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Acyclic Aminocarbenes in Catalysis

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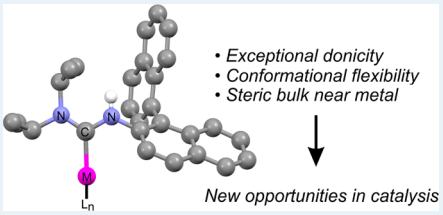
ABSTRACT: Acyclic aminocarbenes have received much less attention as ancillary ligands in homogeneous catalysis compared with their cyclic relatives (i.e., N-heterocyclic carbenes, NHCs), despite having a longer history and greater structural variety. Although these species are generally more fragile than NHCs, recent advances in the synthesis and catalytic application of metal complexes of acyclic carbenes have brought increased attention to these underutilized ligands. It is increasingly clear that acyclic carbenes possess unique properties that distinguish them from other ligand classes and make them potentially valuable for catalysis. These include exceptional donor ability, conformational flexibility, and wide N−C(carbene)−N angles that can place bulky or chiral substituents near catalytic substrate binding sites. This purpose of this Perspective is to review and critically assess recent progress in this forefront area of catalyst design. Syntheses and ligand properties of acyclic diaminocarbenes, aminooxycarbenes, and other aminocarbenes are reviewed with a view toward catalytic relevance. A special focus is to highlight catalytic reactions in which acyclic carbene ligands confer unusual selectivity or activity on metal catalysts compared with conventional ligand types. Particularly promising catalytic results have been obtained with acyclic carbene complexes of gold, including some highly enantioselective catalytic transformations.

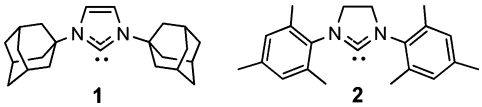


KEYWORDS: *ligand design, carbene ligands, homogeneous catalysis, asymmetric catalysis, gold catalysts*

1. INTRODUCTION

When N-heterocyclic carbenes (NHCs) made their quiet debut as ligands for transition metals over 40 years ago,[1,2] it is unlikely anyone could have predicted that they would eventually become one of the most powerful classes of ancillary ligands for homogeneous catalysis. Indeed, two early reports of catalytic hydrosilylations using rhodium−NHC complexes evidently did not inspire further work along these lines.[3−5] It was only after Arduengo's discovery of stable, "bottle-able" free imidazol-2-ylidenes such as **1** (Chart 1) in 1991[6] and

Chart 1. Prototypical NHCs



1 **2**

Herrmann's pioneering studies of these stable carbenes as phosphine mimics in organometallic catalysis[7] that this formerly obscure class of neutral donor ligands came into the spotlight. As ligands, NHCs possess a powerful combination of strong donor ability,[8−10] thermal stability,[11] and oxidative stability[12] that has resulted in their widespread adoption across virtually every area of inorganic and organometallic chemistry.[13−16] The area in which NHCs continue to have the greatest impact is undoubtedly catalysis, where the unique ability of NHCs to stabilize reactive or low-coordinate metal species has led to some of the most exciting advances in homogeneous catalysis of the past 10−15 years.[17−22]

As applications of NHC−transition metal catalysts have grown, chemists have begun to search for new variants of carbene ligands that might provide access to catalysts with a broader range of electronic and structural features.[23] The vast majority of reported NHC−metal catalysts have employed only two types of carbene: imidazol-2-ylidenes (e.g., **1**, Chart 1) and their saturated analogues, imidazolin-2-ylidenes (**2**). Although an impressive number of variations on the basic five-membered heterocyclic structure of these carbenes have been achieved by modification of the N-substituents and backbone as well as by incorporation into fused-ring systems and chelates,[24,25] several lines of evidence suggest that the donor abilities of these carbene types occupy a fairly narrow range and are generally little affected by the ring substitution pattern.[26−30] In addition, although significant steric shielding can be achieved by use of bulky N-substituents,[30,31] the ability of these groups to directly affect reactions at the metal center may be limited due to the fairly small carbene N−C−N angles (typically 104−107°). As NHCs have continued to evolve, novel ligand architectures that allow for tuning[32−36] or switching[37,38] of donor ability, as well as increased steric bulk near the metal center,[39] have been devised. Other significant developments include expanded-ring NHCs[40] and cyclic alkylaminocarbenes,[41] both of which can exhibit increased donor ability and steric hindrance relative to common NHCs such as **1** and **2**. Despite these many advances, it is clear that NHCs do not yet come close to matching the scope of structural and electronic properties available in the more developed family of phosphorus donor ligands.[42,43] Expanding the range of carbene ligands available for catalysis thus remains an important goal.

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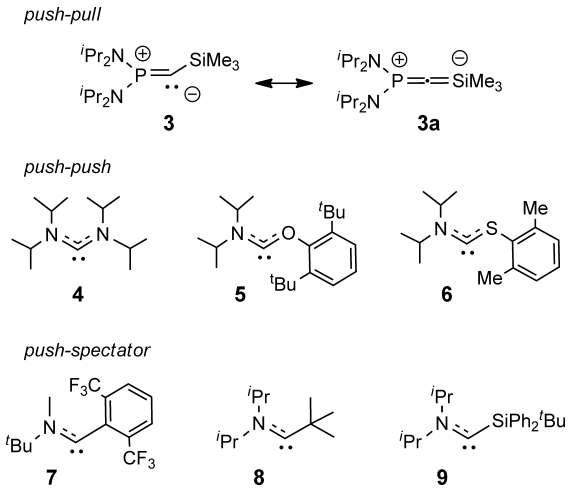
The recent focus on cyclic carbenes notwithstanding, *acyclic* carbenes have arguably played a greater historical role in the development of carbene chemistry and also exist in a greater number of varieties. Here, acyclic carbenes are defined as those in which the carbene carbon is not contained in a ring in the uncomplexed form. The first identified metal−carbene complex, reported by Fischer and Maasböl in 1964, contained an acyclic oxyalkylcarbene prepared by alkylation of a metal carbonyl complex.[44] Free acyclic dihalocarbenes such as CCl_2 were recognized long ago as synthetically useful transient intermediates.[45,46] The first stable free carbene to be isolated and characterized was Bertrand's acyclic phosphinosilylcarbene **3** (Chart 2),[47] which was reported three years before

Chart 2. Classes of Stable Acyclic Carbenes and Representative Examples



Arduengo's seminal study of stable NHC **1**.[6] The stabilization of **3** as well as that of related phosphinophosphonio carbenes[48] arises from a "push−pull" substitution pattern in which the phosphino group acts as a strong π-donor and the second substituent (Y) is weakly electron-withdrawing. Although these carbenes are best described by an ylide structure containing a phosphorus−carbon double bond (e.g., **3**), there is a significant contribution from a heterocumulene resonance form (e.g., **3a**), which is reflected in short C−Y bonds and very wide bond angles (e.g., 153° for **3**). As a consequence, "push−pull" acyclic carbenes do not show significant Lewis basic character and are apparently incapable of acting as ligands for metals.

A major advance in acyclic carbene chemistry came with the isolation of free, sublimable bis(diisopropylamino)carbene **4** by Alder's group in 1996.[49] The presence of two nitrogen π-donor substituents and the resulting "push−push" stabilization of the carbene make acyclic diaminocarbenes (ADCs)[50,51] such as **4** closely analogous to the catalytically important NHCs of types **1** and **2**. However, theoretical studies predict a significantly greater driving force for dimerization of unhindered ADCs compared with their cyclic relatives.[52] This is primarily due to the relatively high energetic destabilization of the free acyclic carbenes, which can be attributed to increased N−$C_{carbene}$−N angles and disruption of π-conjugation due to a low barrier for torsion about the $C_{carbene}$−N bonds. Interestingly, the kinetic barriers for dimerization of ADCs are calculated to be prohibitively high, despite the favorable thermodynamics,[52] and this process probably occurs only when catalyzed by protons[53,54] or trace metal ions.[55] Addition of significant steric bulk, as in **4**, can negate the dimerization driving force and render these acyclic carbenes thermodynamically as well as kinetically stable. This approach has enabled the isolation of other types of "push−push" acyclic carbenes, such as aminooxycarbene **5** and aminothiocarbene **6**,[56] and even "push−spectator" carbenes with only one π-stabilizing amino substituent, including aminoarylcarbene **7**,[57] aminoalkylcarbene **8**,[58] and aminosilylcarbene **9**.[59]

Most importantly, acyclic aminocarbenes have proven capable of acting as strong donor ligands in metal complexes. Herrmann and co-workers demonstrated in 2002 that ADC **4** engenders higher electron density at Rh^{I} than either saturated or unsaturated five-membered NHC ligands, as judged by ν(CO) values for the (L)Rh$(CO)_2$Cl complexes.[60] Despite this remarkable result, the homogeneous catalysis community showed little interest in acyclic carbene ligands through most of the subsequent decade, perhaps because of some significant stability issues that came to light subsequent to Alder's initial reports. Free acyclic aminocarbenes generally show greater tendencies to decompose in the presence of air, moisture, and elevated temperature compared with their cyclic analogues,[49,53,54,61] which can hinder attempts at metalation. They also exhibit undesirable reactivity toward metal complexes in some cases. An attempt to displace triphenylphosphine with **4** in a Grubbs-type ruthenium olefin metathesis precatalyst resulted in decomposition, with spectroscopic evidence suggesting a possible reaction of the ADC with the alkylidene ligand.[62] Free ADCs were observed to act as reducing agents in reactions with W^0 carbonyl complexes and Pd^{II} phosphine or phospha−palladacycle complexes, affording $[W_2(CO)_{10}]^{2-}$ and Pd black, respectively.[62,63] For some types of acyclic carbenes, theoretical studies predict that the distortion energy required to convert them to a more bent geometry capable of donating to a metal makes the coordination of these carbenes thermodynamically unfavorable.[64] Such considerations led Bertrand and co-workers to comment in 2010 that "there is little hope that acyclic carbenes could find applications as ligands in transition metal catalysts".[23]

A recent burst of activity in catalytic applications of acyclic carbenes suggests that this assessment may have been overly pessimistic. ADCs, in particular, have emerged as a ligand class with untapped potential. Researchers have devised acyclic aminocarbenes that are sufficiently stable to withstand typical metalation procedures used for NHCs, and synthetic routes that completely circumvent formation of the free acyclic carbene have been honed for certain catalytic metals. Studies of acyclic aminocarbenes with very bulky substituents, including chiral examples, have identified interesting consequences of the wide N−$C_{carbene}$−N angles and inherent conformational flexibility of acyclic carbenes on the selectivities of catalytic reactions. It is increasingly clear that acyclic aminocarbene ligands offer structural and electronic features that are significantly different from those available in the now-ubiquitous NHCs and other ligand types commonly employed in homogeneous catalysis.

The goal of this Perspective is to review and critically assess recent progress in this forefront area of catalyst design. This is not intended to be a comprehensive discussion of the chemistry of acyclic carbenes, as excellent reviews of this topic by Bertrand[65] and Bourissou[48] are available. The focus will be exclusively on applications of acyclic carbenes as ancillary ligands in catalysis. Key synthetic routes and ligand properties of acyclic carbenes will be touched upon because these are

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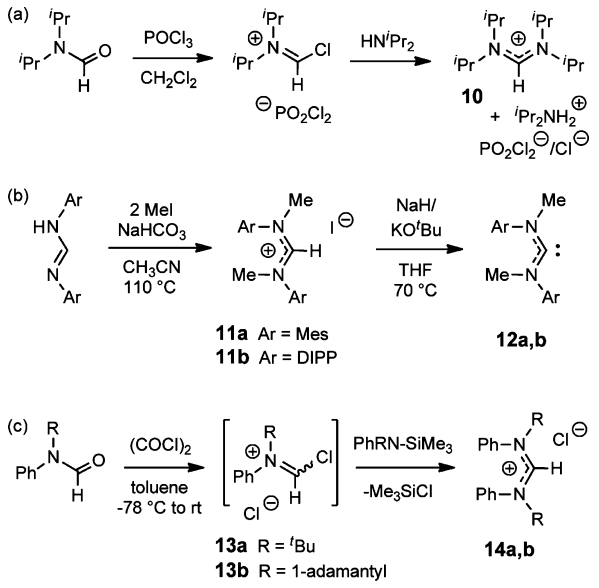
intimately tied to the importance of these ligands in homogeneous catalysis. A special focus of this Perspective will be to highlight catalytic reactions in which acyclic carbene ligands confer unusual selectivity or activity on metal catalysts compared with conventional ligand types. It is hoped that this will inspire more researchers to explore the unique features of this emerging class of ligands in other, perhaps completely novel, metal-catalyzed reactions.

2. SYNTHETIC ROUTES TO ACYCLIC CARBENE COMPLEXES

Despite the known fragility of acyclic carbenes and their propensity to dimerize, many reported synthetic routes to metal−acyclic carbene complexes proceed via the free acyclic carbenes. In the case of ADCs such as **4**, this typically involves deprotonation of tetrasubstituted formamidinium cations. These carbene precursors come with their own set of synthetic challenges. For example, ADC precursor **10** is readily formed by conversion of *N*,*N*-diisopropylformamide to the chloroiminium salt, followed by reaction with $^{i}Pr_2NH$ (Scheme 1a), but the presence of a significant dialkylammonium salt byproduct results in a difficult workup and isolation of a still-impure amidinium salt in only 25% yield.[49,66]

Scheme 1. Synthesis of Amidinium Precursors to ADCs

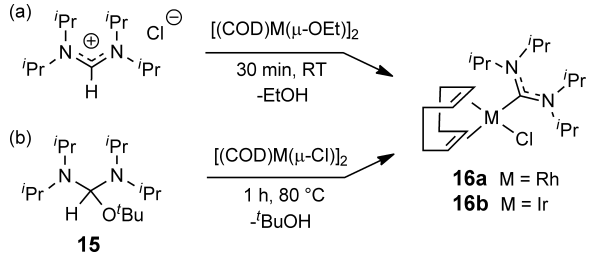


Alkylation of readily available N,N′-disubstituted formamidines[67] is an obvious route to ADC precursors, but it is feasible only for methylations, typically with MeOTf. Undesired alkene elimination chemistry can occur when larger alkylating agents are used and even for methlylations when R is bulky and trace H_2O is present.[66] Bielawski demonstrated that alkylation with MeI under mildly basic conditions is a viable route to amidinium salts containing very bulky aryl substituents [Ar = mesityl, 2,6-diisopropylphenyl (DIPP); Scheme 1b].[68,69] Amidinium salt **11b** (Ar = DIPP) withstood fairly harsh deprotonation conditions (i.e., treatment with NaH/KO^{t}Bu for 16 h at 70 °C) to afford stable, free ADC **12b** in 77% yield,[68] suggesting that the high steric encumbrance of the aryl groups might enhance the stability of both the amidinium precursor and the carbene.

Hong and co-workers devised a route to formamidinium cations containing both phenyl groups and bulky tertiary alkyl substituents through reaction of silylated amines with in situ-generated chloroiminium salts **13a,b** (Scheme 1c).[70] The byproduct is easily removed Me_3Si-Cl, thus avoiding formation of an HCl equivalent and the ammonium salt byproducts that plague other synthetic routes. The free ADCs were not isolated but were generated in situ by reaction of **14a,b** with $LiN(SiMe_3)_2$ at −78 °C, followed by metalation with $(Me_2S)AuCl$. A similar procedure was used to prepare bulky alkoxyiminium salts as synthons for Au^{I} complexes of the corresponding acyclic aminooxycarbene (AAOC) ligands.[71]

Deprotonation of amidinium or iminium cations to give free acyclic carbenes requires strong bases, such as LDA, KH/KO^{t}Bu, or $LiN(SiMe_3)_2$, as these precursors are generally less acidic than their cyclic analogues.[72,73] Herrmann and co-workers reported two alternative metalation procedures for ADC **4** that do not require addition of a base.[60] These involve the use of bridging alkoxides as internal deprotonating agents (Scheme 2a) and in situ carbene formation from an ADC−

Scheme 2. Base-Free ADC Metalation Routes



alcohol adduct (**15**, Scheme 2b). Both reactions gave comparable yields of Ir and Rh complexes **16a,b** to the free carbene route. These procedures have not been generalized to other metals or types of acyclic carbenes, although they closely parallel synthetic routes used for metalation of NHCs.[15] Notably, an attempt to prepare a chelated bis(ADC) complex by the alkoxide route (Scheme 2a) was unsuccessful.[74]

Building on earlier reports,[75,76] Fürstner's group investigated syntheses of metal−acyclic carbene complexes starting from chloro-substituted amidinium and related precursors.[77] These synthons are readily prepared from thioureas, ureas, or analogous carbonyl compounds by treatment with oxalyl chloride. Oxidative addition of the precursor salts to $Pd(PPh_3)_4$ provided cationic Pd^{II} complexes of acyclic diamino-, amino-oxy-, aminothio-, and aminoarylcarbenes (Scheme 3). This procedure avoids the stability problems associated with the free carbenes and the parent (e.g., amidinium) salt precursors, both of which are often too reactive to survive reaction conditions when little steric protection is present (as in **20**, for example).[61,66] This synthetic strategy could not be extended to Rh, Co, and Fe, and the scope was limited to ADC ligands in the case of Ni^{II}.[77] Hong and co-workers reported a different, nonoxidative ADC metalation route involving lithium−halogen exchange from some of the same chloroamidinium salts (Scheme 4).[78,79] So far, the scope of this reaction has been limited to bis(*N*-pyrrolidyl)carbenes (e.g., **23**, **24**) and bis(*N*-piperidyl)carbenes (e.g., the ADC in **21**), and only Rh^{I}, Ir^{I}, and Pd^{II} complexes have been obtained this way. Intermediacy of lithium−ADC adducts was suggested by a moderate upfield shift of the carbene carbon atoms relative to the expected range

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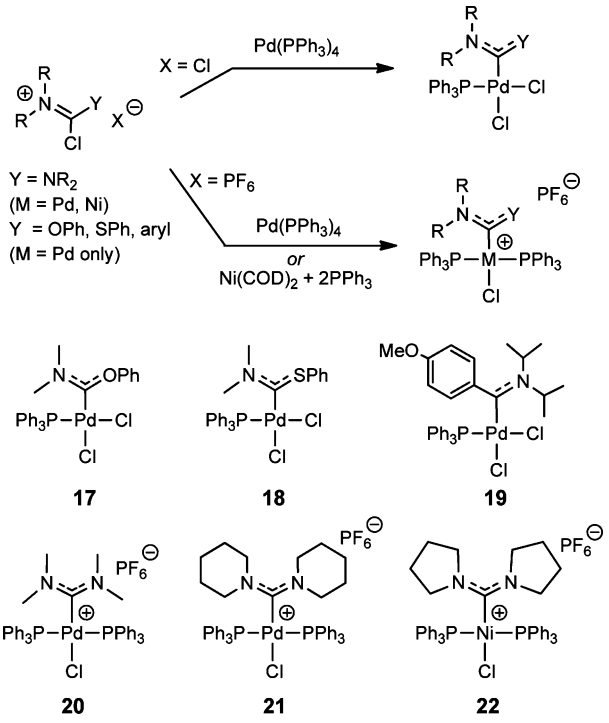
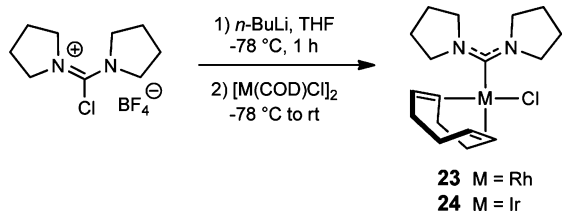
Scheme 3. Synthesis of Acyclic Carbene Complexes From Chloroiminium Precursors and Examples of Complexes Prepared By This Route



Scheme 4. ADC Metalation Via Lithium–Halogen Exchange

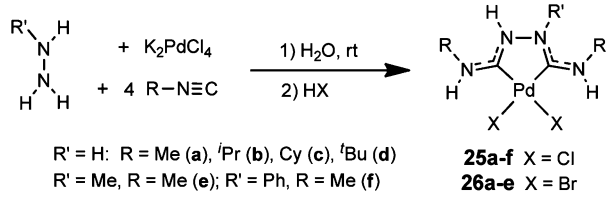


for free ADC,[80] in line with previous studies demonstrating complexation of ADCs by alkali metals.[55]

The intense interest in stable carbenes has somewhat overshadowed the fact that the earliest examples of metal–acyclic carbene complexes arose from metal-templated reactions that do not involve a free carbene.[81] The first reported metal complexes of acyclic AAOCs and ADCs were obtained by nucleophilic addition of alcohols and amines, respectively, to coordinated isocyanides,[82−85] although these ligands received little attention in subsequent decades. Importantly, the availability of stable isocyanide complexes of metals in electrophilic oxidation states, such as Pt^{II}, Pd^{II}, and Au^{I},[86−88] obviates the need for highly basic nucleophiles and sensitive alkylating agents that are typically required in analogous carbene-forming reactions of metal carbonyls.[44] Due to this practical synthetic advantage and the ability to readily tune the ligand structure by simple variation of amine and isocyanide substituents, the metal–isocyanide route has emerged as the preferred method for the preparation of new ADC complexes of catalytically important Pd^{II} and Au^{I} in recent years.[89]

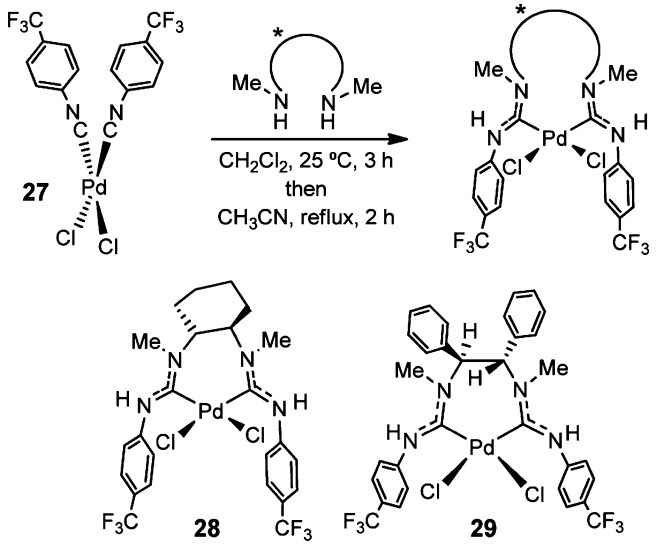
Chugaev evidently prepared the first synthetic metal carbene complex as early as 1915 via platinum-templated addition of hydrazine to methylisocyanide.[90,91] Remarkably, this unusual chelated bis(ADC) complex predates Fischer's first report of an acyclic oxyalkylcarbene ligand[44] by almost 50 years, although it was not recognized as a carbene complex until its characterization by Shaw[92] and Balch and Enemark[93] in 1970. Slaughter and co-workers revisited this chemistry in 2005–2006 and demonstrated that a series of modular Chugaev-type bis(ADC) complexes of Pd^{II} could be generated from unhindered or hindered alkylisocyanides and hydrazine, or even monosubstituted hydrazines when MeNC was used (Scheme 5).[94−96] The simple, aqueous synthetic procedure allowed rapid isolation and catalytic screening of this set of complexes.

Scheme 5. Modular Synthesis of Chugaev-Type Bis(ADC) Complexes By Pd-Templated Addition of Hydrazines to Isocyanides



This strategy has been extended to other bifunctional nitrogen nucleophiles, opening avenues to more structurally elaborate bis(ADC) chelates. Addition of commercially available chiral-backbone diamines to palladium arylisocyanide complex **27** resulted in assembly of the first chiral ADC ligands in single-step reactions (**28** and **29**, Scheme 6).[97,98] By the

Scheme 6. One-Step Synthesis of Chiral Bis(ADC) Complexes



same approach, bis(ADC) ligands with chiral N-substituents and larger chelate rings were constructed.[99] An interesting example of sterically controlled regioselectivity in the formation of Chugaev-like chelate ligands at Pd and Pt was recently reported.[100] Nucleophilic addition of the phenyl-substituted nitrogen of *N*-phenylbenzamidine[101] took place for R = 2,6-xylyl (**30**, Scheme 7), but attack occurred from the less hindered end when bulkier *tert*-butylisocyanide was used (**31**). The metal-bound carbon of **31** shows nearly equal C–N bond

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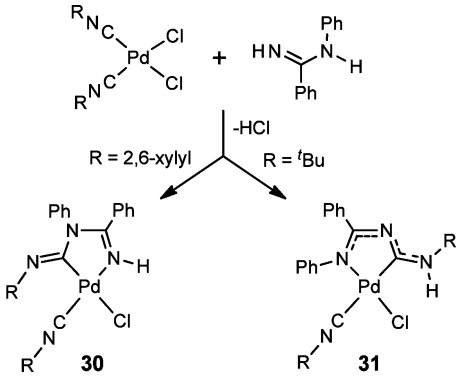
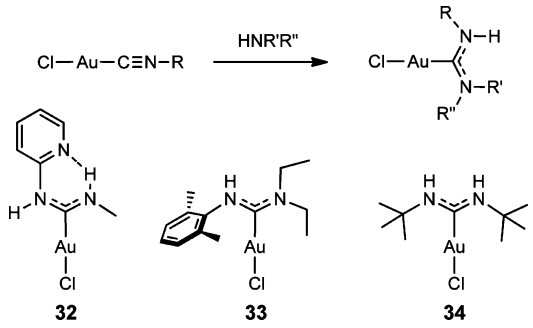
Scheme 7. Regioselectivity Switch in the Addition of *N*-Phenylbenzamidine to Coordinated Isocyanides



lengths, as expected for a diaminocarbene, whereas the carbon of **30** is better described as an anionic imidoyl.

Formation of monodentate acyclic carbene–gold(I) complexes by addition of protic nucleophiles to gold-bound isocyanides has long been known.[102,103] This type of carbene complex has seen renewed interest due to the explosive growth of gold catalysis. Echavarren and Espinet[51] and Hashmi[104] demonstrated the generality of this route by preparing Au^{I}–ADC complexes having a wide range of aromatic and alkyl substituents from readily available amines and isocyanides (e.g., **32**–**34**, Scheme 8). The use of 2-pyridyl isocyanide as a

Scheme 8. Synthesis of Gold(I)–ADC Complexes by the Isocyanide Route and Representative Examples



synthon results in an intramolecular hydrogen bond that is retained in nonprotic solvents (e.g., **32**); this subset of ADCs has been dubbed hydrogen-bond-supported heterocyclic carbenes (HBHCs).[105] Most importantly in terms of potential catalytic utility, the isocyanide route has been successfully used to prepare chiral Au^{I}–ADC complexes.[106−108]

A potential pitfall in the isocyanide-based approach is that addition of amines to isocyanides can be reversible in some cases.[109,110] By studying the reversible ring-opening of a sterically crowded bis(ADC)–Pd^{II} complex, Wanniarachchi and Slaughter were able to estimate that up to 16 kcal mol^{-1} of strain energy can be accommodated in the Pd-templated addition of amines to isocyanides.[111] There is no evidence yet that amine extrusion can occur from ADC complexes of gold, which appear to be particularly robust and promising for catalysis.

Another early route to ADC ligands, based on extrusion of N_2 from a 1,4-disubstituted tetrazolium cation upon reaction with a metal hydride, is also worthy of mention.[112,113] This reaction affords the cyclic tetrazole-derived carbene complex in a mixture with the ADC complex, and it has not been further investigated since the initial reports.

3. LIGAND PROPERTIES OF ACYCLIC CARBENES

Acyclic carbene ligands possess both electronic and structural features that distinguish them from the more commonly studied cyclic carbenes. As interest in these ligands has grown, researchers have begun to direct more effort toward exploiting these unique properties in catalysis.

Few experimental data on the donor properties of acyclic carbene ligands are available. The chlorodicarbonyl-Rh^{I} adduct of ADC **4** showed an average ν(CO) of 2021 cm^{-1}, ~20 cm^{-1} lower than the corresponding complexes with five-membered saturated or unsaturated NHC ligands.[60] This is consistent with increased electron density at Rh^{I} and a concomitant increase in π-backbonding to CO. The only other (acyclic carbene)–metal carbonyl complexes available for direct comparison are those of Bielawski's bulky N-aryl ADCs (e.g., **12b**)[68,114] and Bertrand's push–spectator carbenes **8** and **9**,[58,59] all of which appear to donate more weakly than tetraalkyl ADC **4** but still more strongly than five-membered NHCs (Figure 1). ^{13}C NMR

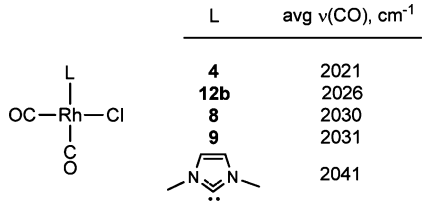


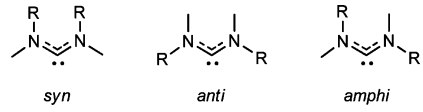
Figure 1. Carbonyl stretching frequencies of Rh^{I}–(acyclic carbene) complexes in comparison with an NHC.

shifts of an NHC probe ligand trans to the carbene of interest provide another useful measure of donicity,[10] but no such data exist for acyclic carbenes. Computationally determined proton affinities[27,72] and LUMO energies[70] for a limited number of ADCs support the notion that these carbenes are more basic than five-membered NHCs.

Using MeNC rather than CO as an IR reporter ligand, Slaughter showed that the chiral bis(ADC) of **28** is a weaker effective donor to Pd^{II} than either a bis(NHC) or a bisphosphine, consistent with the electrophilic reactivity of **28**.[98] It is not yet clear whether this surprising trend is attributable to weak intrinsic donicity arising from the $-CF_3$ substituents, the nonideal bite angle of the bis(ADC) (82°),[97] or both. There is also evidence that ADCs can be more labile than similarly substituted NHCs, despite exerting a stronger trans influence as judged by the elongation of metal–ligand bonds opposite the ADC.[69]

The lack of a cyclic backbone means that all four nitrogen substituents (in the case of ADCs) can potentially influence the favored ligand conformation. Depending on the bulkiness of these groups, ADCs and related acyclic carbenes can adopt different conformations denoted syn, amphi, or anti (Chart 3).[115−117] When at least one sterically hindered substituent is

Chart 3. Possible Conformations of Acyclic Carbenes



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present on each side of the carbene, the latter two configurations tend to be favored. In addition, metal-bound ADCs exhibit N−$C_{carbene}$−N bond angles of 116−124°, much wider than the typical 104−107° angles seen in five-membered NHCs. Consequently, substituents on nitrogen (or other heteroatoms) are placed much closer to the metal in bulky acyclic carbene ligands than in NHCs. These substituents can therefore exert a stronger influence on the regioselectivity or stereochemistry of reactions occurring at the metal center. This could have particularly important implications for enantioselective catalysis.

Another consequence of the acyclic structure is that hindered rotation about the C−N (or other C−X) bonds can occur, despite their partial π-bond character.[72] This has been observed in both free[49] and complexed[89,104,110] acyclic carbenes. The resulting interconversion between different conformers endows these carbene ligands with "flexible steric bulk" that could potentially have useful effects on catalytic activity.[118] These conformational changes can also affect the ligand electronic properties, as demonstrated by Bielawski's group.[114] They found that syn and amphi conformations of the same bulky ADC ligand exhibit different donicities toward Ir^{I}, with the syn form being the weaker donor (Figure 2).[119]

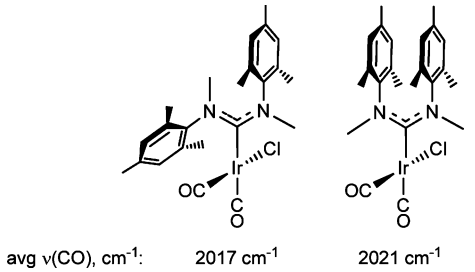


Figure 2. Conformation-dependent donicities of bulky ADCs.

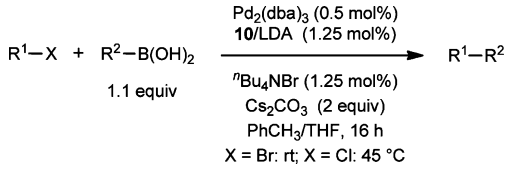
4. COUPLING REACTIONS

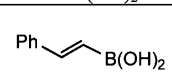
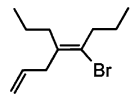
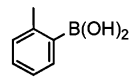
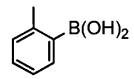
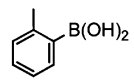
The first reports of catalysis with acyclic carbene ligands appeared in 2005 and addressed palladium and nickel-catalyzed coupling reactions.[77,94] These and later studies provide valuable comparisons of ADCs with other ligand classes, including NHCs,[22] given the broad synthetic utility of these reactions and the vastness of their catalytic literature.[120]

4.1. Suzuki−Miyaura Coupling. Slaughter's group reported that Chugaev-type palladium bis(ADC) complexes are robust catalysts for Suzuki−Miyaura coupling reactions of aryl bromides and chlorides.[94] A series of complexes with six differently substituted bis(ADC) ligands were screened to identify trisubstituted catalysts **25e** and **25f** (Scheme 5) as the most active.[95,96] Catalyst **25e** gave high coupling yields for reactions of both electron-rich and electron-poor aryl bromides, even when the reaction was done in open-flask conditions, making **25e** a rare example of an air-tolerant Suzuki catalyst. For aryl chlorides, the substrate scope was limited to those with electron-withdrawing groups, and high temperatures (120 °C) were required for maximum yields even with aryl bromides. It seems likely that the bidentate geometry of these bis(ADC) ligands places limitations on catalyst activity, given that monoligated Pd^{0} species are thought to be key intermediates in Suzuki coupling.[121] Nevertheless, these studies provided the first proof of principle that the isocyanide-based synthetic route is amenable to rapid structural variation and catalytic optimization of ADC ligands.

Concurrent with Slaughter's initial communication, Fürstner's group reported that Pd^{II} complexes of several monodentate acyclic carbenes, including AAOC complex **17**, aminothiocarbene complex **18**, and aminoarylcarbene complex **19** (Scheme 3), were effective Suzuki precatalysts under milder conditions (refluxing THF, 66 °C).[77] However, only couplings of *para*-acetylphenyl halides were examined, and heating to 120 °C was still needed when X = Cl. The following year, Dhudsia and Thadani reported a highly active catalyst system for Suzuki couplings of a range of aryl and vinyl bromides at room temperature based on Pd complexes of Alder's bulky ADC **4**, generated in situ from amidinium precursor **10** (Table 1).[122]

Table 1. Selected Examples of Suzuki−Miyaura Coupling with an In Situ-Generated Pd−ADC Catalyst



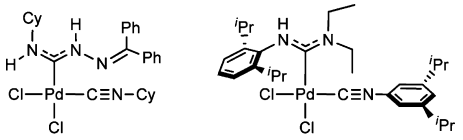
entry	R^1-X	R^2-B(OH)$_2$	yield (%)
1			89
2			88
3			80
4			92

Heterocycles and polar groups were well tolerated, and even ortho-substituted aryl partners were efficiently coupled to give di- and triortho-substituted biaryls, making these systems comparable to some of the most active NHC- and phosphine-ligated catalysts.[118,123,124] Similar yields were obtained with hindered and electron-rich aryl chlorides at 45 °C (entries 3,4). It seems likely that the increased steric bulk of **4** is responsible for the higher activity of this system relative to other ADC-containing catalysts.[77,96] The in situ generation of the ADC ligand represents an additional advantage because it avoids the time and materials costs associated with synthesis of a defined Pd-carbene precatalyst; similar catalytic systems utilizing imidazolium salts as in situ NHC precursors were reported earlier by Nolan.[125,126] Despite this obvious advantage, only one other report of in situ generation of an acyclic carbene ligand in catalysis has appeared.[127]

More recently, reports of highly active Suzuki catalysts containing monodentate ADC ligands prepared by the isocyanide route have provided further evidence of the value of this synthetic method for catalyst tuning. Catalyst **35** (Chart 4), selected from four Pd^{II}−ADC complexes synthesized by addition of benzophenone hydrazone to different isocyanides, gave near-quantitative yields in couplings of the "deactivated" substrate *p*-bromoanisole with catalyst loadings as low as 0.001 mol %, even under air in undried EtOH.[128] At extraordinarily low Pd loadings of 0.00001 mol %, turnover numbers (TON)

dx.doi.org/10.1021/cs300300y | ACS Catal. 2012, 2, 1802−1816

Chart 4. Palladium–ADC Precatalysts Giving Exceptionally High TON (35) and TOF (36) in Suzuki–Miyaura Coupling of Aryl Bromides

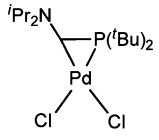


35 36

up to 1.4×10^6 could be achieved, albeit with only 14% yield. Hashmi studied a related series of seven Pd–ADC complexes derived from two different isocyanides and seven different amines and found that they gave lower yields than analogous Pd–NHC complexes in a room-temperature coupling reaction of phenyl bromide with 2,5-dimethylphenylboronic acid (e.g., 60% yield with 0.1 mol % of **36**; Chart 4).[129] However, high initial turnover frequencies (TOF) of up to 18 000 h^{-1} were measured for another aryl bromide, and some dependence of TOF on ADC structure was observed but not explained. Mixed chelates complexes having both ADC and anionic nitrogen donors have also been shown to effect Suzuki coupling of aryl bromides with low catalyst loadings.[130,131]

Unknown for catalysts such as **35** and **36** is the fate of the remaining isocyanide ligand, which is likely to be reactive under catalytic conditions. Acidic N–H protons on isocyanide-derived ADCs represent additional reactive sites, and these were shown to be deprotonated by the base used in catalysis in the case of Chugaev-type complex **26e**.[89] Further work is needed to determine whether these types of ADC complexes merely serve as precursors to undefined low-ligated, or even nonligated, palladium species that are the true catalysts.[132]

4.2. Aryl Amination. Fürstner achieved room-temperature catalytic aminations of bromobenzene and 2-chloropyridine with morpholine using acyclic carbene–Pd precatalysts. ADC complex **20**, AAOC complex **17**, and aminoarylcarbene complex **19** (Scheme 3) all provided excellent yields, but only these two substrates were examined. Bertrand's group reported high-yielding aminations of four aryl bromides with morpholine using aminophosphinocarbene complex **37** (Figure 3) as a catalyst, albeit under harsh conditions (140 °C, xylene).[133] This remains the lone example of catalysis with an acyclic phosphino-substituted carbene ligand. A distinguishing feature of **37** is the η^2-(C,P) binding mode of the carbene ligand. Similar η^2-(C,N) binding of ADC ligands has been observed in M(ADC)$(CO)_4$ complexes (M = Cr, Mo, W),[62,134] but it is not yet known whether this binding motif has any relevance for catalytic intermediates.



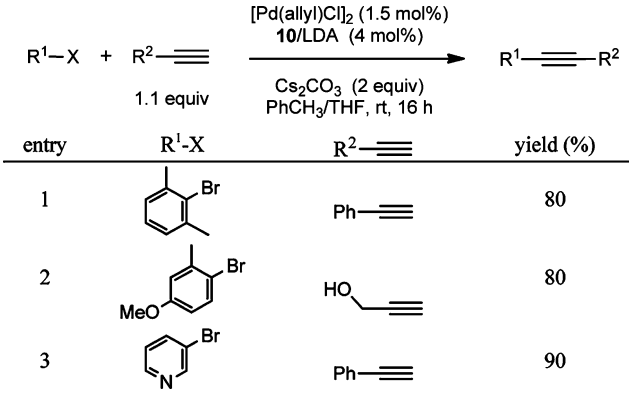
37

Figure 3. Aminophosphinocarbene–palladium complex examined in catalytic amination of aryl bromides.

4.3. Mizoroki–Heck Coupling. Fürstner's cationic Pd–ADC complexes (Scheme 3) effected coupling of aryl bromides or iodides with butyl acrylate at 120 °C, with precatalyst **21** giving yields approaching those attained with analogous NHC complexes.[77] Thadani reported coupling of two aryl bromides with methyl acrylate under similarly harsh conditions (110 °C) using an in situ-generated Pd–ADC catalyst.[122] Useful yields could not be obtained with aryl chlorides in either case, in contrast to successful aryl chloride Heck couplings achieved with some NHC-based systems.[135,136]

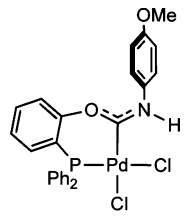
4.4. Sonogashira Coupling. Thadani reported efficient room-temperature Sonogashira couplings using a Pd–carbene catalyst generated in situ from bulky ADC **4**.[122] High yields were obtained with ortho-substituted, electron-rich, and heterocyclic aryl bromides and with both aromatic and hydroxy-substituted aliphatic alkynes without a copper cocatalyst (Table 2). These are perhaps the most promising results obtained with acyclic carbene ligands in palladium-catalyzed coupling reactions to date, given that reported NHC–Pd catalysts for the Sonogashira coupling require higher temperatures[137−140] and usually a CuI cocatalyst for activity.[137,138]

Table 2. Selected Examples of Room-Temperature Sonogashira Coupling with an In Situ-Generated Pd–ADC Catalyst



entry	R^1-X	R^2—	yield (%)
1			80
2			80
3			90

A series of 16 mixed chelate ligands containing phosphines tethered to AAOCs or ADCs were prepared by addition of amine- or alcohol-substituted phosphines to palladium-bound isocyanides, and three (e.g., **38**, Figure 4) were examined in Pd-catalyzed Sonogashira coupling reactions.[141] The catalysts required a CuI cocatalyst and high temperatures (110 °C), only aryl iodides gave reasonable activity, and conversions were low in most cases, with significant amounts of alkyne homocoupling product also obtained. However, the novel phosphine–acyclic carbene chelate ligands seem potentially useful for other applications, as the more weakly donating phosphine moiety could result in hemilability.



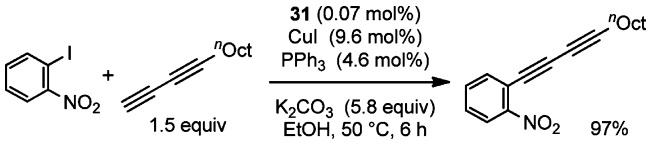
38

Figure 4. Representative acyclic carbene–phosphine chelate complex examined in Sonogashira coupling of aryl iodides.

dx.doi.org/10.1021/cs300300y | ACS Catal. 2012, 2, 1802–1816

The differing regioselectivities observed in the formation of isocyanide-derived chelates **30** and **31** (Scheme 7) had interesting consequences for catalysis.[100] ADC-containing chelate complex **31** gave much faster reactivity in Sonogashira couplings of aryl iodides compared with imino−imidoyl complex **30**, allowing catalyst loadings as low as 0.05 mol %, although CuI and PPh_3 cocatalysts were required. Complex **31** was also shown to exceed the activity of published catalyst systems for the rarely studied Sonogashira coupling of a terminal diyne (Scheme 9).[142]

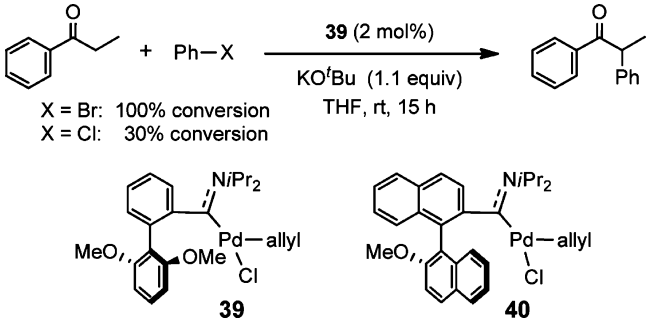
Scheme 9. Sonogashira Coupling of a Terminal Diyne



4.5. Kumada−Corriu Coupling. Fürstner examined three cationic Ni^{II} complexes of unhindered ADCs in room-temperature Kumada−Corriu couplings of aryl bromides and chlorides with *p*-methoxyphenylmagnesium bromide.[77] ADC complex **22** (Scheme 3) gave slightly better yields than an analogous complex containing an *N*,*N*′-dimethyl-substituted NHC, but there is not enough information to judge its performance against the best Ni−NHC and Ni-phosphine systems,[143,144] given the limited number of substrates studied.

4.6. α-Arylation of Ketones. Acyclic aminoarylcarbene palladium complex **39** gave promising preliminary catalytic results in the α-arylation of propiophenone with bromobenzene (Scheme 10), furnishing quantitative yields at room temperature with 2 mol % catalyst loading.[145] This is comparable to the best reported palladium phosphine systems. Unprecedented room-temperature arylation with chlorobenzene was also achieved, albeit in only 30% yield. Chiral aminoarylcarbene complex **40** was also prepared but was apparently not examined in asymmetric α-arylation reactions, despite evidence for intramolecular Pd−arene interactions in solution that could favor chiral induction.

Scheme 10. α-Arylation of Propiophenone Catalyzed by an Acyclic Aminoarylcarbene−Pd Complex

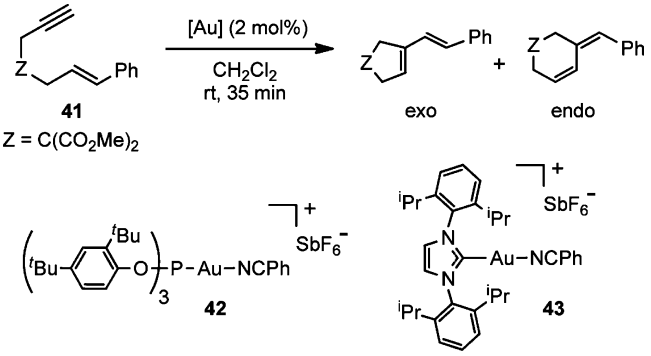


5. GOLD-CATALYZED REACTIONS

Although long assumed to be relatively inert, gold(I) complexes have emerged in recent years as powerful catalysts for a broad range of reactions involving activation of unsaturated bonds toward nucleophilic attack.[146,147] This is rapidly becoming the most active area of research involving acyclic aminocarbenes, as Au^I complexes of these ligands seem to be particularly stable and easy to prepare.

5.1. Cyclizations of Enynes. Echavarren and Espinet reported that Au−HBHC complexes catalyze cyclizations of 1,6- and 1,7-enynes with some interesting differences in selectivity compared with established catalysts.[105] For example, Au−HBHC catalyst **32** (Scheme 8) favored the endo product in cyclizations of enyne **41**, whereas catalysts **42** and **43**, containing a bulky phosphite and the very hindered NHC ligand "IPr", respectively, favored the exo product (Table 3).

Table 3. Differing Selectivities in Enyne Cyclization With HBHC−, Phosphite−, and NHC−Au^I Catalysts



entry	catalyst	yield (%)	exo/endo
1	**32**/$AgSbF_6$	100	1:2.7
2	**42**	76	2.2:1
3	**43**	73	50:1

This selectivity difference appears to be at least partly attributable to electronic rather than steric effects, as an analogous HBHC complex with ^{t}Bu in place of methyl gave an almost identical exo/endo ratio (1:2.8). These authors later surveyed a series of 12 non-hydrogen-bonded Au−ADC complexes prepared from different isocyanides and amines in related reactions.[51] Catalytic activity was found to strongly depend on the steric bulk of the ADC substituents, and in some cases, improved yields over both HBHC and NHC complexes were obtained in methoxycyclizations of 1,6-enynes in methanol.

The extremely bulky Au−ADC complex **44** (Chart 5) was found to give opposite selectivity to IPrAuCl (**45**) in the catalytic addition of indole to 1,6-enyne **47** to give either alkene product **48** or cyclopropane product **49**,[70] even though the steric hindrance of **44** and **45** are comparable as judged by their buried volume (% V_{Bur}) parameters (Table 4).[148] Hong postulated that the noncoplanarity of the carbene N-substituents of **44**, which results from unusually large C−N−$C_{carbene}$−N dihedral angles, might lead to enhanced π-acceptor ability for the bulky ADC versus an NHC, which could disfavor

Chart 5. Extremely Hindered Au^I−Carbene Precatalysts

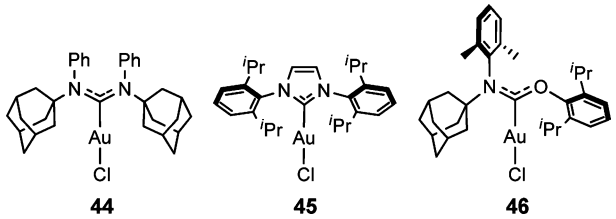


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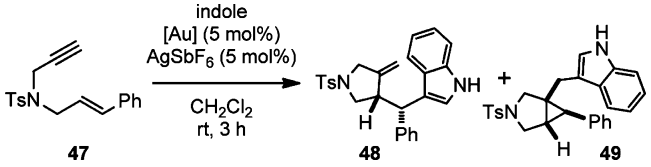
Table 4. Differing Selectivities in Indole Addition to 1,6-Enyne with Bulky ADC–Au^{I} and NHC–Au^{I} Catalysts

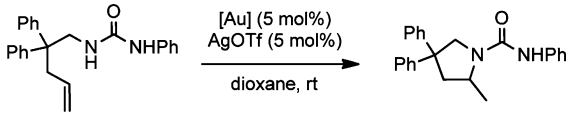


precatalyst	% V_{Bur}	yield (%)	48:49
44	45.7	78	82:18
45	45.6	76	26:74

the putative Au^{III}–carbenoid intermediate that leads to the minor product **49**. As yet, there is no experimental or theoretical evidence to support this hypothesis.

5.2. Hydrofunctionalizations of Allenes and Alkenes. Espinet's group found that moderately bulky Au–ADC complex **33** (Scheme 8) gave yields comparable to those obtained with previously reported gold complexes of bulky biarylphosphines[149] in exo-selective intramolecular hydroaminations and hydroalkoxylations of allenes containing pendent carbamate and alcohol groups.[150] Hong reported effective catalysis of a related but more challenging intramolecular alkene hydroamination[151] with various hindered Au–ADC complexes and obtained the best results with **44**.[70] The similarly hindered IPr complex **45** gave faster reactivity and better conversion, whereas less bulky NHC and ADC ligands having % V_{Bur} parameters less than 40 (e.g., **34**, Scheme 8) showed almost no activity (Table 5). With bulky AAOC

Table 5. Steric Bulk-Dependent Activity in Au^{I}–Catalyzed Intramolecular Hydroamination of an Alkenyl Urea

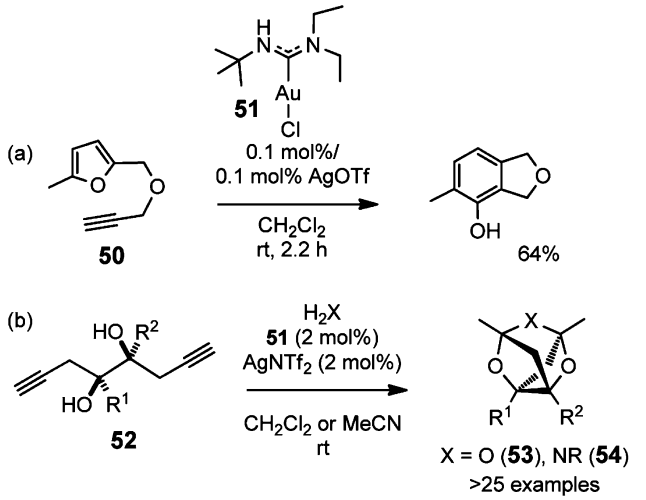


precatalyst	% V_{Bur}	time (h)	% conversion
34	39.2	24	3
44	45.7	24	87
45	45.6	16	>98
46	45.8	15	>98

complex **46**,[71] improved activity and substrate scope were observed compared with ADC complex **44**, although the results still did not surpass those obtained with IPr complex **45**.[152] It should be mentioned that related alkene hydroaminations with sulfonamides, benzamides, and carbamates are known to be catalyzed by Brønsted acids at elevated temperatures,[153,154] and Brønsted acids can be generated by side reactions of substrates with electrophilic metal complexes;[155] however, control experiments with the same alkenyl urea substrate have shown that a Brønsted acid-catalyzed pathway is not operational under the catalytic conditions used with **44** and **46**.[152]

5.3. Reactions of Alkynes. Espinet examined Au–ADC catalyst **33** in the hydroarylation of an alkynyl carboxylic acid ester with mesitylene and found activity comparable to that of the analogous PPh_3 complex.[150] In the related phenol synthesis with furanyl alkyne **50**—considered a problematic substrate for this reaction (Scheme 11a)—Hashmi identified three catalysts that gave comparable yields and much higher TON compared to the best reported Au^{I}–phosphine system[156] by screening a

Scheme 11. Reactions of Alkynes Catalyzed By Isocyanide-Derived Au–ADC Complexes



library of 21 Au–ADC complexes obtained by addition of various amines to gold isocyanide complexes.[104] The most active catalysts all had bulky *tert*-butyl groups located syn to the gold center (e.g., **51**). The same catalyst library yielded several effective catalysts for the hydration of phenylacetylene to benzophenone.[104] Au–ADC complex **51** was also found to show superior activity to bulky phosphine and NHC complexes in cyclizations of diyne-diols **52** with added nucleophiles to give novel tricyclic compounds **53** and **54** (Scheme 11b).[157] This is one of the few cases in which superior activity and broad substrate scope have been demonstrated for a metal–acyclic carbene catalyst in a completely new reaction.

5.4. Benzylation of Arenes. Au–ADC complex **33** and its NTf_2^- derivative were found to catalyze the benzylation of anisole with 1-phenylethyl acetate with slightly better yields and a similar ratio of ortho and para benzylation products compared with the previously reported H[$AuCl_4$] catalyst.[158] However, when the less hindered and less electrophilic benzyl alcohol was used as the benzylating agent, both Au–ADC complexes were superior catalysts, giving much higher benzylation yields than H[$AuCl_4$], albeit with little difference in regioselectivity.

6. ALLYLIC ALKYLATION

Using a Cu–ADC catalyst generated in situ from a commercially available chloroimidazolium precursor and copper(I) thiophene carboxylate (CuTC), Hong and co-workers achieved high-yielding allylic alkylations of allylic esters with ethyl Grignard (Table 6).[127] Yields and γ/α selectivities were consistently high for allylic alkylations of six different substrates, and comparisons with an IMes-ligated catalyst showed significantly better yields for the ADC complex (e.g., entries 1 and 2). Interestingly, nearly opposite selectivity was observed for unligated CuTC catalyst compared with the ADC and NHC-containing systems (entry 3). No further investigations of these synthetically useful reactions[159] with ADC ligands have yet appeared.

7. OLEFIN METATHESIS

Despite the key role played by NHC ligands in the development of ruthenium-catalyzed olefin metathesis,[17] only one report of the use of acyclic carbene ligands in this reaction has appeared.[69] Bielawski's group found that bulky Ru–ADC

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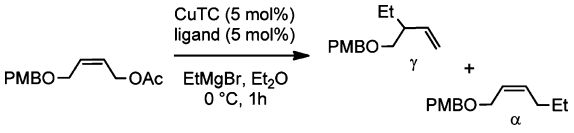
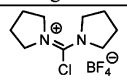
Table 6. Allylic Alkylation With In Situ-Generated Cu−ADC Catalyst

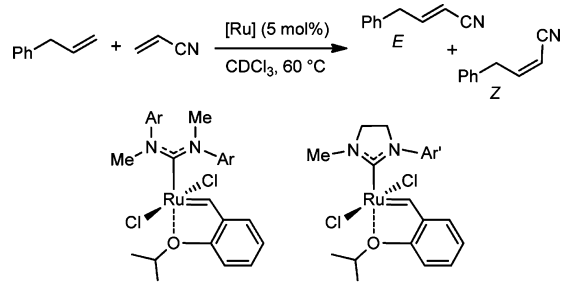


entry	ligand	yield (%)	γ:α
1		83	94:6
2	IMes[a]	57	92:8
3	none	9	13:87

[a]IMes = 1,3-dimesitylimidazol-2-ylidene.

complexes **55a,b** afforded significantly lower *E*/*Z* ratios at low conversions (~30%) in cross-metathesis (CM) reactions of allylbenzene with alkenes compared with unsymmetrically substituted NHC complexes **56a,b** (Table 7). This is

Table 7. Ruthenium-Catalyzed Olefin Cross-Metathesis With Hindered ADC Ligands Giving Low *E*/*Z* Ratios



55a Ar = DIPP
55b Ar = Mes

56a Ar' = DIPP
56b Ar' = Mes

entry	[Ru]	*E*/*Z*[a]
1	**55a**	1.2:1
2	**55b**	0.6:1
3	**56a**	2.8:1
4	**56b**	1.8:1

[a]At ~30% conversion.

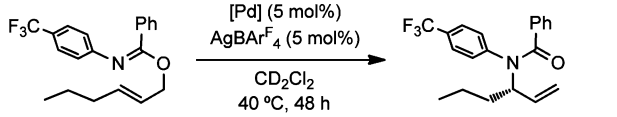
significant, because *Z*-selective CM catalysis is considered a major challenge in olefin metathesis and has been achieved in only a few cases.[160−162] The promising selectivities of **55a,b** are likely due to the closer proximity of one bulky aryl substituent to the metal, which could influence the stereochemistry of the metathesis reaction both directly, through steric interactions with alkylidene intermediates, and indirectly, by inhibiting olefin isomerization and other secondary metatheses. However, the increased hindrance appeared to significantly reduce catalyst activity compared with IPr/PCy_3-ligated ruthenium catalysts in ring-closing metathesis reactions.

8. ENANTIOSELECTIVE CATALYSIS

Chiral NHC ligands[163] are still underdeveloped and generally less successful in asymmetric catalysis relative to the more established chiral phosphines.[43] Because of their ability to place chiral groups close to the metal, acyclic carbene ligands could potentially provide significant advantages over chiral NHCs in enantioselective reactions.

In the first report of enantioselective catalysis with acyclic carbene ligands, the catalytic aza-Claisen rearrangement of an achiral allylic benzimidate (Scheme 12) in the presence of cationic derivatives of chiral bis(ADC)−Pd^{II} complexes **28** and

Scheme 12. Enantioselective Aza-Claisen Rearrangement Catalyzed by Chiral Palladium Bis(ADC) Complexes

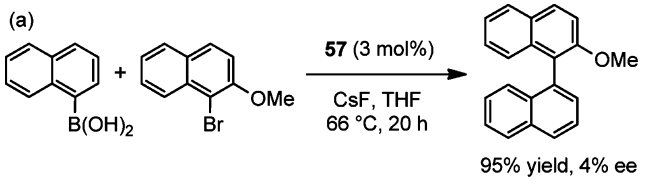


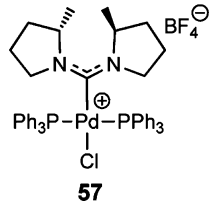
[Pd] = **28**: 50 % yield, 30% ee
29: 34 % yield, 59% ee

29 (Scheme 6) was examined. With enantiomerically pure **28**, the chiral allylic amide product was obtained in 30% ee, although yields were moderate and significant amounts of side products were obtained. Precatalyst **29**, which has a more pronounced chiral environment at Pd by virtue of a protruding Ph substituent on the ligand backbone, provided a higher ee of 59%, albeit with no improvement in yield or selectivity. Although better activities and enantioselectivities have been attained with fairly elaborate chiral palladacycle catalysts,[164,165] this study demonstrated that rational catalyst modification by simple addition of chiral amines to metal-bound isocyanides can lead to significant improvements in an asymmetric reaction.

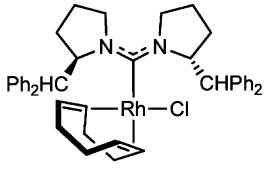
The first attempts at monodentate chiral acyclic carbene ligands did not deliver significant enantioselectivities in catalytic reactions. Hong's 2-alkylpyrrolidyl-based chiral ADCs (e.g., **57** and **58**, Scheme 13) provided low ee values in the palladium-

Scheme 13. Enantioselective Catalysis With Monodentate Chiral Bis(*N*-Pyrrolidyl) ADC Ligands





57



58

catalyzed asymmetric Suzuki coupling of naphthyl substrates and the rhodium-catalyzed asymmetric 1,2-addition of 1-napththyl boronic acid to *o*-anisaldehyde,[79] although achiral versions of these catalysts gave promising yields in the corresponding nonenantioselective processes.[78,79] The poor chiral induction may be due to the tendency of the pyrrolidyl groups to adopt a syn conformation that orients the alkyl substituents away from substrate binding sites when other bulky ligands are present on the metal.[79]

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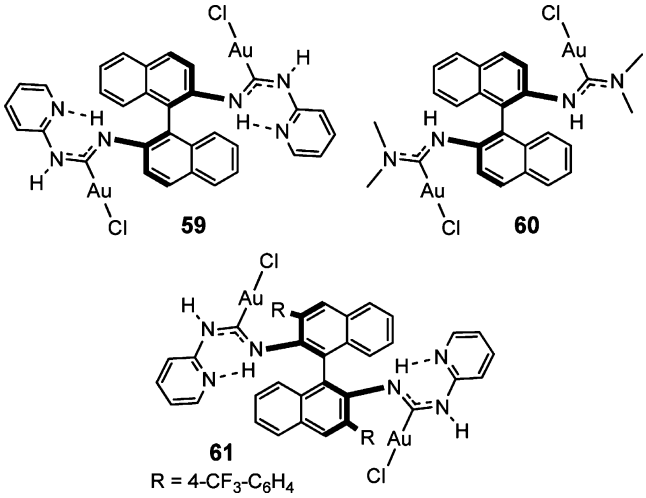
Using an approach similar to that of Slaughter,[97−99] Espinet prepared a series of bridged bis(HBHC)− and bis(ADC)−digold(I) complexes using either chiral diamines (e.g., **59**, Chart 6) or chiral bis(isocyanides) (e.g., **60**) as backbone

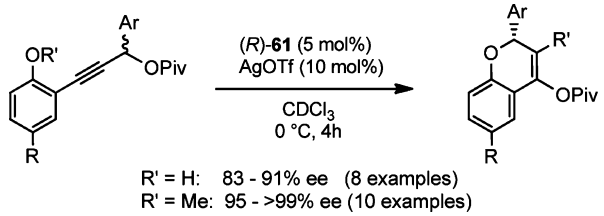
Chart 6. Chiral Bis(HBHC)− and Bis(ADC)−Digold(I) Precatalysts



precursors.[106] Complexes **59** and **60**, containing binaphthyl backbones, showed more promising catalytic results in two enantioselective test reactions, the cyclopropanation of styrene with propargyl pivaloate and the intramolecular hydroalkoxylation of a γ-hydroxyallene, compared with similar catalysts containing chiral 1,2-diaminocyclohexane or 1,2-diphenylethylene linkers. However, ee values of only 20−24% were obtained, falling far short of the 81−90% ee obtained with the chiral bisphosphine (*R*)-DTMB-SEGPHOS.

While investigating gold-catalyzed dynamic kinetic asymmetric transformations of propargyl esters, Toste and coworkers systematically modified Espinet's chiral bis(HBHC)−digold catalyst **59** by using seven binaphthyl diamines with variously substituted 3,3′-aryl groups and thereby achieved the first example of highly enantioselective catalysis with an acyclic carbene ligand.[107] Trifluoromethylphenyl derivative **61** gave the best results, providing chromenyl pivalates with ee values ranging from 83% to >99% from a range of racemic substrates containing phenol and phenol ether groups (Scheme 14).

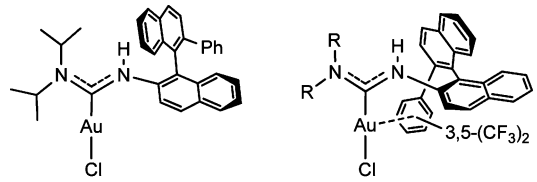
Scheme 14. Dynamic Kinetic Asymmetric Transformation of Propargyl Esters Catalyzed by a Chiral Au^{I}−HBHC Complex



Higher enantioselectivities were obtained with the bis(HBHC) ligands than with chiral bisphosphine and phosphoramidite ligands that perform well in other Au^{I}-catalyzed asymmetric reactions. This supports the authors' hypothesis that a more strongly donating chiral ligand could favor a planar, achiral allyl cation-like intermediate that leads to chiral induction. However, the role of the trifluoromethylphenyl substituent in promoting enantioselectivity was not apparent.

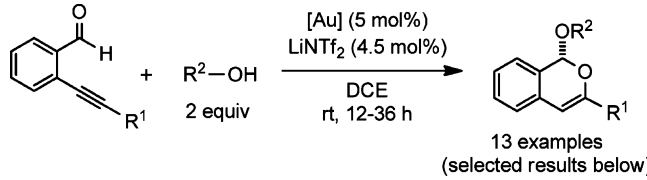
Concurrently with Toste's work, Handa and Slaughter studied the tandem acetalization/cycloisomerization of *ortho*-alkynylbenzaldehydes using Au^{I} complexes of monodentate chiral ADC ligands derived from binaphthyl monoisocyanides.[108] Profound effects of the binaphthyl 2′-substituent of the Au−ADC complex on both the ligand conformation (as judged by X-ray crystallography) and catalyst performance were observed. In complex **62**, the binaphthyl group has an orientation that directs the 2′-phenyl substituent away from the coordination sphere (Chart 7). By contrast, **63a** adopts a

Chart 7. Chiral Au^{I}−ADC Complexes Showing Substituent-Dependent Rotameric Conformations of the Binaphthyl Group



different rotameric form with the bulkier bis(trifluoromethyl)-phenyl substituent located directly adjacent to gold (Au-ring centroid distance 3.4 Å). Density functional theory calculations supported the presence of a weak, likely electrostatic gold−aryl interaction in **63a** but not in **62**, and **63a** also provided much higher yields and enantioselectivities in alkynylbenzaldehyde cyclizations (Table 8, entries 1−3). Enforcement of the close

Table 8. Au^{I}−ADC Catalyzed Enantioselective Alkynylbenzaldehyde Cyclizations: Dependence of Activity and Enantioselectivity on ADC Substituent



			% yield (% ee) with catalyst:		
entry	R^1	R^2	**62**	**63a**	**63b**
1	Ph	Cy	5 (43)	70 (98)	
2	Ph	^{n}Oct		87 (99)	
3	Ph	^{i}Pr	28 (61)	68 (84)	70 (>99)
4	Ph	^{n}Bu		12 (nd)[a]	59 (92)
5	^{n}Pr	^{n}Oct		5 (nd)[a]	86 (99)

[a]Not determined.

metal−aryl contact through use of bulky chiral amine substituents (**63b**) resulted in greatly improved yields and enantioselectivities with less-hindered alcohol/alkyne combinations that were not effectively cyclized with **63a** (entries 4, 5). Thus, the wide N−C−N angle of the ADC, the syn-to-gold orientation of the binaphthyl substituent, and the steric bulk of the R groups may all act in synergy with a weak Au−aryl interaction to create an enhanced chiral environment at the metal and possibly also to stabilize reactive intermediates.

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These results constitute the first example of highly enantioselective catalysis with a monodentate ADC ligand.[166] Notably, the ee values attained with **63a,b** and Toste's digold complex **61** are the highest yet achieved with chiral nonphosphorus ligands in gold catalysis.

9. CONCLUSION AND OUTLOOK

It is clear that applications of acyclic aminocarbene ligands in catalysis are still in their infancy. In most catalytic studies to date, acyclic carbene-containing catalysts have been tested on only a small number of substrates, thus providing a limited basis for comparison with more established systems. Nevertheless, promising selectivity differences or enticing improvements in activity relative to catalysts with NHC or phosphine ligands have been obtained in isolated instances, although in most of these, the underlying structure−function relationships have not yet been explained. These successes should inspire more researchers to add acyclic carbenes to the arsenal of ligands used to attack challenging or novel catalytic reactions.

Key to the growth of the field has been a move away from synthetic methods involving the intermediacy of rather fragile free acyclic carbenes. Alternative metalation strategies based on chloroamidinium precursors or metal-templated conversions of isocyanides to carbenes have so far been limited to a few late transition metals, but there are clearly opportunities to expand the scope of these procedures. It will be equally important to delineate under which conditions acyclic carbenes are compatible with catalysis, given that ADCs appear to be surprisingly labile in some complexes[69] and are sometimes prone to unusual decomposition processes that do not affect NHCs.[97,134] Finally, an improved understanding of the donor properties of acyclic carbenes would be useful. Although the catalytic properties of ADC−metal complexes support the presumed strong donicity of these ligands in many cases, the ability of some ADCs to promote electrophilic catalytic reactions at Pd^{II} or Au^{I} suggests a possibly broader range of electronic properties than can be discerned from currently available data.

The area in which the unique properties of acyclic carbenes appear to have the greatest potential to make an impact is enantioselective catalysis. The combination of conformational flexibility and wide N−$C_{carbene}$−X angle seems likely to engender a dynamic chiral environment at the catalytic site that could be quite different from what is attainable with other chiral ligand types. The recent achievement of highly enantioselective catalysis with chiral Au−ADC complexes[107,108] is particularly significant because the linear coordination geometry of Au^{I} generally makes it difficult for chiral ancillary ligands to sterically influence the substrate binding site.[167] The possible importance of intramolecular Au−aryl interactions in ADC complexes **63a,b** adds to growing evidence that secondary interactions of the ancillary ligand might play an important role in attaining chiral induction at Au^{I}.[168−170]

The future of acyclic carbenes in catalysis seems limited only by the creativity of chemists. Novel classes of acyclic carbenes will undoubtedly be devised,[171−173] perhaps uncovering surprising new ligand properties and opening new doors in catalytic reactivity. Applications of acyclic carbenes in organocatalysis, which are so far almost nonexistent,[174,175] could become a reality if sufficiently robust free acyclic carbenes are devised. Years from now, perhaps researchers in the catalysis field will wonder why acyclic carbenes lay hidden for so long in the shadow of their more popular cyclic cousins.

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Notes

The authors declare no competing financial interest.

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