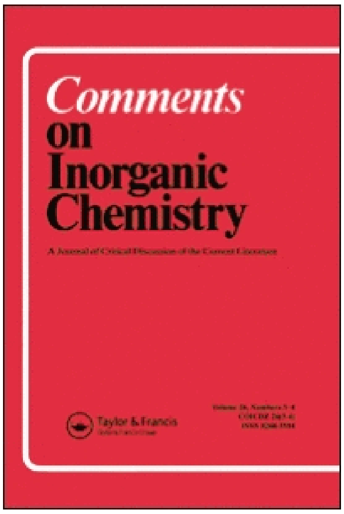

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"COVALENT SELF-ASSEMBLY" OF ACYCLIC DIAMINOCARBENE LIGANDS AT METAL CENTERS

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Chelating bis(acyclic diaminocarbene) ligands can be prepared by addition of diamines or hydrazines to coordinated isocyanide ligands in a process that resembles self-assembly. This procedure is potentially generalizable to a range of structurally and electronically diverse bis(carbene) ligands with catalytic utility. A series of 12 palladium complexes of 5-membered chelate bis(carbene) ligands have been prepared by a simple aqueous protocol and screened to identify moderately active, air tolerant Suzuki-Miyaura cross-coupling catalysts. Aryl isocyanide synthons provided more structurally elaborate acyclic diaminocarbenes, including chiral examples that supported enantioselective electrophilic catalysis at palladium. These carbene ligands have distinct stereoelectronic properties that complement those of the widely used N-heterocyclic carbenes.

INTRODUCTION

The discovery of novel homogeneous catalysts is critically dependent on the availability of suitable ancillary ligands. Cyclic diaminocarbenes, commonly known as N-heterocyclic carbenes or NHCs, have risen to prominence in recent years as a powerful class of ligands for transition metal-based catalysis.[1–5] Although NHCs have been known as ligands

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since the seminal work of Wanzlick[6] and Öfele[7] in 1968, recognition of their enormous potential in catalysis only occurred following Arduengo's isolation of a stable, free imidazolylidene (**1**, Figure 1) in 1991.[8] Five-membered ring imidazolylidenes (e.g. **1**) and their saturated analogues, imidazolinylidenes (e.g. **2**, Figure 1),[9] are the NHC ligand types most commonly used in catalysis. The enhanced catalytic activities reported for NHC-containing catalysts compared to catalysts containing more traditional phosphine ligands have frequently been attributed to the strong σ-donor abilities of NHCs, which are evidenced by calorimetric studies showing metal-NHC bond dissociation energies exceeding those of the most basic phosphines by up to 10 kcal mol^{-1}.[10] This high donicity promotes certain types of reactivity at the metal center while also preventing ligand dissociation that could lead to catalyst deactivation. A second advantage of NHCs over phosphines is their stability toward oxidation, even at elevated temperatures, when bound to a metal.[11] While tuning of NHC steric properties is readily accomplished by variation of the N-substituents,[12] several lines of evidence implicate a narrow range of donor abilities in commonly used NHCs.[13–17] Another deficiency is the relatively small number of chiral NHC ligands that have been reported to promote highly enantioselective catalytic reactions.[18] In particular, few effective examples of chiral bis(carbene) ligands have appeared,[19,20] in contrast to the vast array of chiral bis(phosphine) ligands that effect highly enantioselective catalysis.[21] In order to

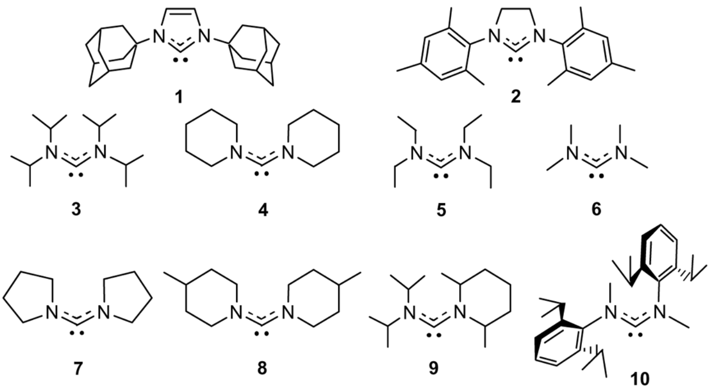
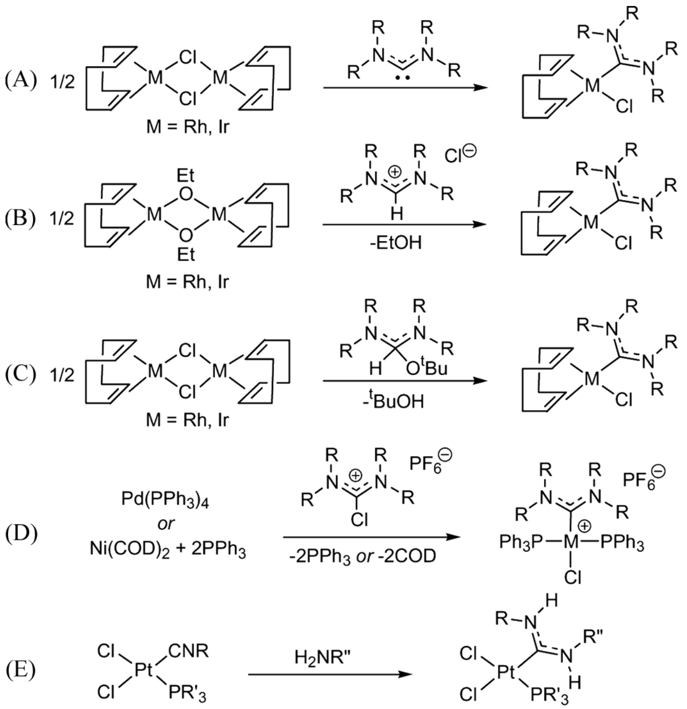


Figure 1. Prototypical N-heterocyclic carbenes (**1**, **2**) and known acyclic diaminocarbenes (**3**–**10**).

approach the breadth of steric and donor properties[22] and chiral structures[21] available in phosphorus-based ligands, it is clear that exploration of novel and unusual carbene ligand types is an important goal.

Acyclic diaminocarbenes (ADCs) have received considerably less attention as ancillary ligands than NHCs. The strongly σ-withdrawing, π-donating nitrogen atoms attached to the carbene carbon should endow ADCs with electronic stabilities and ligand donor properties similar to those of NHCs.[2] Indeed, Alder and co-workers demonstrated in 1996 that ADCs, like NHCs, are isolable as the free carbenes.[23] Bis(diisopropylamino)carbene **3** (Figure 1), generated by deprotonation of the corresponding formamidinium ion with lithium diisopropylamide, was found to be stable in solution and could be sublimed without decomposition, although it exhibited higher sensitivity to air and moisture than free NHCs.[23] Less hindered bis(*N*-piperidyl)carbene (**4**)[24] and bis(diethylamino)carbene (**5**),[25] however, were observed to slowly dimerize to tetraazaethylenes in solution, and bis(dimethylamino)carbene (**6**)[26] decomposed to unidentified products at 0°C. Careful studies by Alder provided evidence that these carbene dimerizations require catalysis by protons[25] or possibly alkali metals associated with the deprotonating base.[27] This is in accordance with theoretical predictions of prohibitively high kinetic barriers for the uncatalyzed dimerization of even unhindered ADCs, despite a strong thermodynamic driving force for the process.[28] By contrast, dimerization of imidazolylidenes such as **1** is thermodynamically uphill even without steric bulk,[29] and imidazolinylidenes (e.g. **2**) have a substantially lower driving force for dimerization than ADCs.[28] Although dimerization can be disfavored by sufficient steric hindrance as in **3**,[23] the generally lower stability of ADCs relative to NHCs presents a potential pitfall in devising routes to metal-ADC complexes that involve generation of the free carbene.

Despite these stability issues, effort to develop the coordination chemistry of ADCs subsequent to Alder's reports have focused primarily on metalation routes that proceed via the free acyclic carbenes. Herrmann and co-workers demonstrated that Rh and Ir complexes of ADC **3** could be prepared in good yields by three such routes (Scheme 1):[30] (**A**) reaction of a metal precursor with pre-isolated ADC; (**B**) in situ deprotonation of a formamidinium salt with an internal base, in this case a bridging alkoxide; and (**C**) in situ ADC generation from an alcohol adduct. All three pathways mirror common NHC metalation procedures.[1–5] Variations on these routes have provided metal



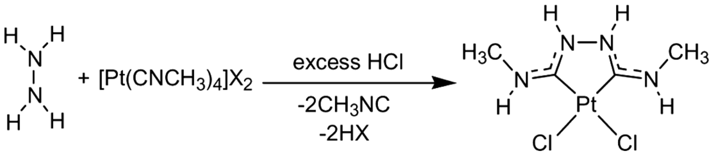
Scheme 1. Synthetic routes to acyclic diaminocarbene (ADC) complexes.

complexes of ADCs **4–10** (Figure 1),[31–34] but significant problems have appeared. In attempts to photolytically displace CO with ADCs at zerovalent metals, the free carbenes acted as reducing agents with concomitant formation of C-C coupled bis(amidinium) ions.[31] Reactions of ADCs with several Pd(II) precursors were reported to result in reduction to palladium black,[32] and free ADCs failed to displace phosphine ligands in Grubbs-type Ru alkylidene catalysts.[31] Finally, none of these synthetic methods has been extended to chelating bis(ADC) ligands, and the only reported attempt (by route **B**) was unsuccessful.[35] Fürstner and co-workers reported a preparative procedure that does not involve the free ADC, based on oxidative addition of 2-chloroamidinium salts to Pd(0) and Ni(0) complexes (route **D**).[36] This method afforded Pd(II) and Ni(II) complexes of several ADCs including **6**, which is highly unstable as the free carbene,[26] but it was not adaptable to other metals such as Rh, Co, and Fe.[36]

It is clear that more versatile synthetic routes are needed if ADCs are to be significantly developed as ancillary ligands. ADCs possess several unique attributes that make them worthy targets for use in catalysis. (1) They are stronger bases,[14,37] and thus intrinsically stronger σ-donors,[30] than NHCs. (2) Their larger N-C-N angles relative to NHCs place the N-substituents closer to the metal center,[30,31,33,34] potentially giving greater control of steric shielding and chirality. (3) Hindered rotation about the carbene C-N bonds is possible, as judged by experimental[23,38,39] and theoretical[40] estimates of rotation barriers as low as 13 kcal mol^{-1}, even for complexed ADCs.[38,39] This could lead to "flexible steric bulk"[41] that accommodates different catalytic reaction steps having different steric requirements at the same metal center. This Comment details our efforts to develop facile and generalizable routes to new, chelating ADC ligands.

CHUGAEV CARBENES: A STARTING POINT FOR "COVALENT SELF-ASSEMBLY" OF NEW BIS(ACYCLIC DIAMINOCARBENE) LIGANDS

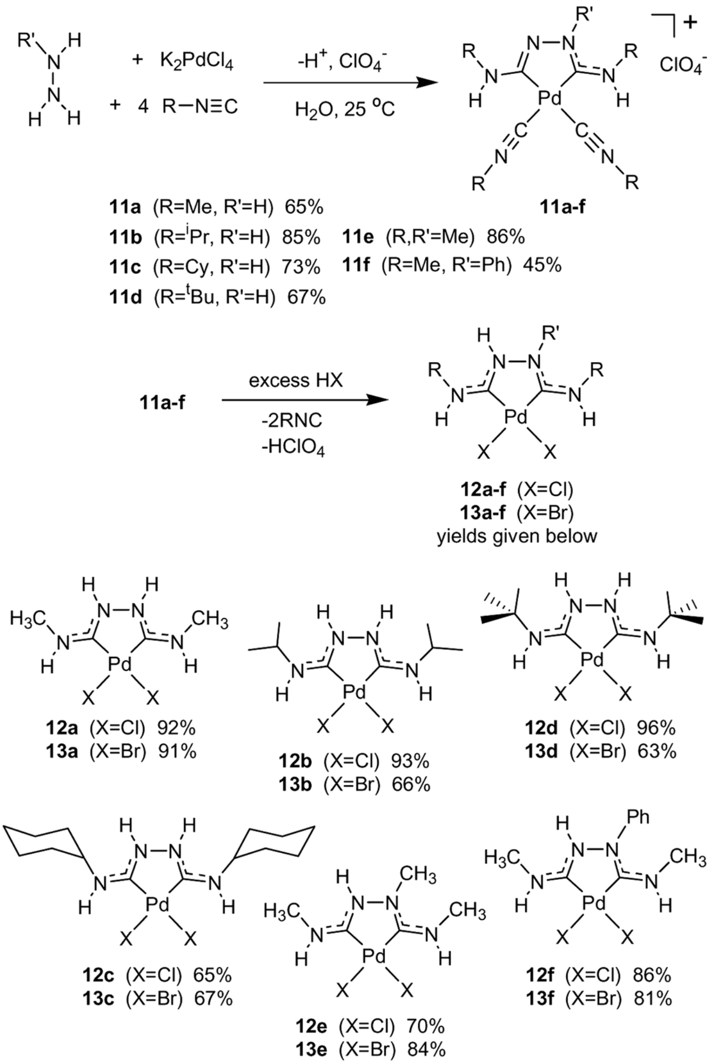
We have begun a research program to design structurally and electronically diverse diaminocarbene ligands, especially ADCs, without relying on the reactive free carbenes. As a starting point, we turned to a well-established but recently neglected synthetic route: [42] the 1,2-addition of protic amines to coordinated isocyanides (route E, Scheme 1).[43] The first reported metal complexes of ADCs were prepared this way[43–46] following Fischer's seminal carbene synthesis by an analogous conversion of a coordinated CO ligand.[47] We were intrigued by an even earlier example, prepared by Chugaev as early as 1915,[48,49] of a chelating bis(ADC) complex that formed spontaneously upon addition of hydrazine to a solution of platinum(II) and methyl isocyanide (Scheme 2). Although this carbene complex was not recognized as such until its characterization by Shaw[50]



Scheme 2. Chugaev's synthesis of the first metal carbene complex.

and Balch and Enemark[51] in 1970, it represents the first synthetic carbene complex, predating even the first Fischer carbenes.[47] The availability of isocyanide complexes of a wide variety of metals,[52–54] as well as reports of Chugaev-type bis(ADC) complexes prepared from isocyanide complexes of Pd^{II},[51,55] Fe^{II},[56] Ru^{II},[57] and Au^{III},[58] suggested to us that this ligand synthesis strategy could possibly be extended to a range of catalytically important metals. Additionally, similar reactions of amines with coordinated isocyanides have been reported to provide chelating bis(ADC) complexes with 4-membered,[57] 7-membered,[59] and 8-membered[59] chelate rings in addition to the 5-membered Chugaev-type chelates. A particularly appealing aspect of this chemistry is that the synthesis and metalation of a new chelating ligand can be accomplished in one step with no byproducts. This facile bis(ADC) synthesis can be regarded as a type of "covalent self-assembly." It resembles supramolecular self-assembly in that it involves simple components combining in a highly specific way, but it proceeds with formation of robust covalent bonds rather than reversible non-covalent interactions. We viewed such a synthetic strategy as potentially useful for generating structurally diverse arrays of new bis(ADC) ligands without multistep syntheses.

As a first test of the viability of "covalent self-assembly" as an approach to catalyst discovery, we sought to prepare a series of palladium complexes of Chugaev-type bis(ADC) ligands. Although a few Chugaev carbene complexes derived from substituted hydrazines had been previously reported,[56,58,60] and one example of a Pt^{II} Chugaev carbene complex derived from bulky *tert*-butyl isocyanide was known,[61] no general procedure for preparing a series of these chelate complexes with different substitution patterns and varying steric bulk had been reported for any metal. A modification of previously reported aqueous conditions[62] proved suitable for synthesizing the desired Pd bis(ADC) complexes from a set of four readily available alkyl isocyanides (R = Me, ^{i}Pr, Cy, ^{t}Bu).[63] Aqueous solutions of $[Pd(CNR)_4]Cl_2$, prepared by addition of isocyanide to tetrachloropalladate generated in situ from $PdCl_2$, converted swiftly to cationic complexes **11a–d** upon addition of hydrazine (Scheme 3). These "intermediate" salts, containing formally anionic carbene-imidoyl chelate ligands, likely result from deprotonation of the initially formed bis(ADC) ligand by excess hydrazine. Treatment of these compounds with 3 M HCl or HBr readily afforded the neutral dihalo bis(ADC) palladium complexes **12a–d** and **13a–d**. The same procedure led to trisubstituted palladium bis(ADC) complexes **12e,f** and



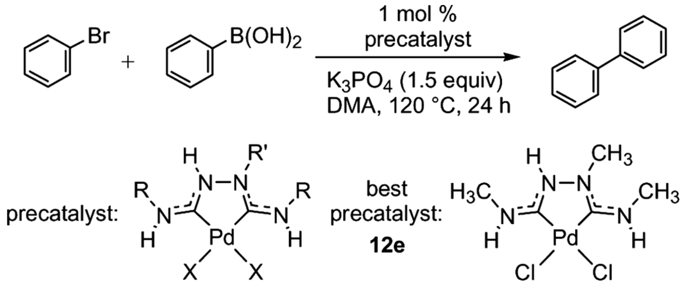
Scheme 3. General procedure for the synthesis of Chugaev-type palladium bis(ADC) complexes. Adapted from Refs. 63–65.

13e,f via intermediates **11e,f** when methyl isocyanide was used in combination with methyl or phenyl hydrazine.[63–65] Although **12a–f** and **13a–f** could be obtained in one pot by acidification of intermediates **11a–f** in situ, they were reproducibly pure only if the intermediate cations were isolated as the ClO_4^- salts and recrystallized. The only parameter that needed adjustment to obtain good to excellent yields (65–96%) was the amount of perchlorate added. Thus, a general, two-step benchtop procedure, proceeding in water and under air, allowed the preparation of an array of palladium bis(ADC) complexes with variation of the "terminal" carbene substituents (R), backbone substituent (R′), and dissociable halide ligand (X = Cl or Br). In comparison to the poorly soluble parent complexes **12a** and **13a**, the new bis(ADC) complexes with larger alkyl groups showed improved solubilities in polar organic solvents such as DMF, DMA, and CH_3CN.

Spectroscopic and structural data for Chugaev-type Pd bis(ADC) complexes **12a–f** and **13a–f** are consistent with electronic structures and donor abilities similar to those of known diaminocarbenes. ^{13}C NMR chemical shifts of the carbene carbons are in the fairly narrow range 176–183 ppm. This is more downfield than the values of 157–159 ppm reported for the closest NHC analogues, a series of chelated bis(imidazolylidene) palladium dichloride complexes,[66] but upfield of the range of 194–227 ppm found in Pd complexes of the more basic monodentate ADCs.[32,36] This suggests that the donor abilities of these Chugaev-type bis(ADC) ligands are likely intermediate between those of common NHC and ADC ligands. The Pd-$C_{carbene}$ distances of 1.96–1.99 Å are within the range observed for comparable bis(NHC)PdX_2 complexes.[66,67]

The next goal was to test whether the easily accomplished variation of bis(ADC) ligand structure could be used to optimize activity in a catalytic reaction. The Suzuki-Miyaura cross-coupling reaction was judged suitable for this purpose, as NHC-ligated palladium catalysts had shown some of the best reported activities and substrate scope for this type of reaction.[41,68] An initial study of cyclohexyl-substituted palladium bis(ADC) precatalyst **12c** revealed good activity for Suzuki-Miyaura couplings of a range of aryl bromides with aryl boronic acids, but poor to no activity for aryl chloride couplings.[69] Given that activities in these reactions are often highly sensitive to small changes in catalyst structure, we reasoned that screening a "library" of ten bis(ADC) palladium complexes would afford a higher probability of identifying a synthetically useful catalyst. Examination of **12a–e** and **13a–e** as precatalysts in the prototypical Suzuki-Miyaura coupling of bromobenzene with phenylboronic acid revealed substantial changes in activity upon variation of ligand substituents, with yields ranging from 31% for di(*tert*-butyl)-substituted **13d** to 95% for trimethyl-substituted **12e** (Table 1).[63] The

Table 1. Optimization of catalytic Suzuki-Miyaura cross-coupling activity by screening a "library" of Pd bis(ADC) precatalysts. Adapted from Ref. 63.

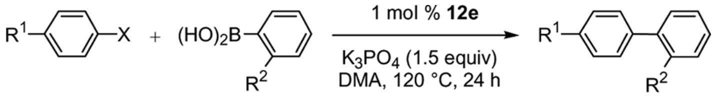


Entry	Precatalyst	R	R′	X	Yield (%)^{a}
1	**12a**	Me	H	Cl	74
2	**13a**	Me	H	Br	75
3	**12b**	^{i}Pr	H	Cl	80
4	**13b**	^{i}Pr	H	Br	81
5	**12c**	Cy	H	Cl	84
6	**13c**	Cy	H	Br	78
7	**12d**	^{t}Bu	H	Cl	34
8	**13d**	^{t}Bu	H	Br	31
9	**12e**	Me	Me	Cl	95
10	**13e**	Me	Me	Br	92

^{a}Yields determined by ^{1}H NMR.

changes in activity did not correlate with ligand sterics and were best explained as a result of subtle electronic effects, with the trisubstituted bis(ADC) ligand of **12e** and **13e** proposed to be the most strongly donating of these ligands. Optimized catalyst **12e** showed broad functional group tolerance in coupling of aryl bromides (Table 2), similar to **12c**,[69] and substantially better activity with activated aryl chlorides, but it still showed very poor activity with electron-rich aryl chlorides. The use of chelating ligands was probably a limiting factor in catalyst activity given that the best systems, which show high activities for aryl chlorides and can operate at lower temperatures, typically utilize monodentate phosphines or NHCs in a 1:1 ligand to Pd ratio.[41,68,70] Nevertheless, **12c** and **13e** are among a very few catalysts reported to retain high activity in Suzuki-Miyaura reactions performed under air in wet

Table 2. Functional group tolerance and air/moisture tolerance of Suzuki-Miyaura cross-coupling reactions with optimized catalyst **12e**. Adapted from Ref. 63.



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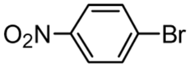
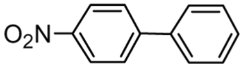
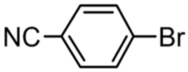
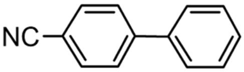
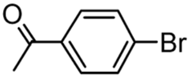
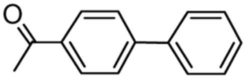
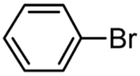
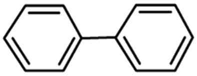
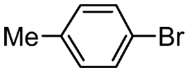
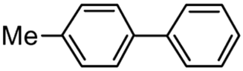
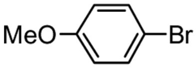
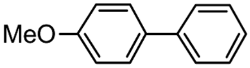
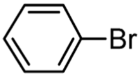
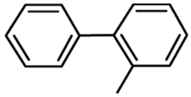
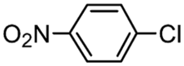
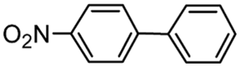
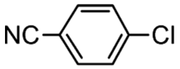
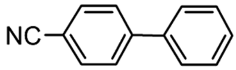
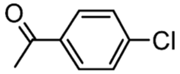
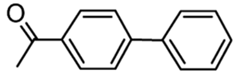
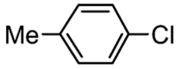
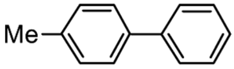
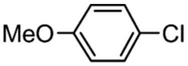
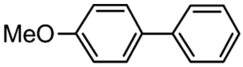
	H		N_2/air	92 (92)/90
	H		N_2/air	97/97
	H		N_2/air	98 (91)/98
	H		N_2/air	97/92
	H		N_2/air	98/76
	H		N_2/air	89/62
	Me		N_2/air	87/74
	H		N_2	92
	H		N_2	93
	H		N_2	37

(*Continued*)

Table 2. Continued

Aryl halide	R^2	Product	Atmosphere	Yield (%)[a]
	H		N_2	4
	H		N_2	4

[a]Yields determined by ^{1}H NMR; isolated yields in parentheses.

solvent.[63,69] The chelating bis(carbene) ligands may guard against the formation of oxidation-sensitive, low-coordinated intermediates, somewhat offsetting the disadvantage of lower activity and substrate scope.

While this work was in progress, two reports of organometallic catalysis promoted by monodentate ADC ligands appeared from the research groups of Fürstner[36] and Thadani.[71] The use of ADCs as ligands in Pd-catalyzed Suzuki-Miyaura,[71] Sonogashira,[71] and Heck[36] coupling reactions, as well as Ni-catalyzed Kumada coupling reactions,[36] resulted in catalytic activities that were in several cases comparable to or better than the corresponding NHC-based systems. Along with Fürstner's study,[36] our initial communication[69] of a palladium Suzuki-Miyaura cross-coupling catalyst ligated by a Chugaev-type bis(ADC) was one of the first two reports of the use of ADC ligands in catalysis.

An unusual aspect of Chugaev-type bis(ADC) ligands is the presence of acidic hydrogens on the "internal" nitrogen atoms of the chelate ring.[72] Treatment of Suzuki-Miyaura coupling precatalyst **13e** with 10 equiv of K_3PO_4 in DMF-d_7 resulted in clean formation of a product with only two N-H groups as monitored by ^{1}H NMR (Figure 2), consistent with monodeprotonation at the internal position.[65] Thus, the base required for Suzuki-Miyaura cross-coupling activity converts the bis(ADC) ligand into its anionic form under catalytic conditions, suggesting an anionic Pd^0 species as a key intermediate in the catalytic cycle. Similar anionic Pd^0 species have been implicated in Heck reactions.[73]

Although the aqueous synthetic procedure described above was generally useful for preparing bis(ADC)s from alkyl isocyanides and

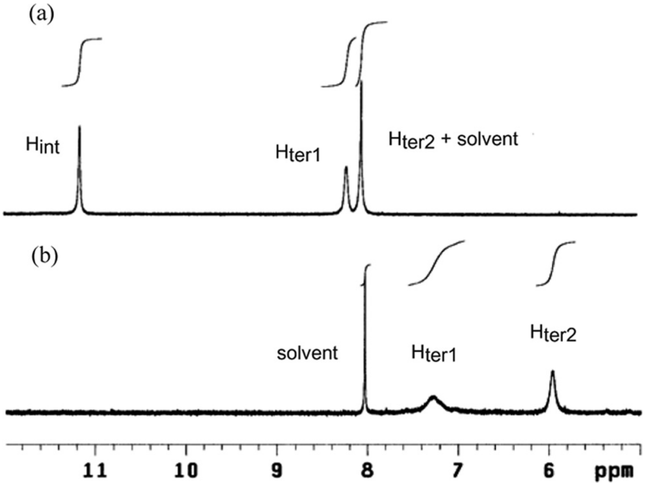
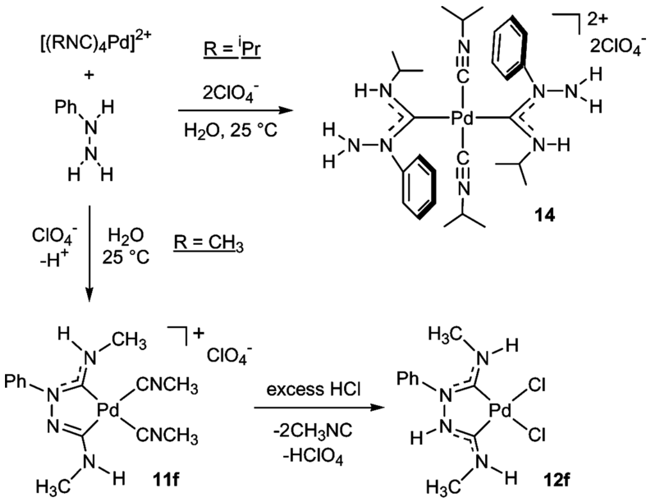


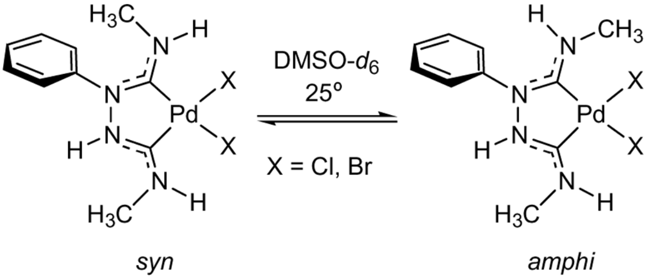
Figure 2. Partial ^1H NMR spectrum of **13e** in DMF-d_7 (a) before addition of base, and (b) immediately after addition of 10 equiv K_3PO_4. H_{int} and H_{ter} designate internal and terminal N-H groups, respectively.

unsubstituted or monosubstituted hydrazines, attempts to extend this procedure to the synthesis of bis(ADC) ligands that project steric bulk toward the metal center were unsuccessful. This is illustrated by the reaction of phenyl hydrazine with $[Pd(CNR)_4]^{2+}$ generated in situ from methyl or isopropyl isocyanide (Scheme 4).[64] When methyl isocyanide was employed, the reaction proceeded to the neutral bis(ADC) complex **12f** as in other cases. However, the use of bulkier isopropyl isocyanide led to isolation of complex **14**, which contains two monodentate ADC ligands resulting from nucleophilic attack of phenyl hydrazine on a single isocyanide. The monodentate ADC ligand of **14** can be regarded as an intermediate in the formation of a Chugaev-type bis(ADC): attack of the pendent hydrazino group on a neighboring isocyanide would complete the cyclization to the bis(ADC) chelate. Evidently, this second step is sterically prohibited upon changing the isocyanide methyl substituent to a moderately larger isopropyl group. An *amphi* configuration of the ADC, which would direct one isopropyl group toward the Pd center, would likely result if the bis(ADC) were formed, given that this geometry is seen in the deprotonated forms of trisubstituted Chugaev carbene ligands.[58,62] In fact, splitting of the ^{13}C NMR signals of the methyl



Scheme 4. Sterically controlled synthesis of monodentate versus chelating acyclic carbene ligands. Adapted from Ref. [64].

and phenyl groups of bis(ADC) ligands of **12f** and **13f** was consistent with the presence of both *syn* and *amphi* conformations in solution (Scheme 5),[65] suggesting that steric pressure in the *syn* form leads to equilibration by rotation about the carbene C-N bond. Attempts to form bis(ADC) ligands from 1,2-disubstituted hydrazines and alkyl isocyanides also failed,[65] consistent with high sensitivity to sterics in these reactions.

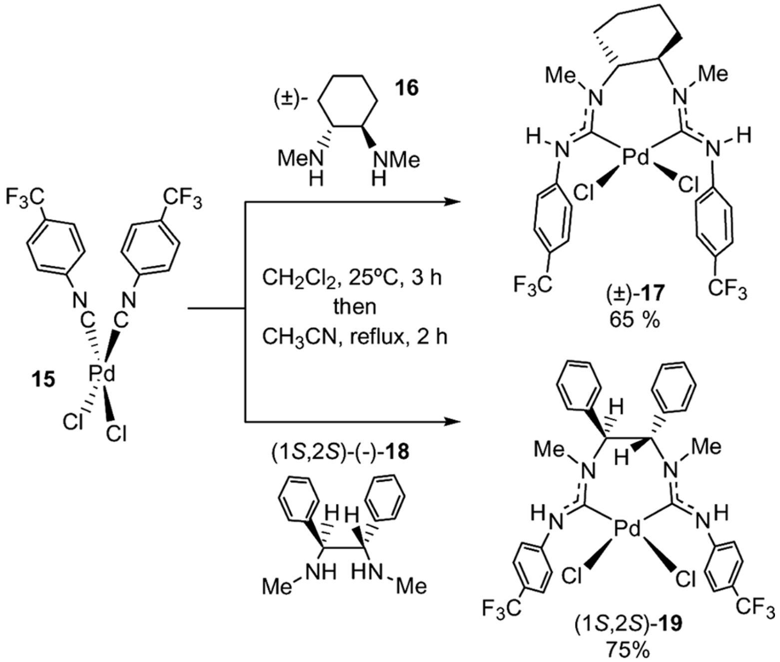


Scheme 5. Proposed solution equilibrium between two bis(ADC) conformations in **12f** (X = Cl) and **13f** (X = Br).

PREPARATION OF CHIRAL BIS(ACYCLIC DIAMINOCARBENE) LIGANDS

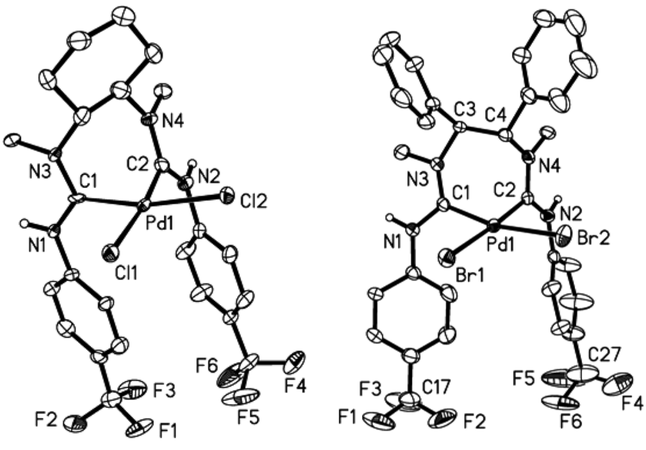
To gain access to more structurally elaborate bis(ADC) ligands, including chiral examples, we turned to aryl isocyanide synthons. Aryl isocyanides with a variety of substitution patterns are readily synthesized in one or two steps,[74] potentially allowing wide variation of steric and electronic properties in the subsequently prepared ADC ligands. Trifluoromethyl-substituted bis(aryl isocyanide) palladium dichloride complex **15** (Scheme 6) was prepared as an initial synthon for "covalent self-assembly" of novel bis(ADC) ligands from a variety of diamine backbones.[75] It was anticipated that the electron-withdrawing $-CF_3$ group would boost the electrophilicity of the isocyanide carbon, increasing the driving force for carbene formation and possibly overcoming some steric strain in the resulting chelate ligand.

Upon treatment of **15** with a racemic sample of commercially available N,N′-dimethyl-1,2-cyclohexanediamine (**16**) at room temperature,



Scheme 6. One-step assembly of chiral palladium bis(ADC) complexes.

2chiral bis(ADC) complex (±)-**17** was cleanly formed (Scheme 6).[75] In addition to providing the first example of a chiral ADC ligand, this facile, one-step procedure was remarkable in that it was scalable to >600 mg syntheses and produced no byproducts. The X-ray structure of (±)-**17** revealed a C_1-symmetric geometry for the chiral chelating ligand (Figure 3), with a 7-membered twist-boat chelate ring accommodating near perfect planarity of the N-substituents at each ADC unit. Notably, the C_2 symmetry of the diamine precursor is lost upon conversion to a bis(ADC). Density functional theory calculations showed that C_2-symmetric conformations of the bis(ADC) ligand of (±)-**17** are enthalpically disfavored by at least 18 kcal mol^{-1} relative to the C_1 geometry, evidently due to increased strain in the chelate ring and attendant disruption of carbon-nitrogen π-conjugation. Thus, a strong driving force for planar ADC units appears to be the primary determinant of chelate geometry. The same one-step synthetic procedure was also used to prepare the two resolved enantiomeric forms of **17** as well as a second chiral bis(ADC) complex (1S,2S)-**19** (Scheme 6), the latter using the commercially available resolved diamine (1S,2S)-(-)-**18** to form the chiral backbone.[76] The bis(ADC) ligand of (1S,2S)-**19** creates a more asymmetric environment at palladium compared with **17**, due to the phenyl



(a) (b)

Figure 3. X-ray crystal structures of chiral palladium bis(ADC) complexes (±)-**17**(**a**) and the dibromide derivative of (1S,2S)-**19** (**b**), with 50% probability ellipsoids. Adapted from data in Refs. 75 and 76.

ring on C3 that protrudes over the coordination plane (Figure 3). This has important consequences for asymmetric catalysis (vide infra).

BIS(ADC) DONOR PROPERTIES AND ELECTROPHILIC CATALYSIS

In order to assess the suitability of the new bis(ADC) ligands for catalysis, it was of interest to compare their donor properties with those of other bidentate ligands.

Whereas most studies of this type have used CO as an IR spectroscopic probe ligand,[15,17] we hypothesized that isoelectronic methyl isocyanide (MeNC) would provide a more useful assessment of relative σ-donor strengths. Alkyl isocyanides are stronger σ-donors and weaker π-acceptors than CO, so the increase in ν(CN) upon binding to Pd^{II} should reflect stabilization of the weakly σ^* HOMO, i.e. σ-donation to Pd^{II}, with no significant contribution from π-backbonding. Analysis of the shift in ν(CN) relative to free MeNC ($\Delta\nu$) for a series of palladium methyl isocyanide complexes (Figure 4) containing a new chiral bis(ADC) (**20**), the most common type of bis(NHC) (**21**),[77] and the common bis(phosphine) DPPE (**22**) provided a ranking of the σ-donor

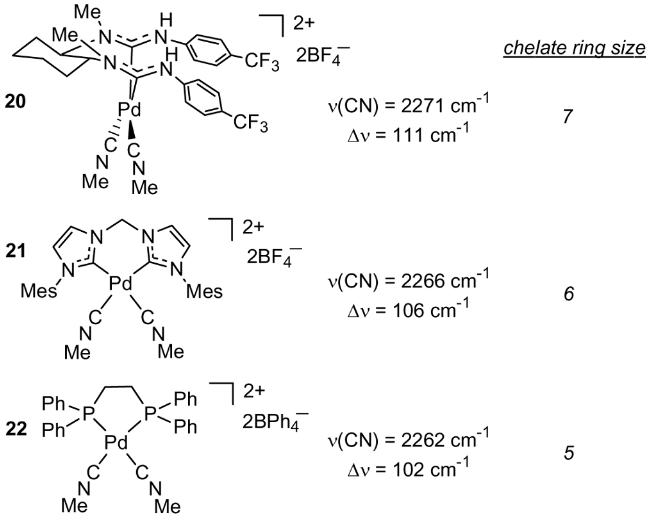
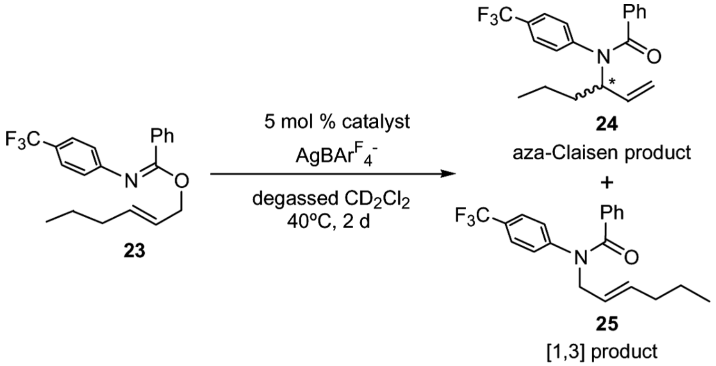


Figure 4. Comparison of σ-donor properties of different chelate ligands using MeNC as an IR spectroscopic probe ligand. $\Delta\nu$ is quoted relative to ν(CN) of free MeNC (2160 cm^{-1}). Adapted from Ref. 76.

abilities of the different chelate ligands.[76] A larger $\Delta\nu$ indicates stronger σ-donation from MeNC, induced by weaker σ-donation from the chelate ligand in accordance with the *trans* influence. The bis(ADC) was identified as the weakest donor of the series, with the bis(NHC) intermediate in donicity and the bis(phosphine) the strongest donor. This is in contrast to previous studies identifying NHCs as stronger donors than phosphines.[10,15] However, it is not clear to what extent this ranking reflects differences in the intrinsic donor abilities of the ligands given that the three ligands have different chelate ring sizes. The seven-membered chelate ring of the bis(ADC) ligand results in a constrained bite angle of 82.3(2)° that could prevent optimal orbital overlap,[75] whereas the smaller chelate rings of the bis(NHC) and the bis(phosphine) should allow bite angles closer to the ideal 90°. Nevertheless, this study shows that the *effective* donor strength of the bis(ADC) ligand is lower than those of common bis(NHC) and bis(phosphine) ligand types.

The relatively low effective donor strength of the seven-membered chelate bis(ADC) suggested that this type of ligand could engender electrophilic reactivity at the metal center. Thus, palladium bis(ADC) complexes were evaluated as catalysts for aza-Claisen rearrangements, a reaction type that involves electrophilic activation of a carbon-carbon double bond.[78] Palladium bis(ADC) precatalyst (±)-**17** was activated with one or more equivalents of a silver salt to provide a catalytically active cationic species for the rearrangement of the benchmark allylic benzimidate **23** (Scheme 7, Table 3).[76] The highly sensitive nature of this reaction was evident in that none of the desired product was obtained



Scheme 7. Palladium-catalyzed aza-Claisen rearrangement of benzimidate **23**.

Table 3. Results of palladium-catalyzed aza-Claisen rearrangements of **23**. Selected from data in Ref. 76.

Entry	Catalyst	$AgBAr^F{}_4$[a] (%)	Yield (%)[b] **24**	**25**
1	(±)-**17**	5 mol	70 (54)	14[c]
2	(±)-**17**	10 mol	6	51[c]
3	$(DIMes^{Me})PdBr_2$ (**26**)[d]	5 mol	6	28[c]
4	(1*R*,2*R*)-**17**	5 mol	50 (41) 30% ee (S)-(+)	14 (12)[c]
5	(1*S*,2*S*)-**17**	5 mol	36 (24) 32% ee (R)-(−)	14[c]
6	(1*S*,2*S*)-**19**	5 mol	34 (33) 59% ee (S)-(+)	11[c]

[a] $[BAr^F{}_4]^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

[b] Yields determined by ^{19}F NMR; isolated yields in parentheses.

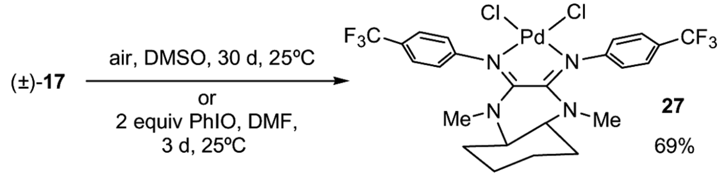
[c] A significant amount of the amide elimination product was also detected, typically 10–20%.

[d] $DIMes^{Me}$ = 1,1′-dimesityl-3,3′-methylenediimidazol-2,2′-diylidene; see compound **21**.

when coordinating anions or coordinating solvents (e.g. THF) were used. Good yields (70%) of the desired rearrangement product **24** were obtained only when 1 equiv of the non-coordinating tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr^{F-}_4) anion was used to activate the catalyst (Table 3, entry 1); the undesired [1,3] rearrangement product **25** was favored when two equiv of $AgBAr^F{}_4$ were employed (entry 2). Notably, an analogous bis(NHC)Pd precatalyst **26** was ineffective for the rearrangement under identical conditions (entry 3), demonstrating that the stereoelectronic properties of the bis(ADC) ligands are quite distinct. Enantioselective aza-Claisen rearrangements were also accomplished. The two resolved enantiomers of diaminocyclohexane-derived bis(ADC) complex **17** gave nearly equal and opposite enantiomeric excesses (ee's) of 30–32% (entries 4,5), and the more conspicuously asymmetric precatalyst (1S,2S)-**19** gave a much improved enantioselectivity of 59% ee (entry 6). In addition to providing an usual example of electrophilic catalysis promoted by diaminocarbene ligands, this study represents the first use of chiral ADC ligands in enantioselective catalysis. Importantly, it appears possible to systematically tune enantioselectivity by rational modification of the bis(ADC) ligand backbone.

STABILITY ISSUES OF BIS(ADC) LIGANDS

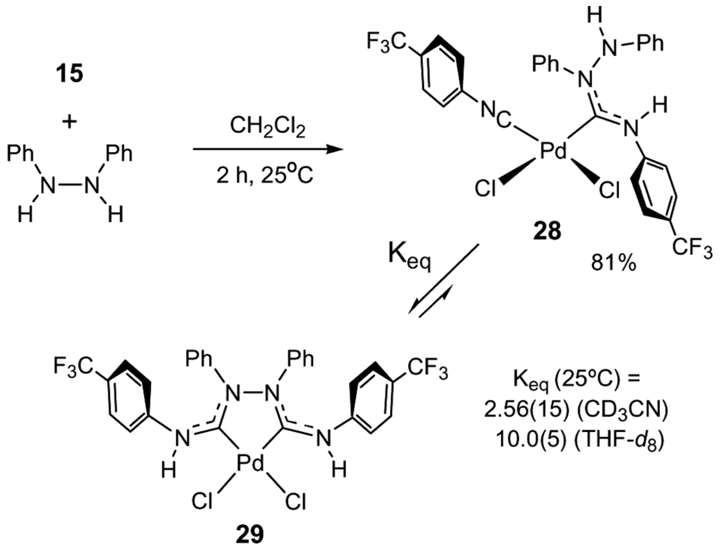
Although the "self-assembled" bis(ADC) ligands clearly possessed sufficient stability to support some types of organometallic catalysis,



Scheme 8. Oxidation of a palladium bis(ADC) complex to a bis(amidine) complex.

two observations pointed to potential limitations that might need to be addressed. First, a sample of bis(ADC) palladium complex (±)-**17** that was left in DMSO under air for ~1 month converted into the red-orange bis(amidine) complex **27** (Scheme 8).[75] The N-bound bis(amidine) chelate results from a two-electron oxidation of the bis(ADC) ligand, accompanied by coupling of the carbene carbons and formal loss of two hydrogen atoms from the NH groups. The same oxidation of (±)-**17** was effected by the oxygen surrogate iodosobenzene (PhIO). No carbene coupling to give either an oxidized bis(amidinium) ion or an unoxidized tetraazaethylene was observed under any conditions, suggesting that oxidation precedes the coupling reaction. An intriguing possibility is the intermediacy of Pd^{IV} in this transformation.[79] The degradation of the NH groups in this unprecedented oxidative carbene coupling reaction implicates these moieties as a potential "Achilles' heel" in these ligands. Hence, alkylation of NH groups is a future goal for attaining more stable bis(ADC) ligands. In degassed DMSO solutions, (±)-**17** was found to be thermally stable up to 80°C.[75] It should also be noted that Chugaev-type bis(ADC) ligands are quite stable toward oxidation, remaining intact upon oxidation of bound Pt(II) to Pt(IV).[80]

A second potential problem with bis(ADC) ligands became apparent upon discovery of a palladium bis(ADC) complex that exhibited reversible chelate ring opening.[81] Addition of hydrazobenzene to palladium bis(isocyanide) synthon **15** did not directly afford a bis(ADC) complex, but instead led to complex **28** containing a monodentate hydrazinocarbene and an unreacted isocyanide (Scheme 9). Complex **28** partially converted to the sterically crowded Chugaev-type bis(ADC) complex **29** over time. Both complexes **28** and **29** were isolated and structurally characterized, but they were found to be in equilibrium in CD_3CN or THF-d_8 solutions. Steric strain in the bis(ADC) of **29**, evident in expanded NCN angles and close contacts between aryl *ipso* carbons, was invoked to account for the reversibility of the chelate-forming nucleophilic addition. A similar type of



Scheme 9. Synthesis and reversible chelate ring opening of a sterically crowded bis(ADC) complex. Adapted from Ref. 81.

chelate ring opening was previously invoked to explain the mobility of substituents in complexes of strained 4-membered chelate bis(ADC) complexes.[82] A van't Hoff analysis of the equilibrium, in combination with DFT calculations, provided an estimate of $16\,\mathrm{kcal\,mol^{-1}}$ for the strain energy present in the bis(ADC) ligand of **29**. This value can be considered an approximate upper limit on the amount of chelate ring and steric strain that can be accommodated in "covalent self-assembly" of a bis(ADC) ligand. It is notable that the strong enthalpic driving force derived from forming a new carbon-nitrogen bond can overcome both an unfavorable reaction entropy and a significant amount of ligand strain, suggesting that a wide range of bis(ADC) structures are attainable without the problem of reversible chelate ring opening seen in **29**.

SUMMARY AND OUTLOOK

Acyclic diaminocarbene ligands (ADCs) are a largely unexplored frontier in the design of ancillary ligands for catalysis. Their unique attributes, including higher intrinsic basicity relative to NHCs, render them attractive synthetic targets, but the substantially lower stabilities of the free carbenes necessitate new synthetic routes that circumvent formation of the free ADCs. This Comment has shown that "covalent self-assembly" of bis(ADC) ligands by nucleophilic addition of diamines to metal-bound isocyanides is one synthetic approach that could provide access to a range of structurally diverse bis(ADC) ligands, at least in the case of palladium.

It was demonstrated that a small "library" of 12 palladium complexes of bis(ADC) complexes containing 5-membered chelate rings could be generated by a simple, generalizable, aqueous reaction from various alkyl isocyanide and hydrazine precursors. Screening of this "library" allowed identification of moderately active, air-tolerant Suzuki-Miyaura cross-coupling catalysts. However, the high sensitivity of alkyl isocyanide-based reactions to changes in steric bulk prompted a shift to aryl isocyanide synthons. A trifluoromethyl-substituted palladium bis(aryl isocyanide) precursor enabled facile one-step assembly of the first chiral bis(ADC) ligands upon reaction with commercially available chiral diamines. The unique stereoelectronic properties of these chiral ligands make them suitable for supporting electrophilic catalytic reactions at palladium, as shown by promising activity in the aza-Claisen rearrangement. Initial studies showed that enantiomeric excesses in this reaction can be tuned up to 59% ee by rational modification of the ligand backbone.

Although some stability issues have been identified, the outlook for bis(ADC) ligands prepared from isocyanides by "covalent self-assembly" is promising. Due to the favorable thermodynamics of forming new carbon-nitrogen bonds, the bis(ADC) ligands can tolerate a substantial amount of steric or chelate ring strain. The availability of a variety of chiral diamines, coupled with the synthetic accessibility of arylisocyanides with a range of substitution patterns, opens the door to a structurally and electronically diverse new class of bis(carbene) ligands that could potentially be prepared in a "high throughput" fashion without time-consuming multistep syntheses. Extensions of this ligand design strategy to metals other than palladium will provide stimulating avenues for future research.

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