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Introduction of bulky *tert*-butyl substituents on the core of *N*,*N*'-diaryl *N*-heterocyclic carbenes through the corresponding vicinal diamines

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ABSTRACT

Highly bulky *N*,*N*'-diaryl imidazolinium salts substituted by one or two *tert*-butyl groups on the heterocyclic backbone and the corresponding silver *N*-heterocyclic carbene complexes are obtained by the addition of *tert*-butyl magnesium chloride or *tert*-butyl lithium on symmetrical 1,2-bisimines derived from 2,6-diisopropylaniline, 2,6-diethylaniline and 2,4,6-trimethylaniline.

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N-heterocyclic carbenes (NHCs) are now recognized as an essential family of ligands in organometallic chemistry.¹ More particularly NHCs substituted by aryl groups on the nitrogen atoms have been extensively investigated for the development of metalcatalyzed reactions.² The most widely used N,N'-diaryl-substituted NHCs are characterized by the presence of substituents (Me, *i*-Pr) at the ortho positions of the aryl groups providing an efficient protection of the metal and of the carbenic center, inducing steric hindrance around the metal and therefore, affecting the stability and/ or activity of the catalysts (Fig. 1a). NHCs or metal-NHC complexes can readily be obtained from the corresponding imidazoli(ni)um salts. Many efficient methods are available for the preparation of N,N'-diaryl azolium salts from vicinal diamines, bisimines, or amidines.³ As a consequence, chiral N,N'-diaryl NHCs possessing stereogenic centers on the heterocyclic skeleton have soon been considered as attractive analogues for the development of applications in asymmetric catalysis (Fig. 1b).⁴ However, the synthetic approaches are much less general than for achiral NHCs.³ The Pdcatalyzed double N-arylation of chiral enantiopure vicinal diamines was used to prepare N,N'-diaryl diamines from 1,2-diphenyl-1,2-diaminoethane or 1,2-diamino-cyclohexane.⁵ The method enables the introduction on the nitrogen atoms of bulky aryl groups with substituents (e.g., *i*-Pr groups) at the ortho positions.

However, double arylation on both nitrogen atoms is hindered by the presence of more bulky substituents (e.g., tert-butyl groups) on the backbone.⁶ Alternatively, the reductive coupling of *N*-aryl imines derived from aromatic aldehydes was shown to be efficient for synthesizing bulky N,N'-diaryl vicinal diamines, although the diastereoselectivity is relatively low.7 Addition of Grignard reagents to bisimines was used to generate bulky NHCs possessing gem-dimethyl groups at positions 3 and 4.8 This method was previously exploited for the preparation of chiral tert-butyl substituted vicinal diamines and NHCs.^{9,10} Here, good diastereoselectivities have been obtained and enantiopure diamines could be isolated. The method was applied to the formation of *N*,*N*'-dialkyl diamines. We considered that the addition of *t*-Bu-metal species on bulky N.N'-diaryl 1,2-bisimines could be an alternative strategy for the synthesis of the corresponding diamines and NHCs (Fig. 1b; $R^2 = t$ -Bu, R = Me or *i*-Pr) which are attractive ligands for asymmetric catalysis.

Preliminary experiments performed with bisimine **1a** demonstrated that the addition of *t*-BuMgCl under the conditions previously developed for the preparation of 1,2-di-*tert*-butyl-1,2diaminoethane (hexane, 50 °C),^{9a} and under various other conditions, led exclusively to the formation of the imino-imine **2a** resulting from the addition of a single *tert*-butyl group on precursor **1a** (Scheme 1).¹¹ Compound **2a** was isolated in 94% yield and the method, applied to the less sterically demanding bisimines **1b** and **1c** affords similarly the mono-adducts **2b** and **2c** in 90–99% yields. Addition of less bulky or more reactive organometallic re-





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Figure 1. (a) Commonly used *N*,*N*'-diaryl NHCs (*R* = *i*-Pr, Me) and (b) backbone substituted (chiral) analogues.



Scheme 1. Synthetic pathway for the preparation of *N*,*N*'-diaryl 3-*tert*-butyl-substituted NHCs.

agents such as *i*-PrMgCl, MeMgCl, allylMgBr, *t*-BuLi, *n*-BuLi or MeLi to isolated **2a** or to the intermediate magnesium amide was unsuccessful. Reduction of imines **2a–c** was not observed with NaBH₄ and requires the use of LiAlH₄ to produce the corresponding diamines **3a–c** in 43–76% yield after purification. The diamines were then cyclized with triethylorthoformate in the presence of HCl by using standard conditions,³ to give the mono-substituted imidazo-linium chlorides **4a–c** in 68–85% yields.¹² Finally, treatment of **4a** and **4b** with Ag₂O leads to the silver–NHC complexes **5a** and **5b**. These complexes are characterized by the presence of two doublets in the ¹³C NMR spectrum which are centered at 211.9 ppm for **5a** and 210.6 ppm for **5b** and correspond to the signal of the carbenic carbon associated with Ag–C coupling constants of 257 and 223 Hz in both cases.¹³

Next, we focussed on the synthesis of *N*,*N*'-diaryl diamines substituted by two *tert*-butyl groups. We assumed that the use of more reactive lithium reagents would favor the expected double addition of *tert*-butyl carbanions onto the bisimines.¹⁴ The treatment of bisimine **1a** with *t*-BuLi yields a mixture of non-identified compounds along with **2a** and therefore is not suitable for the synthesis of the di-substituted diamine. A marked difference is observed with the mesityl-substituted bisimine **1b** that leads to the expected diamine **6**, isolated in 80% yield as a single *d*,*l* diastereomer, after addition of *t*-BuLi at low temperature in THF (Scheme 2).



Scheme 2. Preparation of the *N*,*N*'-bis(mesityl) diamine **6** substituted by two *tert*-butyl groups and of the corresponding silver–NHC **8**.



Figure 2. ORTEP diagram of diamine **6.** Selected torsion angles: N2–C11–C10–N1 = 87.78°; C21–C10–C11–C25 = 144.14°.



Scheme 3. Example of Pd-catalyzed allylation with 5a as the NHC transfer agent.

The molecular structure of **6** was confirmed by X-ray analysis of single crystals obtained by slow evaporation in acetonitrile. The ORTEP view is depicted in Figure 2.

Attempts to resolve the racemic diamine **6** by crystallization of diastereomeric salts with camphorsulfonic acid or tartaric acid derivatives under reported conditions remained inconclusive.¹⁵ This is in accordance with previous observations on the resolution of *N*,*N'*-diaryl vicinal diamines substituted by aromatic groups on the carbon chain (i.e. on the stereogenic centers), that could be resolved by chiral HPLC.⁷ Resolution of monosubstituted diamines **3** and imino-amines **2** was also unsuccessful.

In contrast to mono-subsituted diamines **3**, the cyclization of the more hindered diamine **6** to produce the imidazolinium salt could be achieved neither under the standard conditions described previously for **3** (Scheme 1), nor under less acidic conditions (NH₄-Cl, cat. HCOOH).¹⁶ In all cases, the starting material was recovered unchanged. Finally, with the aim of forming the aminal, diamine **6** was treated with formaldehyde. Surprisingly, we found that the imidazolinium salt **7** is formed in a reproducible manner, although in moderate yields (29%), by heating the mixture at 100 °C (Scheme 2). The salt **7** is presumably formed by O₂-mediated oxidation of the intermediate aminal. Oxidation of aminals by various oxidizing agents has been reported in the literature.^{3,17} However, examples of direct oxidation with molecular O₂ or air are scarce.¹⁸ Note that the aminal could not be formed or isolated by the treatment of **6** with formaldehyde, regardless of the conditions.

The treatment of **7** with Ag₂O at 20 °C led to the symmetrical disubstituted silver complex **8** in 94% yield. Similarly to **5a** and **5b**, the ¹³C NMR spectrum of **8** exhibits two doublets for the carbenic carbon centered at 213.7 ppm ($J\{^{13}C^{-109}Ag\}$ = 260 Hz; $J\{^{13}C^{-107}Ag\}$ = 225 Hz). Silver(I)–NHCs have been used as carbene transfer agents for the in situ preparation of other metal complexes.¹³ Complex **5a**, used as the NHC transfer agent in the palladium-catalyzed allylation of aldehydes in the presence of diethylzinc,¹⁹ produces the expected homoallylic alcohol in 78% yield (Scheme 3).

In conclusion, we demonstrate herein that either one or two sterically demanding *tert*-butyl groups can be introduced on the backbone of NHCs possessing bulky aryl substituents on the nitrogen atoms. The Grignard reagent (*t*-BuMgCl) is suitable for the preparation of mono-substituted derivatives whereas *t*-BuLi is required to enable a double addition on the least substituted bisimine. The most bulky di-*tert*-butyldiamine could be cyclized to form the imidazolium salt by an original method, that should be further explored, that involves formaldehyde and likely molecular oxygen. Three chiral racemic silver–NHCs substituted by *tert*-butyl groups have been prepared. These complexes might be of interest for (asymmetric) catalysis and biological applications.

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Supplementary data

Preparation and characterization of **1a–c**, **2a–c**, **3a–c**, **4a–c**, **5a**, **5b**, **6**, **7**, and **8**, and crystal structure information (**6**), this material can be found in the online version at http://dx.doi.org/10.1016/j.tetlet.2013.06.132. Crystallographic data (excluding structure factors) for the structure of diamine **6** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 939920. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06. 132.

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