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Synthesis and evaluation of indole-substituted *N*-heterocyclic carbene ligands

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ABSTRACT

Indole-substituted *N*-heterocyclic carbene ligands were synthesized and evaluated through both computational and experimental methods. The performances of medium-sized imidazolylidenes **IIn3** and **IIn4** were comparable to IPr in the Cu(I)-catalyzed carboxylation of organoboronic esters.

Introduction

The development of bulky *N*-heterocyclic carbenes (NHCs) has drawn significant attention as they often provide better catalyst performance and asymmetric induction in transition metal-catalyzed reactions [1]. To increase the size of readily accessible imidazolylidene and imidazolinylidene NHCs [2], large side chains or backbone substituents could be introduced. Remarkable catalytic activities and stereoselectivities have been obtained with bulky 2,6-disubstituted phenyl groups (Fig. 1A). 1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidene (IPr), one of the earliest member of this class, is now a standard ligand for metal catalysis. The Organ group [1d,3] demonstrated that Pd-PEPPSI-IPent, containing a large IPent ligand, is an excellent catalyst for challenging cross-coupling reactions. The groups of Schomaker [4a], Markó [4b] and Bertrand [4c] designed even bulkier IHept, IPr* and IPr** ligands, while the Nelson group [4d] developed a "bulky yet flexible" IPaul ligand. For the development of asymmetric catalysis, the groups of Gawley [5] and Shi [6] found that C_2-symmetric chiral IPE/SIPE ligands are privileged in establishing highly enantioselective Cu-, Ni- and Pd-catalyzed transformations.

Efforts have also been paid to the investigation of NHCs with polycyclic aryl side chains (Fig. 1B). The Mori group [7] reported the use of a 1-naphthyl-containing NHC-Pd catalyst in the bismetallative cyclization of enynes. The Dorta group [8] found that introducing 2-alkylated naphthyl side chains resulted in a class of bulky NHCs (INap/SINap) with excellent performance. SINap ligands have also been employed in demanding Ru-catalyzed olefin metathesis reactions by the Blechert group [9] and in the Fe-catalyzed cross-coupling of aryl halides with aryl Grignard reagents by the Huynh and Duong group [10]. The Andrus group [11] designed bis-phenanthryl NHCs (SIPhe) and found the Pd complexes could effectively catalyze the Suzuki-Miyaura coupling of aryl chlorides. Bulky aryl side chains have also been included in the design of chelating NHC ligands, as demonstrated by the Hayashi group [12] (Fig. 1B).

Nevertheless, it was brought to our attention that the known bulky aryl side chains are all based on aromatic hydrocarbons. Reports on heterocyclic side chains are rare, mostly as additional binding sites in chelating NHC ligands [13–15]. To the best of our knowledge, indole-substituted NHCs have not been reported in metal catalysis [16]. We envisaged that indole has the potential to be used as an NHC side chain due to the following considerations: 1) the large bicyclic motif could provide good protection of the metal atom; 2) its electron-rich nature may result in strong NHC-metal coordination; and 3) its unique geometry would provide opportunities for developing new ligands. We disclose herein our proof-of-concept results on the synthesis and evaluation of 4-indolyl-based NHCs (IIn/SIIn, Fig. 1C). Synthetic routes for these ligands and their Cu(I) complexes are established from the

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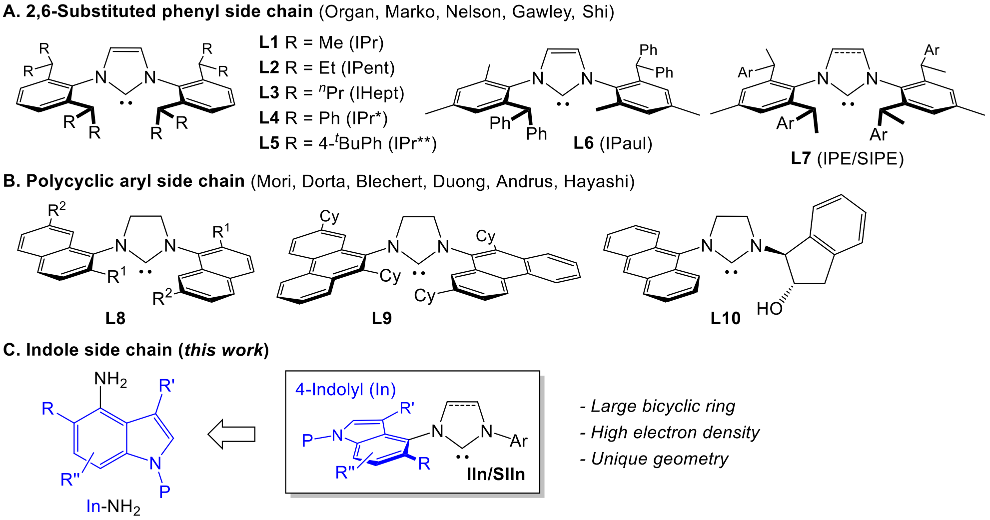


Fig. 1. NHCs with bulky aryl side chains.

corresponding 4-aminoindoles. In the Cu(I)-catalyzed carboxylation of arylboronic esters, selected ligands exhibited high levels of performance comparable to the current best ligand IPr [17].

Results and discussion

We started our investigation with the synthesis of 4-aminoindole intermediates (**1**) (Scheme 1). Alkyl groups were installed at the 1-, 2- and 3-positions to avoid undesired reactions, and changes to the 5-substitution (H or Me) were introduced to adjust the bulkiness of the side chain. From 2-methyl-5-nitroanilines (**1a** and **1b**), the corresponding 7-methyl-4-nitroindoles could be obtained following a diazotization, reduction and Fischer cyclization sequence, and then converted to 4-aminoindoles **2** by methylation and hydrogenation.

The synthesis of indole-substituted imidazolium and imidazolinium NHC precursors was then explored. Symmetric imidazolium **3**, as a 7:3 mixture of *trans*-/*cis*-isomers, was obtained by the condensation of 5-methyl-substituted **2a** with glyoxal and then paraformaldehyde. However, compound **2b**, which has no substituent at the 5-position, failed to give the corresponding imidazolium chloride. Polymerization between **2a** and glyoxal presumably takes place in the reaction.

Unsymmetric imidazoliums **4** were prepared from 4-aminoindoles **2** and arylamine-derived 3-acetoxyoxazolinium perchlorates **A**, according to a protocol developed by the Fürstner group [18]. 4-Hydroxy imidazolinium intermediates are first obtained in the procedure, and then dehydrated in concentrated sulfuric acid to yield the corresponding imidazoliums. Mesityl (Mes) and 2,6-diisopropylphenyl (Dipp) groups were used to adjust the overall bulkiness of the ligands.

With the same consideration, unsymmetric imidazoliniums **5** were prepared by a three-step procedure. 4-Aminoindoles **2** were reacted with an excess amount of triethyl orthoformate to give ethyl formimidates, which were then condensed with a second arylamine to afford formamidines [19], followed by cyclization with 1,2-dichloroethane (DCE) [20] to form the NHC precursors. It is worth noting that in early trials of imidazoliniums synthesis, we also tested 4-bromoindole intermediates (**7**, Fig. 2) which could presumably couple with mono-protected ethylene diamine and be used in further transformations. Unfortunately, the Buchwald-Hartwig coupling of **7** was unsuccessful in our hands.

For comparison, unsymmetric imidazoliums with large anthracyl side chains (**6a** and **6b**) were also synthesized from 9-aminoanthracene (Ant-NH_2).

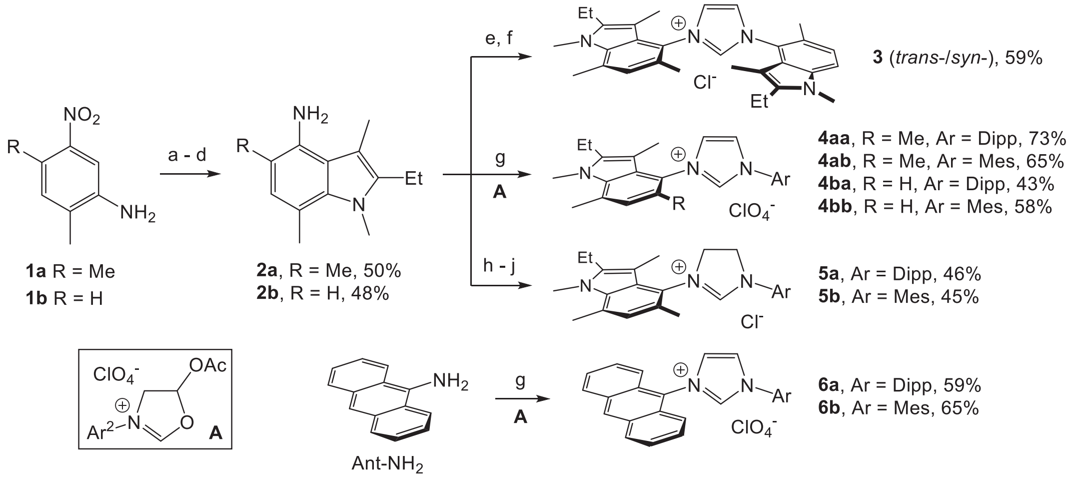
Imidazoliums and imidazoliniums **3**–**6** could be converted to the corresponding free NHCs under basic conditions. Trapping the free NHC derived from imidazolinium **5b** with sulfur [21] yielded thiourea **8** (Scheme 2).

The synthesis of the corresponding (NHC)CuCl complexes [22] was then carried out (Scheme 3). After several attempts, conditions using Cu_2O and KO^{t}Bu were established for reactions from imidazolium and imidazolinium chlorides (**3** and **5**), affording corresponding complexes **9** and **11** in 30–77% yield. For the reactions of imidazolium perchlorates (**4** and **6**), tetrabutylammonium chloride (TBAC) was found to be an effective chloride source. The nine new complexes are air- and moisture-stable, and could be purified by silica gel column chromatography.

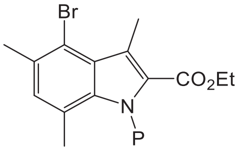
The NMR spectra indicate that complex **9** is a single isomer, although its precursor **3** is a mixture of *trans*-/*cis*-isomers. The crystal structure of **9** (Fig. 3, CCDC 2008743) [23] confirmed the *trans*-configuration of the NHC ligand, and also the linear two-coordinate geometry, with a Cu-C(1) bond length of 1.873(4) Å and a Cu-Cl bond length of 2.1073(11) Å. Density functional theory (DFT) calculations at the B3LYP/6–311 + g(d, p) level suggest that in the gas phase the *trans* isomer is 2.11 kcal/mol more stable than the *cis* isomer. The computed Cu-C(1) and Cu-Cl bond lengths of the *trans* isomer are 1.8939 and 2.1333 Å (Table 1), respectively. These data are in good agreement and comparable to the corresponding experimental results.

The electronic and steric properties of the obtained NHCs were also evaluated by calculations (Table 1). The percent buried volumes (%V_{bur}) of the ligands (36.5–41.1) are mostly between the values of IPr (46.3) and IMes (36.7). The bond dissociation energies (BDE) of the Cu-C(1) bonds exhibit the following trend: IIn > SIIn > IAnt ≈ IPr/IMes, indicating that introducing the indole side chain indeed strengthens the coordination bonds, although the bond lengths remain similar to the values of (IPr)CuCl [24] and (IMes)CuCl. These results show that the properties of the indole-substituted NHCs are different than phenyl-substituted IPr and IMes.

To evaluate the role of indole-substituted NHC ligands in Cu(I)-catalyzed reactions, we selected the carboxylation of organoboronic esters developed by the Hou group [17] as a model system

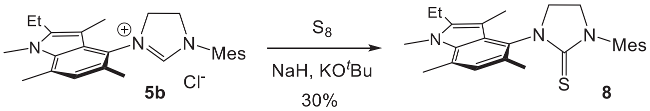


Scheme 1. Synthesis of imidazoliums and imidazoliniums. Reagents and conditions: a. conc. HCl, $NaNO_2$, 0 °C then $SnCl_2$, 0 °C; b. 3-pentanone, TsOH·H_2O, reflux; c. MeI, NaOH, acetone; d. N_2H_4, Pd/C, EtOH, reflux; e. glyoxal, cat. HCO_2H, MeOH; f. $(CH_2O)_n$, TMSCl, 70 °C; g. **A**, HCO_2H, acetonitrile, reflux, then conc. H_2SO_4; h. $HC(OEt)_3$ (excess), AcOH, 140 °C; i. $ArNH_2$, 140 °C; j. DCE, DIPEA, 120 °C.



7a P = Me
7b P = Ts
7c P = Boc

Fig. 2. 4-Bromoindoles used in early trials.



Scheme 2. Reaction of **5b** with sulfur.

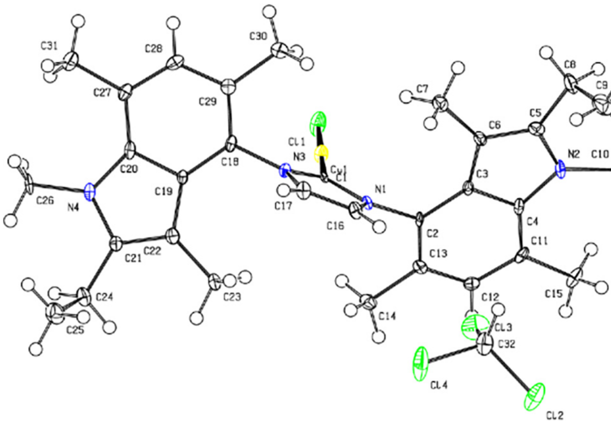
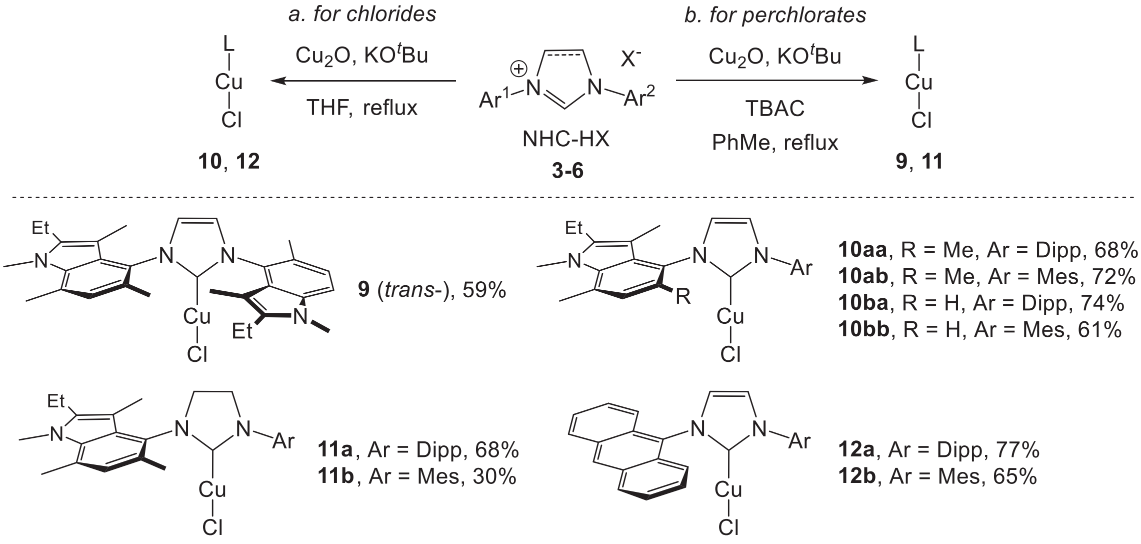


Fig. 3. Single crystal structure of **9**•$CHCl_3$.

(Table 2). With the reported best catalyst (IPr)CuCl, the reaction of 4-fluorophenylboronic ester **13** reached full conversion and gave **14** in 89% yield (Entry 1). Sterically less demanding (IMes)CuCl delivers only 79% conversion and 53% yield (Entry 2). Among the indole-bearing NHC complexes synthesized in this work, five of them were inferior (Entries 3, 4, 7–9), but **10ab** and **10ba** (Entries



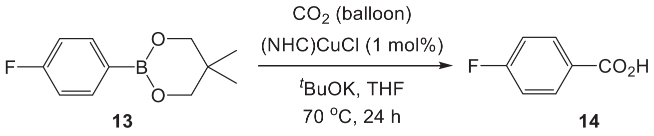
Scheme 3. Synthesis of the (NHC)CuCl complexes.

Table 1
Calculated parameters of the (NHC)CuCl complexes.

Entry	Complex	NHC	Cu-C(1) (Å) [a]	Cu-Cl (Å) [b]	%V_{bur} [c]	BDE (kcal/mol) [d]
1	(IPr)CuCl	IPr	1.8952	2.1289	46.3	61.11
2	(IMes)CuCl	IMes	1.8925	2.1282	36.7	62.81
3	**9**	IIn1	1.8939	2.1333	37.5	64.95
4	**10aa**	IIn2	1.8927	2.1305	40.4	63.83
5	**10ab**	IIn3	1.8932	2.1309	37.2	63.91
6	**10ba**	IIn4	1.8931	2.1313	39.8	63.75
7	**10bb**	IIn5	1.8938	2.1313	36.5	63.68
8	**11a**	SIIn1	1.8975	2.1312	40.4	63.01
9	**11b**	SIIn2	1.8976	2.1296	38.5	62.87
10	**12a**	IAnt1	1.8957	2.1277	41.1	61.42
11	**12b**	IAnt2	1.8959	2.1268	37.6	61.09

[a] Calculated Cu-C(1) bond length.
[b] Calculated Cu-Cl bond length.
[c] Calculated buried volume parameters; radius of the sphere (R) is 3.5 Å.
[d] Calculated bond dissociation energies.

Table 2
Performance of (NHC)CuCl complexes in the carboxylation of arylboronic ester **13**.[a]



Entry	Complex	NHC	Conv (%)[b]	Yield **14** (%)[c]
1	(IPr)CuCl	IPr	100	89
2	(IMes)CuCl	IMes	79	53
3	**9**	IIn1	78	64
4	**10aa**	IIn2	86	72
5	**10ab**	IIn3	100	87
6	**10ba**	IIn4	100	87
7	**10bb**	IIn5	80	68
8	**11a**	SIIn1	76	59
9	**11b**	SIIn2	77	62
10	**12a**	IAnt1	85	85
11	**12b**	IAnt2	82	80

[a] Reagents and conditions: **13** (1.0 mmol), (NHC)CuCl (0.01 mmol), ^{t}BuOK (2.0 mmol), THF (5.0 mL), 70 °C, 24 h, CO_2 balloon.
[b] Conversion was calculated based on the recovered starting material.
[c] Isolated yield.

5 and 6) gave results that were similar to (IPr)CuCl. A unique trend in the complex **10** series is that, in terms of the bulkiness of the NHC ligands, the most and the least demanding ligands (IIn2 and IIn5) gave poor yields (Entries 4 and 7), while the medium-sized IIn3 and IIn4 performed better (Entries 5 and 6). It is worth noting that anthracyl-substituted complexes **12a** and **12b** gave higher conversions and yields (Entries 10 and 11) than (IMes)CuCl, suggesting the contribution of the size of polycyclic aryl side chain to the overall performance.

Conclusion

In summary, NHCs with an indole side chain have been synthesized and evaluated in metal catalysis for the first time. Routes for the synthesis of 4-indolyl-containing symmetric/unsymmetric imidazoliums, unsymmetric imidazoliniums and the corresponding Cu(I) complexes have been established. DFT calculations indicate the unique impact of the indole side chain as the %V_{bur} and BDE values of these NHCs are different than IPr. Two medium-sized unsymmetric NHCs, IIn3 and IIn4, perform nearly as well as the currently best ligand IPr in the Cu(I)-catalyzed carboxylation of organoboronic esters. Attempts to further understand their structure-performance relationships and catalytic applications are ongoing in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152450.

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