A simple synthesis of functionalized 3-methyl-1-pyridinyl-1H-imidazolium salts as bidentate N-heterocyclic-carbene precursors and their application in Ir-catalyzed arene borylation

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ARTICLE INFO

ABSTRACT

The selective alkylation of functionalized 2-(1H-imidazol-1-yl)pyridines **1** furnishes 3-methyl-1-pyridinyl-1H-imidazolium salts **2,** which can be deprotonated to deliver strongly electron-donating bidentate N-heterocyclic carbene ligands (NHC). The synthesis of these ligands and their application in the iridium-catalyzed C–H activated borylation of arenes with its current scope and limitations are reported.

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1. Introduction

Since the isolation of stable imidazol-2-ylidenes by Arduengo et al. in the early 1990's, the use of N-heterocyclic-carbene ligands (NHCs) with its strong σ-donor and weak π-acceptor back bonding properties as ligands in homogeneous catalysis has found wide application,[1] such as Stille-,[2] Heck-,[3] Sonogashira-,[4] Suzuki-,[2] Kumada-coupling,[5] olefin ring closing[6] and cross metathesis,[6] hydrosilylation,[7] hydroformylation,[8] or the borylation[9] of aromatic systems. In many cases monodentate ligands are used, but also bi- or tri-dentate systems are applied depending on the transition metal of choice and the required coordination geometry.[10]

In this work we describe a short and convenient access to 3-methyl-1-pyridinyl-1H-imidazolium iodides **2** which function as precursors for bidentate pyridinyl-carbene ligands. The synthetic strategy relies on the selective methylation at the 3-position of the corresponding imidazole precursors **1** (Scheme 1). In addition, we present the application of several ligands synthesized from these precursors in the Ir-catalyzed borylation of arenes.

In an ongoing project in our group in which differently substituted arylboronic esters are assembled to teraryls as α-helix mimetics, we identified the Ir-catalyzed borylation of arenes under CH-activation introduced by Smith[11] and Miyaura.[12] as an attractive option for the preparation of arylboronic esters building blocks

4 (Scheme 2). Commonly used conditions for the C–H activated borylation of arenes involve bis(pinacolato)diboron (B$_2$Pin$_2$) (**5**) as borylation species, 4,4′-di-tert-butyl-2,2′-bipyridine (dtbpy) (**6**) as ligand and methoxy-bridged iridium precursor **7** as precatalyst in a nonpolar solvent like n-hexane, at room temperature, respectively (Scheme 2).[12]

The aromatic C–H borylation is distinguished by a certain regioselectivity which is primarily controlled by the steric effects of the substituents of the substrate and more or less independent of the electronic influence of the substituents. An investigation of the electronic effects within 4,4′-disubstituted 2,2′-bipyridine ligands revealed the superiority of electron-rich derivatives containing -NMe$_2$, -OMe, or -^{t}Bu groups.[12] Although the method of choice for certain substrates, the established ligand **6** gave less satisfactory results for other substrates.

We speculated that bidentate pyrido-carbenes might be suitable and tunable ligands, which could overcome the deficits of the established ligands. In this we would create a hybrid ligand
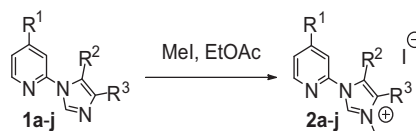
Scheme 1. Selective methylation in the 3-position of the corresponding imidazole precursors **1**.

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E-mail address: breinbauer@tugraz.at (R. Breinbauer).
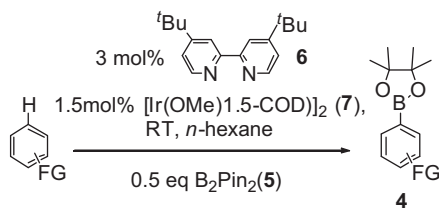
Scheme 2. Standard conditions of C–H activated borylation of arenes by Miyaura and co-workers 1.5 mol % [Ir(OMe)(1.5-COD)]₂ (**7**), 3.0 mol % dtbpy (**6**), 0.5 equiv B₂Pin₂ (**5**), 1.0 equiv arene, *n*-hexane, rt.[12]

Scheme 4. Common synthetic strategy for the synthesis of 3-substituted 1-pyridinyl-1*H*-imidazolium salts **2**. The residue R can be alkyl like -Me,[17] -*n*-Bu,[18] -*i*Pr,[19] or aryl like mesityl[20] or 2,6-diisopropylphenyl.[19]

system between the Miyaura bipyridyl ligands and the biscarbene iridium complexes introduced by Herrmann and co-workers.[9] Similar pyridocarbene ligands have already been used for the synthesis of metal complexes[13] and in metal catalyzed reactions.[5,7c,14] In our design of suitable NHC precursors we were guided by the following reasoning (Scheme 3):

- A distinctive +M/+I-effect of -R¹ in 4-position on the pyridine ring system should increase the electronic density on the metal center.
- A *tert*-butyl- (or phenyl-) residue at -R³ ought to increase the solubility of the NHC precursors in moderately polar solvents, like MTBE or *n*-hexane.
- For the choice of the substituents -R², -R³ at the imidazole ring system two oppositely acting sterically imposed effects have to be considered: first substituents at these positions should disable the possibility of deprotonation at the C-5 position to prevent the formation of a C-5 carbene on the imidazole moiety;[15] second, the residues should not constrain the opportunity of planarization of the bidentate ligand necessary for electronic communication between the ligand fragments.

2. Results and discussion

### 2.1. Synthesis of carbene precursors

The most commonly used procedure for synthesizing 3-substituted 1-pyridinyl-1*H*-imidazolium salts **2** is the reaction of 2-halo-pyridines **8** (preferably 2-bromopyridines) with 1-substituted imidazole derivatives **9**, which requires high temperatures, long reaction times, and occurs mostly under neat conditions (Scheme 4).[16] In many cases it could be observed that under these circumstances an impure slurry is obtained that is difficult to purify. By repeated recrystallization isolation of pure material is possible but only in moderate yields.[14d,15]

When we used this method for our purposes we could also observe that this method is associated with problems of reaction time and product purity. Consequently, we sought for an alternative method.
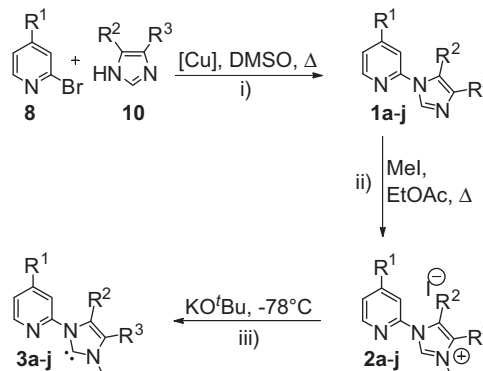
To avoid the problems associated with the synthesis of 3-methyl-1-pyridinyl-1*H*-imidazolium iodides **2** as described above
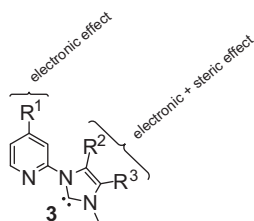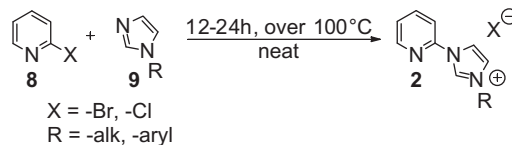
Scheme 5. Overview about the synthetic strategy. (i) Aryl–aryl coupling under Ullmann conditions; (ii) selective methylation at 3-position; (iii) deprotonation of the carbene precursor using KO^tBu as base.

we coupled first 2-bromo-pyridine derivatives **8** via Ullmann reaction with the corresponding substituted imidazoles **10**, followed by selective alkylation of the 3-position of the azole moiety (Scheme 5).[21] The deprotonation of these air-stable carbene precursors can then be performed in situ using KO^tBu in MTBE.

The compounds **1a**–**1j** were synthesized via Ullmann coupling according to a literature procedure[21] by copper induced catalysis using L-proline as the ligand and K₂CO₃ as the base under inert conditions (Scheme 6, Table 1).

The success of the aryl–aryl coupling with copper as the catalyst appears to be largely independent of the electron-donating or electron-withdrawing nature of the substituents in the pyridine moiety. Also sterically hindered imidazoles could be converted into the 2-(1*H*-imidazol-1-yl)pyridines **1** (Table 1, entry 10).

In the next step, the regioselective alkylation of the 2-(1*H*-imidazole-1-yl)pyridines **1** occurred as expected at the more basic imidazole nitrogen (Scheme 7). Conveniently, the methylation delivers the products in good to very good yields. The pure product can be collected from the reaction mixture by simple filtration as an off-white solid without requiring further workup or purification.

The selective methylation with MeI in EtOAc at moderate temperatures takes place in good up to very good yields (Table 2). The moderate yields in some of the methylation-reactions (Table 2, entries 4–6 and 8) could be explained by the sterical hindrance caused by the -^tBu or -Ph group in the 4-position of the imidazole moiety.

Scheme 3. Design elements of the 3-methyl-1-(2-pyridyl)-imidazol-2-ylidene derivatives **3**.
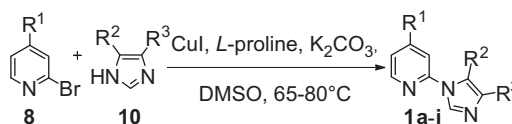
Scheme 6. Synthesis of 2-(1*H*-imidazole-1-yl)pyridine derivatives **1** according to Ullmann conditions.

Table 1
Conditions and yields of 2-(1*H*-imidazol-1-yl)-pyridine derivatives **1**

Entry	Compound	R^1	R^2	R^3	Time/Temperature (h/°C)	Yield[a] (%)
1	**1a**	H	H	H	22/65	91
2	**1b**	^{t}Bu	H	H	47/75	71
3	**1c**	N(Me)$_2$	H	H	48/70	57
4	**1d**	H	H	^{t}Bu	65/70	36
5	**1e**	H	H	Ph	47/80	57
6	**1f**	^{t}Bu	H	^{t}Bu	110/75	49
7	**1g**	^{t}Bu	H	Ph	65/70	25
8	**1h**	N(Me)$_2$	H	^{t}Bu	42/80	67
9	**1i**	N(Me)$_2$	H	Ph	65/70	28
10	**1j**	H	Me	Me	53/80	63

[a] Isolated yields.
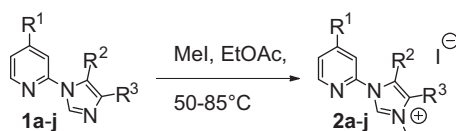
Scheme 7. Regioselective methylation at the more basic imidazole nitrogen in EtOAc as the solvent.

Scheme 8. Optimized conditions for C–H activated borylation with bidentate NHC ligands **3a–3j**; dtbpy (**6**) used as reference.
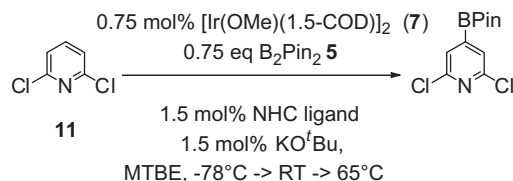
According to the design exigencies for a ligand in the C–H activated borylation a small library of 3-methyl-1-pyridinyl-1*H*-imidazolium iodides **2** was synthesized (Table 2).[21]

2.2. Application as ligands in Ir-catalyzed borylation

Using our synthetic procedure we were able to synthesize a small library of NHC precursors, independent of the electronic behavior of the substituents. The deprotonation at the C-2 position of the imidazolium ring system could be easily performed in situ, by using strong bases like KHMDS, LDA, or even KO^{t}Bu to generate the free carbene **3**.[6] It should be noted that the σ-donor and the weak π-acceptor property of the carbene can be tuned by the substituents of the imidazole moiety. Also the different electron-donating or electron-withdrawing residues of the pyridine ring system influence the electronic properties of the metal-carbene complex. With these parameters it is possible to 'fine-tune' the electronic and steric properties of the bidentate NHC-ligands.[22]

As a test reaction for our ligands (**2a–2j**) we used the Ir-catalyzed borylation according to the procedure of Miyaura and co-workers[12] with 2,6-dichloropyridine (**11**) as a model substrate, for which only one regioisomeric product is expected (Scheme 8).

For reaction optimization, several solvents were tested. MTBE, THF, 2-methyl-THF, *n*-hexane, and *n*-dodecane gave similar results, whereas others like 1,2-dichloroethane or cyclohexane gave low or no conversion. As precatalyst the methoxy- and chloro-bridged

iridium-dimer were tested. The methoxy-bridged precatalyst **7** gave significant better conversion than the chloro-derivative, as has been observed before for dtbpy (**6**).[12] It was necessary to generate the active catalyst in situ first using KO^{t}Bu in MTBE by −78 °C, warming up to room temperature and then addition of the substrate and B$_2$Pin$_2$ (**5**). While several of our ligands exhibited quite decent catalytic activities, none of the pyridyl-NHC-ligands were as active as the most active literature known ligand dtbpy (**6**). This is also reflected by the fact, that with pyridyl-NHC ligands a reaction temperature of 50 °C or higher is required.

Several interesting trends could be observed. When comparing ligand **3d** with **3j** one could conclude that the planarization of the bidentate ligand has a high influence on the catalytic activity (Diagram 1). With an additional methyl group on the imidazole ring system the possibility of planarization in ligand **3j** could be obstructed causing considerable lower activity in the borylation reaction.

Diagram 2 depicts the conversion-time-diagram of the three most active NHCs in our small library. Ligand **3b** is showing nearly quantitative conversion of the starting material after less than 20 h with a conversion of 90% within the first hour. The reference ligand dtbpy (**6**) exhibits quantitative conversion during the first hour at 65 °C and MTBE as the solvent (Diagram 2).

Table 2
Conditions and yields of 3-methyl-1-pyridinyl-1*H*-imidazolium iodides **2** after selective methylation on 3-position

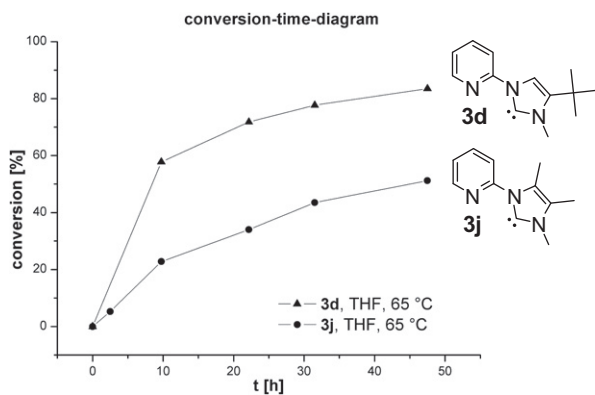| Entry	Compound	R^1	R^2	R^3	Time/Temperature (h/°C)	Yield[a] (%)
1	**2a**	H	H	H	27/65	97
2	**2b**	^{t}Bu	H	H	15/70	74
3	**2c**	N(Me)$_2$	H	H	15/80	94
4	**2d**	H	H	^{t}Bu	38/75	71
5	**2e**	H	H	Ph	13/65	63
6	**2f**	^{t}Bu	H	^{t}Bu	39/85	69
7	**2g**	^{t}Bu	H	Ph	48/75	74
8	**2h**	N(Me)$_2$	H	^{t}Bu	63/85	71
9	**2i**	N(Me)$_2$	H	Ph	64/80	98
10	**2j**	H	Me	Me	24/50	96

[a] Isolated yields.

Diagram 1. Conversion-time-diagram for ligand **3j** in comparison to ligand **3d**. 0.75 mol % [Ir(OMe)(1.5-COD)]$_2$ (**7**), 1.5 mol % ligand, 1.5 mol % KO^{t}Bu, 0.5 equiv B$_2$Pin$_2$ (**5**), 1.0 equiv 2,6-dichloropyridine (**11**), THF, 65 °C.
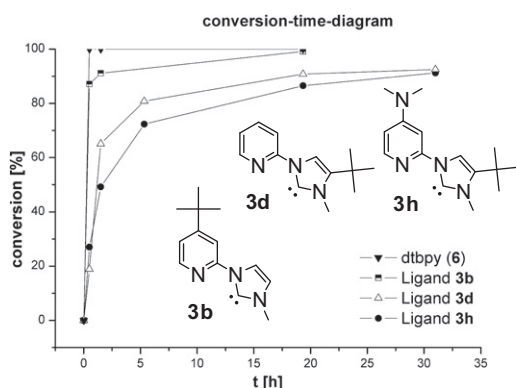

Diagram 2. Conversion-time-diagram for the three most active NHCs in comparison with the dtbpy ligand **6**; 0.75 mol % [Ir(OMe)(1.5-COD)]$_2$ (**7**), 1.5 mol % ligand, 1.5 mol % KO^{t}Bu (for **3b**, **3d**, **3h**), 0.75 equiv B$_2$Pin$_2$ (**5**), 1.0 equiv 2,6-dichloropyridine (**11**), MTBE, 65 °C.

3. Conclusion

We were able to show that bidentate pyrido-NHC complexes can easily be prepared by the deprotonation of pyridinyl-1*H*-imidazolium iodides **2**, which are readily accessible via Ullmann coupling of 2-halopyridines **8** with 1*H*-imidazoles **10** and subsequent alkylation at the imidazole nitrogen. In a test reaction we could demonstrate that these ligands can be successfully applied in the Ir-catalyzed borylation of arenes. While for this particular reaction the mixed pyridyl-NHC-ligands **3** did not exceed the reactivity of the best known literature ligand dtbpy (**6**), we do see considerable potential that these precursors will find application in other organometallic reactions in which electron-rich bidentate ligands are needed, as this ligand class is distinguished by a high tunability regarding electronic and steric properties, made possible by the flexible synthetic approach introduced in this report.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.059.

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