged. This review covers several of these design concepts and their impact on and promise for organometallic chemistry and catalysis. These concepts are: bulky ligands that remain flexible for substrate binding and reactivity; ring-expanded NHCs with different steric and electronic properties; NHCs appended to supramolecular assemblies that control the microenvironment around the metal center; and NHCs with pendant labile functional groups.

Keywords: *N*-heterocyclic carbene ligands; Organometallic chemistry; Homogeneous Catalysis; Ligand Design

1 **The Rise of *N*-Heterocyclic Carbene Ligands**

2 *Ligands of Broad Applicability*

3 The importance and impact of *N*-heterocyclic carbenes (NHCs) upon various fields cannot be
4 understated. While we focus here on homogeneous catalysis, this class of compound has had
5 a profound impact in fields including: organocatalysis, where they enable an exciting range of
6 chemistry including umpolung transformations [1, 2]; coordination chemistry, where they
7 have allowed the isolation and study of highly reactive species including those with heavy
8 element multiple bonds [3]; and organometallic chemistry and catalysis[4], where they
9 feature in many widely used catalysts based on, for example, gold [5], palladium [6, 7], and
10 ruthenium [8, 9]. The structural diversity of NHCs is key to their widespread application, and
11 so the aim of this Review is to highlight and briefly discuss several design concepts that
12 influence the development of new NHCs (Figure 1a); the focus here will be on synthesis and,
13 in some cases, a few key applications illustrating the design's applicability and usefulness will
14 be briefly discussed. For a discussion of the fundamental properties and structures of NHCs,
15 we refer readers to earlier reviews on this topic [10-13].

16

17 *Common Structures*

18 The diversity of heterocyclic carbenes is based on different structural aspects. Indeed, each
19 of the design concepts considered here requires specific and targeted changes to the carbene
20 structure to induce new properties and confer new reactivity and/or selectivity on the
21 corresponding metal complexes. In brief, the structural variations of NHCs usually include:

- 22 • Carbene position: The electron lone pair can be located on different carbon atoms in the
23 heterocyclic ring (Figure 1b). "Normal" NHCs are most widely used, but "abnormal" and
24 "remote" NHCs are increasingly finding utility [14].
- 25 • The nature of the heterocycle: Different atoms and bond types can be contained within
26 the heterocyclic ring structure bearing the carbene, giving rise to numerous combinations
27 and reactivities (Figure 1c).
- 28 • The *N*-substitution: The groups on the nitrogen atoms are probably the most important
29 variable in the structure of NHCs, with a wide range being accessible [15].

30

1 Imidazol(idin)ylidene and imidazolylidene rings are the most common due to their stability
2 and ease of synthesis. Pyrrolidinylidenes afford CAAC-type carbenes (CAAC =
3 cyclic(alkyl)(amino)carbene) which often possess enhanced reactivity (Figure 1d) [16]. NHCs
4 are typically prepared as the corresponding azolium salt, which can then either be
5 deprotonated to give the free carbene or deployed in synthetic routes that avoid the need to
6 prepare the carbene intermediate (Figure 1e) [17-21].

8 **Bulky-Yet-Flexible NHCs**

9 *The Concept*

10 Tuning the steric profile of NHCs is a key consideration for highly efficient and stable catalysts.
11 This can have a significant effect on the longevity and, therefore, turnover number (TON) of
12 catalysts. This requires a balanced approach. Bulky ligands stabilize the active species during
13 catalysis, disfavoring bimolecular decomposition pathways and many other unwanted
14 deactivation routes [22]. Steric bulk can disfavor the approach of the substrate to the metal
15 centre, reducing catalytic activity.

16
17 There can be a delicate balance between the steric bulk and skeletal flexibility of the
18 corresponding NHC; fine-tuning this has been a major factor in improving catalytic activity,
19 most notably for palladium-catalysed cross-coupling [23]. “Bulky-yet-flexible” ligands offer
20 flexible bulk that can adjust for the requirements of each catalytic step. Two early sterically-
21 congested NHC ligands were IPr and its saturated analogue SIPr; widely deployed in catalysis,
22 they are now two of the most common ligands in LTM–NHC (LTM = late transition metal)
23 catalysis, due in part to their ease of synthesis and their commercial availability. Recently,
24 other types of sterically challenging NHCs have emerged addressing various problems
25 concerning decomposition pathways and catalyst deactivation, whilst maintaining the much-
26 desired high catalytic activity. Figure 1f shows a number of ligands that fit this description,
27 but the discussion will focus on three specific classes: IBiox, cyclic (alkyl)(amino)carbenes
28 (CAACs) and *N,N'*-bis(aryl)imidazolylidenes.

30 *IBiox Ligands*

31 The concept of “flexible steric bulk” was introduced by Glorius and coworkers in their seminal
32 work on bisoxazoline-derived *N*-heterocyclic carbene ligands (IBiox) [24]; these comprise a

1 tricyclic backbone that confers rigidity to the NHC core. The tuning of their steric bulk,
2 flexibility and chirality is achieved through changing their substitution pattern. A variety of
3 IBiox ligands with different characteristics have been synthesized with alkyl, cycloalkyl, aryl,
4 and chiral groups (Figure 2a,b). Despite their steric bulk, IBiox ligands exhibit some
5 conformational flexibility (Figure 2c,d). For IBiox6, the cyclohexyl chairs provide three distinct
6 conformations *via* ring-flipping. Low-temperature NMR studies (-80 °C, CD₂Cl₂) revealed that
7 conformations I and II are the most stable in solution (2.4 : 1 : 0 for I : II : III). The steric
8 flexibility of this series was an important factor in several challenging catalytic reactions. In
9 more recent work by Chaplin and coworkers, a different perspective on IBiox ligands is
10 presented: the usefulness of their skeletal rigidity [25]. In this case, several mono-, bis-, and
11 tris-ligated rhodium(I) and iridium(I) IBiox complexes were synthesised and investigated.
12 Since rotation around the N-C_{substituent} bond is not possible in the IBiox system (due to the
13 fused rings), the only way to relieve some of the unfavourable steric stress is through tilting
14 of the whole IBiox ligand; a combination trend of significant pitching and moderate yawing is
15 observed [25]. This has dramatic consequences on complex stability and reactivity which has
16 yet to be fully understood. The core difference in reactivity, when compared to common NHC
17 motifs, is best shown by the latest work of Chaplin and coworkers on C-H activation, using
18 highly reactive yet stable iridium complexes [26, 27]. When reacting >2 equiv. of IBioxMe₄
19 (%V_{bur} = 32%; %V_{bur}: percent buried volume) with [IrCl(COE)₂]₂, a stable bis-IBiox iridium
20 complex [IrCl(COE)(IBioxMe₄)₂] is formed which, upon halide abstraction, readily reacts under
21 mild conditions with a fluoroarene to generate a 14-e⁻ hydride complex. Though unstable, the
22 latter can be quickly trapped by a third ligand (IBioxMe₄ or bipyridine), to afford
23 [IrH(Ar)(IBioxMe₄)₃]⁺ or [IrH(Ar)(bpy)(IBioxMe₄)₂]⁺, respectively. In contrast, similar Ir
24 complexes [IrCl(COE)(NHC)₂] bearing other comparably-sized NHC ligands are highly difficult
25 to access as they are known to undergo spontaneous cyclometallation of the NHC, and thus
26 lead to decreased reactivity; e.g. IMes (%V_{bur} = 32%), IPr (%V_{bur} = 34%) and *It*-Bu (%V_{bur} = 36%,
27 Figure 2d) [28-32]. The formation and stability of complexes such as the bis- and tris-ligated
28 iridium-IBiox complexes, which avoid any intramolecular activation, constitute a good
29 example of IBiox superiority when paired with reactive metal centres. Similar rhodium
30 complexes have also been synthesised and investigated by the Chaplin group [33, 34].

31

32 *Cyclic (Alkyl)(Amino)Carbene Ligands*

1 Based on a pyrrolidine ring bearing two quaternary carbon centres, CAACs are typically more
2 electron-rich than other NHCs and have been pioneered by Bertrand and coworkers. Ligand
3 precursors are accessed from the corresponding imines in a three-step procedure that can be
4 modified to tune the substitution pattern of the CAAC (Figure 3a).

5
6 The flexible bulk concept for this ligand series has been demonstrated numerous times on a
7 wide variety of metal complexes [35, 36]. Most recent activity investigates the effect of these
8 ligands on the stability of the corresponding gold and copper complexes as well as metal
9 complexes with low coordination numbers (Figure 3b). A key example of this flexible steric
10 bulk is observed with Pd-CAAC complexes where the CAAC^{Cy} ligand bearing a cyclohexyl (Cy)
11 group displays an equilibrium between cyclohexyl conformers, indicating flexible steric bulk
12 (Figure 3c). Upon stereoselectively introducing appropriate substituents onto the cyclohexyl
13 ring (CAAC^{menthyl}), the more sterically demanding conformation is locked in place to avoid the
14 unfavourable 1,3-diaxial interactions that are present in the alternative conformation; this in
15 turn lowers the catalytic activity of [PdCl(η^3 -allyl)(CAAC^{menthyl})] relative to its CAAC^{Cy} analogue.
16 This equilibrium has a significant influence on complex stability and catalytic activity. For
17 example, the pairing of CAAC^{menthyl} with Pd(II) and Rh(I) has allowed the isolation of low-
18 coordinate complexes which are stabilised by agostic interactions; attempts to access similar
19 complexes using the more flexible and less-sterically demanding CAAC^{Cy} ligand have proven
20 unsuccessful [35]. However, the CAAC^{Cy} ligand was particularly useful in accessing the bis-
21 CAAC^{Cy} complex of gold(0) owing to a combination of well-suited electronic properties and
22 skeletal flexibility [37]. In other cases, the ability to sustain steric bulk has been shown to be
23 crucial for the isolation of highly sensitive complexes, such as the CAAC^{Ad}-stabilised gold(I)-
24 norbornene complex, a key proof-of-concept for the gold-stabilised ethylene intermediate
25 (Figure 3d) [38]. When paired with Cu(I), CAAC ligands also proved useful in the hydrolytic
26 dehydrogenation of ammonia borane [39]; in this case, steric bulk was detrimental to catalytic
27 activity, with the least sterically demanding complex [CuCl(CAAC^{Et})] being the most active
28 catalyst (Figure 3e).

29

30 *The ITent Series and Analogues*

31 Recent trends showed a direct correlation in some reactions, especially in challenging
32 palladium-catalysed cross-coupling reactions, between catalytic activity and NHC steric bulk

1 [4, 40]. Overall, IPr and its derivatives were found to be the most general class of ligands with
2 a wide range of applications.

3 Several groups have designed analogues with increased steric hindrance -at the *ortho*-
4 position of the *N*-aryl substituents- coupled with a certain degree of flexibility; the series is
5 often referred to as ITent (“Tent” for “tentacular”) (Figure 4a) [41]. Several representative
6 examples are considered here. In their pursuit of more reactive Pd-PEPSI complexes, Organ
7 and coworkers developed several new ligands with various alkyl substitution, including IPent,
8 which exhibited improved catalytic efficiency compared to the previous state-of-the-art [40].
9 A full and detailed ligand synthesis procedure was not disclosed until 2013, where three NHC
10 precursors were synthesised (IPent·HCl, IHept·HCl and INon·HCl) in eight steps starting from
11 inexpensive and readily available 2-nitro-*m*-xylene, with Grignard addition to the 2-
12 nitroisophthalate as a key step (Figure 4b) [41]. The 4,5-dichloro analogues were disclosed by
13 Organ and coworkers, who obtained them from the reaction of the free carbene with carbon
14 tetrachloride (Figure 4c) [42, 43]. The influence of this design on current methodologies is
15 well noted in the report of Liu and coworkers, in which they describe the synthesis of the
16 acenaphthyl-substituted backbone analogue IPent^{An} and its corresponding palladium
17 complex; the latter was shown to be an efficient catalyst in the Suzuki-Miyaura coupling [44].
18 The effect of increased bulk at the *para*-position of the aryl groups was investigated by
19 Holland, who prepared the IPr^{+C} ligand series [45]. Starting from the corresponding anilines,
20 four new ligand precursors were prepared (Figure 4d); these were evaluated in palladium-
21 catalysed Suzuki-Miyaura cross-coupling reactions, and afforded more efficient catalysts than
22 IPr. More recently, Glorius and coworkers modified the NHC backbone structure by
23 substituting the C⁴ and C⁵ positions with long carbon chains (Figure 4e) [46]. The steric bulk
24 induced a high shielding effect for the metal centre and rendered these complexes highly
25 soluble in lipophilic solvents, such as *n*-heptane. Two NHC frameworks were used with two
26 carbon chain substitutions (C₁₁H₂₃ and C₇H₁₅) and were all later successfully evaluated in the
27 Buchwald-Hartwig amination reaction and in the hydrodehalogenation of chloroaryl
28 substrates. The main advantage gained here is the solubility difference compared to typical
29 IMes or IPr analogues, which can expedite catalyst separation and/or recycling if the products
30 are not soluble in alkanes. A similar strategy has been utilized recently in catalyst recovery
31 through nanofiltration, allowing the cross-coupling reaction to be performed in a semi-
32 continuous mode using a membrane-assisted reactor [47].

1

2 *The IPr* series*

3 The IPr* ligand is a bulkier variation of the IPr framework, and is among the most hindered
4 NHC ligands ever synthesized [48]. The initial version of this ligand was first synthesized by
5 Markó and coworkers from the corresponding aniline, although an improved and scaled-up
6 synthetic route has since been reported (Figure 4f) [49]. Subsequently, several derivatives
7 have been obtained, including: IPr*^{tol}, IPr*^{OMe}, and IPr** which vary the arene *para*-
8 substitution [50-52]; IPr*(^{2-Np}) which replaces phenyl with naphthyl [53]; and IPaul and SIPaul
9 which feature only one diphenylmethyl substituent on the arene [54, 55]. These ligands were
10 successfully used in catalysis in combination with several transition metals, including copper,
11 gold, nickel, silver, iridium and palladium. Their extreme steric bulk makes them particularly
12 attractive to applications where the corresponding metal complex is highly unstable.

13

14 **Ring-Expanded Carbenes**

15 *The Concept*

16 'Ring-expanded' NHCs (reNHCs) are directly analogous to the most common imidazolidinyl-2-
17 ene ligands but feature a larger ring as the backbone to the ligand; examples from six
18 members upwards have been reported. These typically take the form of simple alkyl chains,
19 with or without (*gem*-di)-substitution and therefore change the flexibility and steric profile of
20 the resulting ligand.

21

22 *Synthesis*

23 These ligands necessitate a different synthetic approach compared to their five-membered
24 cousins. Two of the most common overall strategies are outlined in Figure 5a,b, and involve
25 either the synthesis and subsequent cyclisation of a diaminoalkane intermediate, or the
26 formation and subsequent cyclisation of a formamidine intermediate [56, 57].

27

28 Requisite diamines have been prepared using alkylation [58] or Buchwald-Hartwig coupling
29 reactions [59]. Microwave irradiation has been used to improve the outcomes of some
30 cyclisation reactions using triethyl orthoformate and ammonium salts [60]. A related class of
31 carbenes are diamidocarbenes, of which various examples are known with six-membered

1 cores [61]. These can be prepared in analogous ways to those noted in Figure 5, substituting
2 the dihaloalkane with a di(acid chloride) reagent.

3

4 Simple examples with six-, and seven-membered rings at their cores are readily prepared in
5 moderate to excellent yields. Larger ring sizes are more difficult to prepare; reNHCs with
6 eight-membered cores have been prepared by alkylation of the formamidine with 1,5-
7 dibromopentane, but the reaction required low concentrations (0.02 mol L^{-1}) and extended
8 reaction times at reflux (10 – 14 days) [62]. The synthesis of larger reNHCs relies on biasing
9 the system towards ring-formation by introducing *gem*-disubstitution (Thorpe-
10 Ingold/reactive rotamer effects) or rendering the backbone more rigid to decrease the
11 entropic cost of cyclisation. A series of reNHCs with eight-membered cores has been prepared
12 by including naphthalene in the backbone (Figure 5c) [63]. The synthetic route proceeded by
13 the alkylation of the corresponding formamidine; the require alkyl bromides were prepared
14 in two steps from 1,8-naphthalic anhydride. Carbenes with cores that are larger still are very
15 challenging to prepare, and the only examples reported to date include biphenyl or diphenyl
16 ether backbones (Figure 5d) [64]. Low concentrations (0.005 mol L^{-1}) and extended reaction
17 times (up to 4 days) were essential to obtain good yields of the ligand precursors.

18

19 *Properties*

20 Several reNHCs have been characterised using X-ray crystallography (e.g., Figure 5e), which
21 clearly shows that the central core cannot sit in one plane, as is observed for NHCs with five-
22 membered cores. Structural changes induced by larger backbones influence the steric impact
23 of the carbene, as can be seen by quantifying the $\%V_{\text{bur}}$ for analogous complexes with the
24 same *N*-substituent (Figure 5f); $\%V_{\text{bur}}$ increases by $>2\%$ with each increase in core ring size,
25 which is greater than the estimated uncertainty in $\%V_{\text{bur}}$ measurement [12].

26

27 TEP (Tolman electronic parameter) data [65] have been reported for some reNHCs [13].
28 reNHCs with 2,4,6-trimethylphenyl *N*-substituents can be compared using ν_{CO} for the
29 corresponding $[\text{RhCl}(\text{CO})_2(\text{L})]$ complexes (Figure 5g) [66]; these data indicate that increasing
30 the size of the core ring significantly increases the net electron-donating ability of the ligand.
31 On the other hand, ^{31}P NMR data for NHC-phosphinidine adducts [67] and ^{77}Se NMR data for

1 NHC-selenium adducts [68] show that reNHCs are more π -accepting than the corresponding
2 imidazolin-2-ylidenes.

3

4 ReNHC ligands have found applications across organometallic chemistry and catalysis,
5 including as ligands for gold catalysts [64, 69], ruthenium alkene metathesis catalysts [70-72],
6 copper catalysts for azide-alkyne cycloaddition reactions [63, 73] and alkyne
7 semihydrogenation [74], palladium cross-coupling catalysts [75], and platinum catalysts for
8 alkene diboration [76].

9

10 **Supramolecular Carbenes**

11 *The Concept*

12 The incorporation of ligands and catalysts into supramolecular assemblies to achieve
13 reactivity and selectivity in catalytic reactions is driven in part by the observation that nature
14 creates large assemblies with specific shapes to efficiently mediate a range of chemical
15 reactions that are essential for life. NHCs have been incorporated into some supramolecular
16 scaffolds to take advantage of this ability to influence the environment in which processes
17 such as catalysis can take place. Three sets of representative examples are described here.
18 The topic of large poly-NHC multinuclear assemblies has been reviewed recently [77] and is
19 not considered here.

20

21 *Calixarenes and Pillararenes*

22 Imidazolium-functionalised calixarenes and pillararenes have several applications including as
23 receptors and for anion binding [78-80], however we will mainly focus here on well-defined
24 metal complexes that have – or might have – catalytic applications [81, 82]. Synthetic routes
25 typically involve the introduction of an imidazolium salt onto the rim of a pillarene or
26 calixarene, by alkylating an *N*-substituted imidazole using a haloalkyl functional group [83] or
27 by copper-catalysed C-N coupling of an aryl halide with imidazole followed by alkylation [84]
28 (Figure 6a). Different numbers (1 to *n*) of imidazolium units can be attached to calix[*n*]arene
29 and pillar[*n*]arene scaffolds [84-86]. The resulting ligand can be coordinated to metal centres
30 using established chemistry – with or without free carbene formation – or used in catalytic
31 reactions where metal coordination occurs *in situ*. Selected examples are displayed in Figure
32 6b. The silver complex can be used to prepare other complexes *via* transmetallation [87, 88].

1

2 These complexes have been applied in reactions including: Suzuki cross-coupling reactions in
3 aqueous solution (where traditional NHCs may yield poorly soluble complexes) [89], Heck
4 reactions [86], and copper-catalysed azide-alkyne cycloadditions [90]. In a study of Suzuki-
5 Miyaura coupling catalysed by a calix[6]arene complex containing three nickel centres it was
6 shown that the best results were obtained using the complexes in which the nickel centres
7 are closest to the calix[6]arene rim [91].

8

9 *Cyclodextrins*

10 The second series of complexes are based on functionalised cyclodextrins, which are
11 cyclooligomeric polysaccharides. These can be water soluble and obtainable in bulk from
12 nature, so are relatively cheap. Their use across catalysis has been discussed recently [92],
13 but here we focus on selected examples of NHC-functionalised cyclodextrins.

14

15 The synthesis of cyclodextrin-based NHCs can be achieved using different strategies, including
16 (i) the selective conversion of pendant primary alcohols to suitable leaving groups (e.g.,
17 mesylate) followed by nucleophilic displacement with (benz)imidazole (Figure 7a) [93]; and
18 (ii) the conversion of these primary alcohols to aldehydes, followed by reductive amination,
19 using e.g., 1,2-diaminobenzene, and finally benzimidazolium formation with formaldehyde
20 (Figure 7b) [94]. These strategies typically anchor the NHC in two points to the cyclodextrin.
21 Other ligands include NHCs that are anchored only to one point within the cyclodextrin, so
22 that the NHC does not necessarily point directly into the cavity [95].

23

24 The resulting complexes have been applied in catalysis and can lead to switches in selectivity
25 or reactivity. The [AuCl(IPr)]-catalysed cycloisomerisation of a dimethyl malonate-derived
26 enyne substrate gives a *ca.* 3:2 mixture of products (Figure 7c) [93]. When a β -cyclodextrin-
27 derived gold complex is employed, a 1:3 mixture of products is obtained, where the major
28 product is the cyclohexene derivative; the cyclodextrin framework chirality provides modest
29 stereoinduction in the reaction of a propargylamine substrate (Figure 7d) [93, 94], as well as
30 in some intramolecular cyclisation reactions of allenols [96].

31

1 Different cyclodextrin frameworks mediate copper-catalysed hydroboration reactions with
2 different selectivities: an α -cyclodextrin-based ligand favoured the linear product in the
3 hydroboration of arylacetylenes using B_2pin_2 , while a β -cyclodextrin-based ligand favoured
4 the branched product [97]. Other catalytic applications include Suzuki-Miyaura cross-coupling
5 in water [95], taking advantage of the ability of cyclodextrins to solubilize species in aqueous
6 solutions, and copper-catalysed ketone hydrosilylation in which a monomeric copper(I)
7 hydride species is stabilised [98].

8

9 *Macrocycles*

10 The final category of supramolecular NHCs considered here are those that comprise a
11 bespoke macrocycle fragment. These can confine certain substrates, promote certain
12 coordination behaviour at the metal, or lead to new behaviours in fundamental reactions
13 and/or catalysis.

14

15 This section focuses on recent results from Chaplin and coworkers, who have prepared
16 several pincer ligands that feature two NHCs attached to a long alkyl chain. Copper and silver
17 complexes have been synthesised and used as carbene transfer agents to prepare rhodium,
18 nickel, and palladium complexes [99]. Complexes such as the rhodium species in Figure 8a
19 show a persistent agostic interaction even in solution (CCl_4), as detected by IR spectroscopy,
20 which disappears when the complex is placed under a carbon monoxide atmosphere [100].

21

22 Rhodium complexes with this ligand scaffold show interesting behaviour in terminal alkyne
23 coupling reactions. Complexes with 'traditional' pincer NHC ligands and with a macrocyclic
24 pincer NHC ligand were compared in the coupling reactions of arylacetylenes and were found
25 to give different selectivities (Figure 8b,c) [101]; the former, which has a simple tridentate
26 pincer ligand, is *gem*-selective, while the macrocycle-derived species changes the selectivity
27 to give the *E*-enyne product under analogous conditions. Intermediate species were isolated
28 from stoichiometric experiments and characterised by methods including single crystal X-ray
29 diffraction. This significant switch in behaviour is proposed to result from the confinement
30 effects introduced by the macrocyclic ligand.

31

32 **NHCs with Pendant Labile Ligands**

1 *The Concept*

2 The incorporation of labile, weakly-coordinating functional groups into NHC ligands allows for
3 systems in which an otherwise vacant site can be occupied but still be available for catalysis.
4 These ligands are formally bidentate but whereas the NHC is strongly coordinated the other
5 donor is not. These might have various applications, such as the stabilisation of species that
6 would otherwise have too low a coordination number, or to keep a site free for binding
7 substrates – which may be better ligands than the labile functional group – during catalysis.
8 The topic has been reviewed recently as part of a larger review of ‘smart NHCs’ [102], and so
9 this section will focus on the key concepts, some illustrative examples, and recent
10 developments. The hemilabile ‘arm’ of the NHC is typically a relatively weak dative ligand,
11 such as an *N*-heterocycle (e.g., pyridine), a chalcogen (e.g., an ether, sulfide, or selenide), or
12 an imine or sulfoxide.

13

14 The synthesis of these ligands can be approached in various ways. For example, imidazolium
15 salts of the corresponding ligands can be prepared by the S_NAr reaction of 2-bromopyridine
16 using the corresponding *N*-arylimidazole, while others are prepared from the alkylation of *N*-
17 arylimidazole using 2-(bromomethyl)pyridine (Figure 8d) [103]. The corresponding silver
18 complexes were prepared from the imidazolium pro-ligands using standard methodology,
19 such as reaction with silver(I) oxide. Analogous complexes with other labile functionality can
20 be prepared using, for example, (chloromethyl)phenyl sulfide to install a phenylthiomethyl
21 group [104]. Pendant ligands can also include alkenes, which have been introduced *via* an
22 alkylation route with 2-(chloromethyl)propene [105].

23

24 These complexes have been used in catalytic reactions including: transfer hydrogenation
25 using iridium [106], ruthenium [105], or manganese [107]; primary amine oxidation using
26 ruthenium [108]; ethylene oligomerisation using nickel and chromium [109]; and
27 enantioselective alkene reduction [110] – particularly for functionalised substituted alkenes
28 such as enol phosphonates – using iridium; and ketone reduction [111] using iridium or
29 rhodium. Ruthenium complexes of this class of ligand with pyridine [112] or thioether [108]
30 functionality have been shown to be biologically active. Imine functionalised
31 cyclic(alkyl)(amino)carbene ligands have been shown to give improved performance in

1 hydroarylation and hydroamination reactions with gold and copper compared to complexes
2 with the non-functionalised ligands [113].

3

4 **Concluding Remarks**

5 One of the enduring strengths of NHCs as ligands is their staggering structural diversity, which
6 is made accessible through often rather simple synthetic routes. As a result, researchers have
7 approached the design and synthesis of new ligands of this type with creativity and
8 imagination, providing the chemistry community with a plethora of useful ligands for
9 organometallic chemistry and catalysis.

10 Many significant challenges remain. The design and application of new NHC ligands is
11 still largely driven by an empirical make-test-evaluate process in which properties are
12 evaluated after a new ligand has already been prepared. There are exciting opportunities,
13 enabled by chemometric and machine learning approaches and the decreasing computational
14 cost of robust modelling methods, to more rationally design new ligands with desirable
15 properties. However, this in turn relies on a closer link between conceptually simple metrics
16 for new ligands (e.g. TEP, %V_{bur}) and the results of (for example) catalysis, the latter of which
17 can often comprise a complex 'black box' of multiple steps that are affected differently by
18 ligand steric and electronic properties.

19 Here, we have discussed only four of the many design concepts that have influenced
20 various directions of NHC development, and these will undoubtedly deliver many future
21 advances in organometallic chemistry and catalysis. Bulky-yet-flexible ligands have found
22 particular application in palladium catalysis, and are less well-explored in other areas;
23 supramolecular NHC ligands have been applied in some areas of catalysis, while in other areas
24 they are yet to make the leap from stoichiometric to catalytic processes, although many of
25 the fundamental steps are now established. There remain many future possibilities in this
26 arena for new and exciting ligands, and for new approaches to their design.

27

28 **Outstanding Questions**

- 29 • How can we best/most efficiently predict the properties of new carbene ligands and
30 guide ligand design?
- 31 • How can we access new NHC ligands efficiently and in a more sustainable manner
32 (from lab scale to large scale)?

- How can we best systematically evaluate/predict the effects of ligand structure on catalytic reactions?
- Where is the optimal design space for bulky-yet-flexible carbenes?
- Why do some catalytic systems (e.g. Pd) benefit from bulky-yet-flexible carbenes more than others (e.g. Au, Cu)?
- How can we take advantage of the supramolecular scaffolds of NHCs to enable new catalytic reactions?
- Can we use supramolecular scaffolds to induce better stereo and enantioselectivity in metal-NHC catalysed organic reactions?

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Conflict of Interest

The authors declare no conflict.

Glossary

%V_{bur}: Percent Buried Volume is a measurement of the bulk of a ligand coordinated to a transition metal. **Agostic**: Interaction of a coordinatively-unsaturated transition metal with a C–H bond. **CAAC**: Cyclic(alkyl)(amino)carbene). **Cyclometallation**: Reactions of transition metal complexes in which an organic ligand undergoes intramolecular metalation with formation of a metal-carbon σ bond. **NHC**: N-heterocyclic carbene. **PEPPSI**: Pyridine-enhanced precatalyst preparation stabilization and initiation. **TEP**: Tolman electronic parameter. **TON**: turnover number.

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45 **Figure Captions.**

1 **Figure 1.** (a) Design concepts for NHC ligands that will be examined in this Review. (b), (c),
2 (e) & (d) Common scaffolds for N-heterocyclic carbenes and the synthesis of their
3 complexes. (f) Examples of bulky-yet-flexible NHC ligands.

4 **Figure 2.** (a) General synthetic route to IBiox ligands. (b) Examples of IBiox ligands. (c)
5 Conformational flexibility in the substituents and in its pitching and yawing. (d) Synthesis of
6 highly reactive low-coordinate iridium complexes.

7 **Figure 3.** (a) Synthesis of CAACs. (b) Examples of coinage metal complexes of CAAC ligands
8 (M = Au, Cu). (c) Conformational analysis of Pd-CAAC complexes. (d) Stabilisation of low
9 coordination number complexes. (e) Application in the dehydrogenation of ammonia
10 borane.

11 **Figure 4.** (a) The ITent ligands. (b) Synthesis of ITent-type ligands. (c) Backbone chlorination
12 of ITent ligands. (d) The IPr^{+C} series by Holland and coworkers. (e) The tailed NHC series;
13 NHCs bearing long alkyl chains at the 4- and 5-positions. (f) Synthesis of IPr*-type ligands.

14 **Figure 5.** Synthetic routes to ring-expanded NHCs: (a) synthesis of diaminoethanes, followed
15 by cyclisation; (b) synthesis of formamidines, followed by cyclisation; (c) synthesis of a
16 precursor to a reNHC with an eight-membered core; and (d) synthesis of a precursor to a
17 reNHC with a ten-membered core. (e) Structures of 6-Mes (left) and 7-Mes (right) as
18 determined by X-ray diffraction analysis.[57] (f) A comparison of %V_{bur} for a series of
19 complexes where the *N*-substituent remains constant but the core ring size varies. (g)
20 Determination of TEP using IR spectroscopic analysis of [RhCl(CO)₂(L)] complexes.

21 **Figure 6.** (a) General protocols for the synthesis of pillarene- or calixarene-based
22 supramolecular ligands. (b) Examples of corresponding metal complexes.

23 **Figure 7.** (a) & (b) Synthetic routes to cyclodextrin-containing *N*-heterocyclic carbene
24 ligands. (c) & (d) Changes in selectivity for reactions conducted using these NHC ligands.

25 **Figure 8.** (a) Agostic interactions within a rhodium complex of a macrocyclic pincer ligand.
26 (b) and (c) Switched selectivity in alkyne homocoupling reactions. (d) Examples of synthetic
27 routes to imidazolium salts functionalised with labile ligands.

28

29 **Highlights**

30 • The design and development of new *N*-heterocyclic carbene (NHC) ligands are crucial
31 elements for the advancement of homogeneous metal catalysis.

- 1 • Design concepts such bulky-yet flexible, ring-expanded and supramolecular NHC
2 ligands, as well as NHC bearing pendant labile ligands, have already made an impact
3 in this field.
- 4 • NHC ligands are nowadays easily accessible and efficiently tuned to meet the
5 necessary reaction requirements, rendering them highly diverse with a wide range of
6 applicability.
- 7 • Parallel to recent design breakthroughs, advancements in NHC understanding and in
8 improved quantification of their properties have widely contributed to their recent
9 success.
- 10