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Synthesis and characterization of κ-2-*bis*-*N*-heterocyclic carbene rhodium(I) catalysts: Application in enantioselective arylboronic acid addition to cyclohex-2-enones

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ABSTRACT

This manuscript describes the synthesis and characterization of new derivatives of di-*N*-heterocyclic carbene (diNHC) ligands derived from trans-9,10-dihydro-9,10-ethanoanthracene-11,12-diylmethanediyl (DEAM) and trans-9,10-dihydro-9,10-ethanoanthracene-11,12-diyl (DEA). Synthesized as the diazolium salts, the new ligands are employed, in conjunction with known derivatives, to examine specific properties than influence the chiral induction in rhodium-catalyzed arylboronic acid addition to cyclohex-2-enones. Three properties of the diNHC ligands are modified and include: 1) the size and composition of the N-heterocyclic substituent (Me, ^{i}Pr, Bn, $CHPh_2$, *o*-MeBn, and *R*-CHMePh), 2) the type of N-heterocycle (benzimidazole versus imidazole), and 3) the size of the chiral pocket (DEAM versus DEA). Results from the catalytic studies indicate the DEAM ligand, which contains an extra CH_2 group compared to DEA, is too flexible to induce enantiomeric excess. The DEA derivatives containing an imidazole or benzimidazole provide distinctly different results despite relatively small differences between the heterocyclic carbene donors. An unexpected source of chiral induction is rationalized using results from catalytic data (% e.e.) and complemented by X-ray structural data and DFT calculations.

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1. Introduction

Enantiopure di-*N*-heterocyclic carbene ligands (diNHCs) are emerging as effective chiral auxiliaries in metal catalyzed asymmetric catalysis [1–25]. However, few design principles exist to guide chiral diNHC catalyst engineering. Representations of a chiral metal ion environment, such as Knowles' quadrant model [26,27] and Trost's version [28], serve as good approximations, especially for asymmetric alkene hydrogenation [29] and allylic alkylation [30,31]. These models fit well for chiral diphosphine ligands, but in some cases they do not, resulting in some modifications to the model [32–35]. Advances in computational techniques [36–40] may ultimately permit catalyst designs that correctly select for a specific product enantiomer prior to any laboratory investigation. The problem is that small energetic differences of 1–2 kcal/mol in the diastereo- or enantio-determining transition states lead to large changes in % enantiomeric excess (% e.e.) [41]. Predicting or designing ligand and catalyst features, that discriminate within such a small energy range is difficult. After factoring in the additional variables of temperature, additives, and solvent choice, it is not surprising that trial and error remains the common method for discovery.

Providing some guidance regarding NHC [42] ligand steric influence on the metal ion coordination sphere is the $\%V_{buried}$ model, but this model applies to monodentate ligands [43,44]. In addition, the relative σ-donation strength of NHCs, and thus the M-NHC bond strength, is becoming clearer from both experiment and computational results [45–53]. Despite possessing a strong M-NHC bond, NHCs can reductively eliminate from corresponding metal-hydrido and alkyl species to give imidazolium salts [18,54–63]. A systematic study by Hermann *et al.* provides some insight into the effects of achiral diNHC ligand bridge length, N-substituent, and heterocycle composition on Rh(I) catalyzed hydrosilylation of ketones [64]. Considering the limited models available for designing effective chiral catalysts using diNHCs, it is important that a chosen ligand platform permit rapid and facile modification. Our previously reported DEAM (*trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-diylmethanediyl) and DEA (*trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-diyl) diNHC ligands provide opportunities to easily modify steric and electron-donating features (Fig. 1) [17,18,65–67]. In addition, the DEAM ligand provides an opportunity to link the two NHC heterocycles through the R groups to create chiral dicarbene cyclophane ligands [17].

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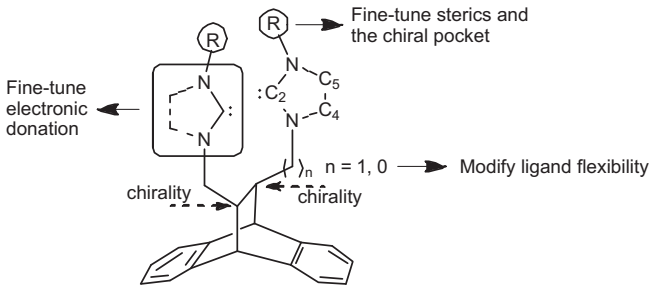


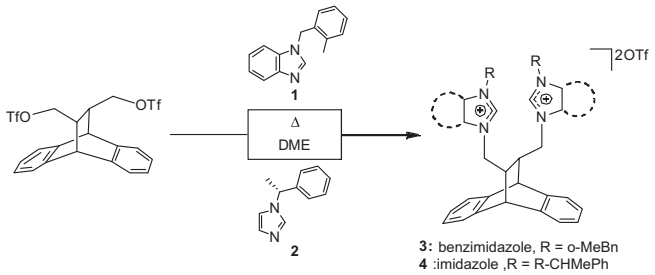
Fig. 1. Parameters of optimization for the dihydroethanoanthracene diNHC backbone.

Probing the parameters depicted in Fig. 1 requires a suitable benchmark reaction. Shi *et al.* report the 1,4-conjugate addition of arylboronic acids to cyclic-enones with a chiral BINAM derived diNHC ligand and Pd(II) as the metal [4]. The catalyst provides good to excellent product % e.e.s ranging from 32 to 97%. Rhodium-phosphine complexes are also common catalysts for this transformation, but often require elevated temperatures [68–74]. In this report, we present evidence indicating the identity of the *N*-heterocycle significantly influences the chiral induction in enantioselective diNHC rhodium-catalyzed arylboronic acid addition to cyclohex-2-enones. Also, adding to the library [17,18,65–67] of DEAM and DEA ligands, we now report four new C_2-symmetric diazolium salt precursors and one isolable free chiral diNHC.

2. Results and discussion

2.1. Synthesis of diimidazolium and dibenzimidazolium ligand precursors

The general procedure for preparing diazolium salt precursors of the DEAM ligand involves direct substitution at the methylene carbon. Scheme 1 is a generic synthetic methodology for the preparation of C_2-symmetric DEAM diazolium triflate salts [17,18,65,66]. The synthesis of the diazolium salts (*S,S*)-*trans*-1,1′-(9,10-dihydro-9,10-ethanoanthracene-11,12-diyldimethanediyl)*bis*(3-(2-methylphenyl-1-benzyl)-1H-benzimidazol-3-ium)bis(triflouromethansulfonate) [DEAM-*o*-MBBI][OTf]$_2$ (**3**) and (*S,S,R,R*)-*trans*-1,1′-(9,10-dihydro-9,10-ethanoanthracene-11,12-diyldimethanediyl)*bis*(3-(*R*-1-phenylethane)-1H-imidazol-3-ium) [DEAM-PEI][OTf]$_2$ (**4**) involves treating two equivalents of 1-benzyl(2-methylphenyl)-benzimidazole (**1**) or *R*-1-(1-phenylethyl)-1H-imidazole (**2**) [75] with an equivalent of (*S,S*)-*trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-diyldimethanediyl *bis*(trifluoromethanesulfonate) [76] in refluxing DME. After 1 h the reactions are complete. In a nitrogen-filled glovebox, evaporation of the solvent in vacuo provides both salts **3** and **4** as off-white, crunchy, hygroscopic solids in 93 and 80% yield, respectively. A combination of 1D and 2D-NMR spectroscopic techniques and combustion analysis confirms the purity and identity of **3** and **4** (see supporting information).

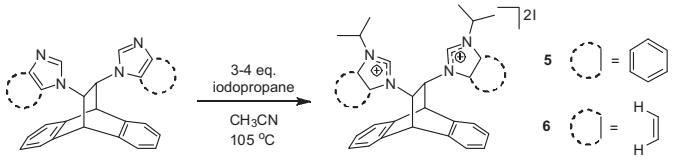


Scheme 1. General synthetic scheme for DEAM salts 3 (benzimidazole, R = *o*-MeBn) and 4 (imidazole, R = *R*-CHMePh).

The ^{1}H NMR spectrum of **3** reveals a resonance attributable to the C2 proton at 9.65 ppm (see Fig. 1 for atom notation). Other diagnostic signals include a singlet at 2.45 ppm for the *o*-methyl protons, a singlet for the bridgehead proton at 4.42 ppm, and a third singlet for the bridge proton at 2.77 ppm. Presumably, the dihedral angle between the bridgehead and bridge proton is ~90° because no coupling occurs, which is in agreement with the Karplus curve [77]. A 2D HETCOR experiment permits the assignment of the other aliphatic carbon resonances (see supporting information).

The ^{1}H NMR spectrum of **4** confirms its identity. The spectrum exhibits the recognizable singlet C2 proton resonance at 9.04 ppm. The methyl and methine protons of the chiral *N*-alkyl fragment resonate at 1.92 (d, J = 5 Hz) and 5.78 ppm (q, J = 10 Hz), respectively. The bridgehead proton resonates at 4.05 ppm as a singlet which is consistent with previously reported azolium salts [18]. Subjecting **4** to a 2D HETCOR experiment permits the assignment of the other aliphatic carbon signals. Precluding water from the synthesis of **4** is important because the *N*-alkyl group is susceptible to hydrolysis. In the presence of a small amount of water, partial epimerization of the *N*-alkyl chiral center occurs, resulting in multiple diastereomers (confirmed by ^{1}H NMR).

Preparation of the DEA diazolium diiodide salts (*R,R*)-*trans*-1,1′-(9,10-dihydro-9,10-ethanoanthracene-11,12-diyl)*bis*(3-*iso*propyl-1*H*-benzimidazol-3-ium) diiodide [DEA-IBI](I)$_2$ (**5**) and (azole = benzimidazole) and (*R,R*)-*trans*-1,1′-(9,10-dihydro-9,10-ethanoanthracene-11,12-diyl)*bis*(3-*iso*propyl-1*H*-imidazol-3-ium) diiodide [DEA-II][I]$_2$ (**6**) (azole = imidazole) requires treating excess 2-iodopropane with one equivalent of the corresponding 1,1′-(9,10-dihydro-9,10-ethanoanthracene-11,12-diyl)di(1H-azole) [67] in CH_3CN at 105 °C (Scheme 2). The ^{1}H and ^{13}C{^{1}H} NMR spectra and combustion analysis confirm the identity and purity of **5** and **6**.



Scheme 2. General synthesis of DEA azolium salts 5 (azole = benzimidazole) and 6 (azole = imidazole).

The ^{1}H NMR spectrum of **5** in $CDCl_3$ indicates the compound is C_2-symmetric and reveals a diagnostic C2 proton resonance at 9.31 ppm. This is 0.55 ppm downfield of the same proton resonance in **6**. Changing the *N*-heterocycle composition at positions C4 and C5 changes the electron-donation properties at the C2 carbon of the corresponding carbene [51–53]. The 0.55 ppm shift in location of the C2 proton resonance between **5** and **6** may reflect this difference; the more electron-withdrawing benzimidazole moiety deshields the C2 proton.

The ^{1}H NMR spectrum of **6** has similar features to **5** including a downfield resonance for the C2 proton at 8.76 ppm. Characteristic resonances in the ^{13}C{^{1}H} NMR spectrum include one at 138.8 ppm for the C2 carbon, two at 22.2 and 22.0 ppm for the *iso*propyl-methyl carbons and one at 52.5 ppm for the *iso*propyl methine carbon.

2.2. Synthesis of the free di-N-heterocyclic carbene 7

It is useful to have access to the corresponding free dicarbene derivative of these ligands for the purpose of in situ catalyst generation. The synthesis of the free diNHC (+/−) *trans*-1,1′-(9,10-dihydro-9,10-ethanoanthracene-11,12-diyl)*bis*(3-*iso*propylbenzimidazolidine-2-ylidene) [DEA-IBY] (**7**) requires treating one equivalent of **5**