ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 12541–12543

www.rsc.org/chemcomm

COMMUNICATION

A facile preparation of backbone-substituted, functionalized and chiral imidazolinium salts†

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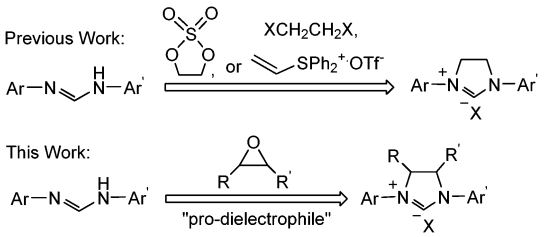
Received 10th September 2011, Accepted 10th October 2011
DOI: 10.1039/c1cc15609h

A versatile and modular method for the preparation of various backbone-substituted, functionalized and chiral imidazolinium salts from the reaction of formamidines with alkene oxides has been described, providing a more straightforward access to substituted imidazolinium salts than the previously reported methods.

Recently, the saturated *N*-heterocyclic carbenes (NHCs), imidazolidin-2-ylidenes, have received much attention partially due to their increased Lewis basicity, which led to an improved catalytic activity in ruthenium-based metathesis compared with their unsaturated counterparts, imidazol-2-ylidenes.[1] Since imidazolidin-2-ylidenes are usually prepared *in situ* by the deprotonation of their precursor imidazolinium salts, the preparation of these imidazolinium salts is highly desirable.[2] Thus far, imidazolinium salts are mainly synthesized from cyclization of triethyl orthoformate with the corresponding diamines. However, these diamines are not readily available, and their preparations generally include either a palladium catalyzed C–N coupling or a condensation and reduction sequence. Moreover, the cyclization processes usually require harsh conditions and have poor reproducibility.[2] An alternative approach, proposed recently by Bertrand, is the deprotonation of formamidine with ^{n}BuLi and further cyclization with "dielectrophiles", 1,2,3-dioxathiolane-2,2-dioxide. This method has been modified by Grubbs and his coworkers.[4] Imidazolinium salts were obtained by alkylation of formamidines with 1,2-dichloroethane in the presence of diisopropylethylamine. Cavell and his co-workers have obtained imidazolinium salts by alkylation of formamidines with dibromides in the presence of K_2CO_3.[5] Very recently, McGarrigle and Aggarwal have reported a modified method to prepare imidazolinium salts from the reaction of formamidines with vinylsulfonium salt, produced *in situ* from bromoethylsulfonium salt[6] (Scheme 1).



Scheme 1 Most important routes to imidazolinium salts.

However, these methodologies suffer from significant limitations; (1) the first approach needs inert moisture free conditions,[3] and (2) the latter three approaches require harsh conditions[4] such as at high temperature (110 °C) or under refluxing in acetonitrile.[5,6] More importantly, these methodologies do not allow the formation of backbone substituted imidazolinium salts, presumably due to the steric hindrance within the dielectrophile reagent.[3] In the NHC-based Ru catalysts, placing substituents on the backbone of the imidazolidin-2-ylidenes has been found to render a decomposition pathway unfavorable by restricting the rotation of the N-aryl groups, which significantly impacts catalyst stability and activity.[7] Following Bertrand's method,[3] we envisioned that epoxide could be used as a "pro-dielectrophile" in the preparation of imidazolinium salts from the ring opening reaction of epoxide with formamidine and subsequent cyclization (Scheme 1). Various epoxides can be easily prepared from cyclodehydrohalogenation of β-halo alcohols and epoxidation of alkenes. As part of our studies on the design and synthesis of novel chiral NHC ligands for asymmetric catalysis,[8] we herein wish to report a new synthetic strategy using epoxide as a "pro-dielectrophile" for the facile preparation of various backbone-substituted, functionalized and chiral imidazolinium salts under mild reaction conditions (Scheme 1).

Our initial study focused on the reaction of *N*,*N*′-dimesityl-formamidine **1a** and commercially available styrene oxide (Table 1, entry 1). Using NaH as a base, the ring opening reaction proceeded smoothly to give **2a** in good yield and weak bases such as K_2CO_3, triethylamine and diisopropylethylamine gave **2a** in poor yields. Subsequent treatment of the intermediate, alcohol **2**, with triflic anhydride (Tf_2O) in Et_3N gives the corresponding triflate derivative, which affords imidazolinium salt **3a** in 83% overall yield (Table 1, entry 1). Reducing the number of substitutes at the *N*-aryl *ortho* positions dramatically decreased the reaction rate of the first ring opening step, and

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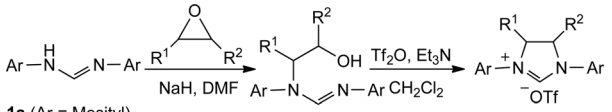
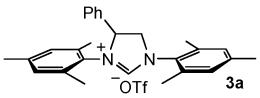
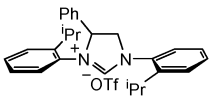
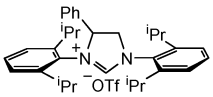
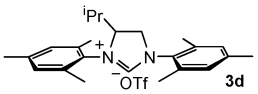
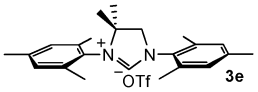
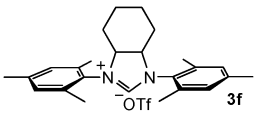
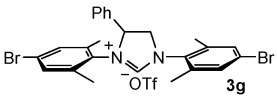
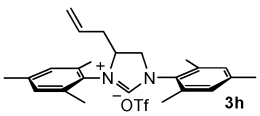
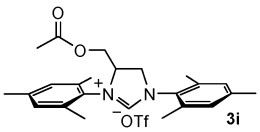
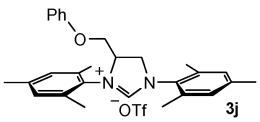
† Electronic supplementary information (ESI) available: CCDC 841930, 841928, and 841931. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15609h

Table 1 Synthesis of various imidazolinium salts[a]



1a (Ar = Mesityl)
1b (Ar = *o*-^{i}PrPhenyl)
1c (Ar = 2,6-^{i}Pr$_2$Phenyl)
1d (Ar = 2,6-Me$_2$-4-BrPhenyl)

Entry	Formamidines	Imidazolinium salts	Time/h Step 1, 2	Yield[b] [%]
1	**1a**	 **3a**	12 h, 5 h	83
2	**1b**	 **3c**	24 h, 5 h 10 h[c], 5 h	14 51[c]
3	**1c**	 **3b**	12 h, 5 h	78
4	**1a**	 **3d**	10 h[c], 5 h	81[c]
5	**1a**	 **3e**	12 h, 5 h	62
6	**1a**	 **3f**	12 h[c], 5 h	68[c]
7	**1d**	 **3g**	12 h, 5 h	85
8	**1a**	 **3h**	12 h, 8 h	61
9	**1a**	 **3i**	12 h, 8 h	75
10	**1a**	 **3j**	12 h, 8 h	73

[a] Reaction conditions. Step 1: **1** (2.4 mmol), epoxide (2 mmol), NaH (3.0 mmol), DMF (15 mL), 25 °C. Step 2: Tf_2O (2.2 mmol), Et_3N (2.2 mmol), DCM (10 mL), 25 °C. [b] Isolated yield of the desired imidazolinium salts. [c] 70 °C.

higher reaction temperature is required (Table 1, entry 2). Notably, the increase of steric hindrance on the *N*-aryl *ortho* positions has no significant influence on the reaction outcome (Table 1, entries 1 and 3). To show the generality and scope of this new synthetic protocol, structurally diverse and functionalized epoxides were treated with formamidines and it was found that our new approach is compatible with several different aliphatic epoxides, leading to various backbone substituted imidazolinium salts in good overall yields (Table 1, entries 4–6). Either functionalities in epoxides such as phenoxy, vinyl, and ester groups or bromo functionality in the aryl group of formamidine were tolerated both on the ring opening of alkene oxides and on the following ring closing, due to the mild reaction conditions of our new method (Table 1, entries 7–10). These resulting imidazolinium salts **3g–3h** with different functionalities indicated that they are useful in terms of flexible synthetic utility for further derivatization.

Very recently, Blechert and his coworkers have developed a successful strategy for the preparation of chiral imidazolidin-2-ylidene **A** used in ruthenium-based asymmetrical metathesis, in which the backbone substituent (isopropyl) was used to induce a significant twist of the monosubstituted arene ring to reach the optimal transfer of chirality, and a planar mesityl substituent was employed on the another side to avoid steric hindrance diminishing the reactivity.[9] Hoveyda and his coworkers also reported a chiral monosubstituted imidazolidin-2-ylidene **B** with a similar backbone for Cu-catalyzed asymmetric allylic alkylation[10] (Fig. 1). The catalysts based on **A** or **B** exhibited excellent enantioselectivities, and, in some cases, improved enantioselectivities compared to those based on their parent C_2-symmetrical NHCs **C**. Thus, we also attempted to use our new synthetic method to prepare chiral monosubstituted imidazolinium salts with commercially available (*R*)-styrene oxide and the results are summarized in Table 2. The desired chiral imidazolinium salt (*S*)-**4a-OTf** was afforded in 83% yield (Table 2, entry 1). To determine its absolute configuration, (*S*)-**4a-OTf** was converted to the corresponding iodide (*S*)-**4a-I** by treatment of (*S*)-**4a-OTf** with excess NaI (p. S41, see ESI†). The X-ray crystal structure of (*S*)-**4a-I** showed that it has the *S* configuration (Fig. S3, see ESI†), indicating that inversion of the configuration of (*R*)-styrene oxide occurred in the two-step synthesis. The ee value of pure (*S*)-**4a-OTf** was determined as 99% on the basis of chiral HPLC analysis of its derivative imidazolidin-2-thione (*S*)-**4a′**, which was obtained by a classic method (Scheme S5, see ESI†).

We further investigated the reaction of (*R*)-styrene oxide with the unsymmetrical *N*,*N*′-diarylformamidines **1e** and **1f**. Only one regioisomer (*S*)-**4b-OTf** or (*S*)-**4c-OTf** in which the backbone-substituted phenyl group is on the carbon atom close to the mono-substituted aryl ring was formed (Table 2, entries 2 and 3). (*S*)-**4b-OTf** and (*S*)-**4c-OTf** are highly desirable chiral monosubstituted imidazolinium salts, from which we could further synthesize the corresponding chiral imidazolidin-2-ylidenes with similar optimal transfer and control of chirality to those described above for chiral carbenes **A** and **B**. The regiochemistry of products (*S*)-**4b-OTf** and (*S*)-**4c-OTf** has been confirmed by X-ray crystal structure of (*S*)-**4b-OTf** (Fig. S4, see ESI†) and NOE spectroscopic investigation of (*S*)-**4b-OTf** and (*S*)-**4c-OTf**.

To gain more mechanistic insight into this intriguing regiochemistry, we further investigated the regioselectivity in the key first ring opening step. We prepared the authentic formamidinyl

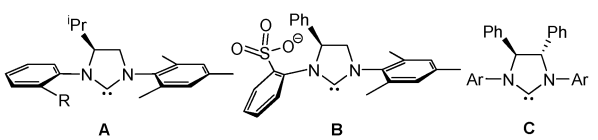
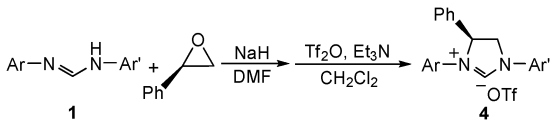
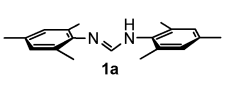
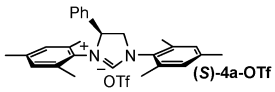
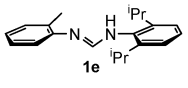
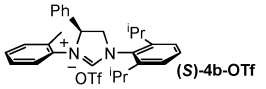
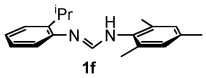
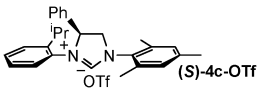
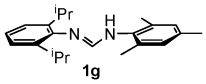
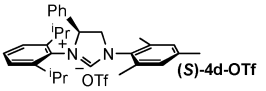
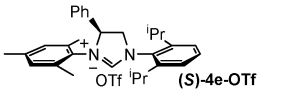


Fig. 1 Chiral backbone-substituted imidazolidin-2-ylidene.

Table 2 Synthesis of chiral imidazolinium salts[a]

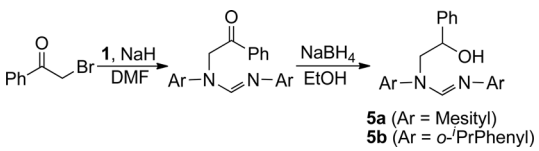


1 4

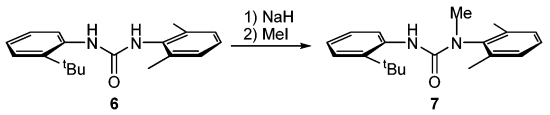
Entry	*N*,*N*′-Diarylformamidine	Imidazolinium salts	Yield[b] [%]
1	 **1a**	 **(*S*)-4a-OTf**	83
2	 **1e**	 **(*S*)-4b-OTf**	45[c]
3	 **1f**	 **(*S*)-4c-OTf**	43[c]
4	 **1g**	 **(*S*)-4d-OTf**	51
		 **(*S*)-4e-OTf**	11

[a] Reaction conditions. Step 1: **1** (2.4 mmol), epoxide (2 mmol), NaH (3.0 mmol), DMF (15 mL), 25 °C, 10 h. Step 2: Tf_2O (2.2 mmol), Et_3N (2.2 mmol), DCM (10 mL), 25 °C, 5 h. [b] Isolated yield of the desired imidazolinium salts. [c] 70 °C (step 1).

alcohols **5a** and **5b** by an alternative method (Scheme 2). The ring opening products **2a** and **2b** from **1a** and **1b** (Scheme S2, see ESI†) have been identified as the same as **5a** and **5b**, respectively, by NMR spectroscopy, indicating that the selective nucleophilic attack occurred at the less hindered carbon of styrene oxide. Thus we postulated that the regioselective products (*S*)-**4b-OTf** and (*S*)-**4c-OTf** probably resulted from the selective attack of the nitrogen atom near the disubstituted arene ring at the less hindered carbon of (*R*)-styrene oxide in the first step and the subsequent cyclization. The regiochemistry observed here is quite similar to that in the methylation of the urea complex **6** (Scheme 3). The treatment of **6** with methyl iodide resulted in regioselective methylation with the nitrogen carrying disubstituted arene ring to afford **7**.[11] The authors presumed that the twist in the Ar–N bond imposed by the steric requirements of two substituents in the *ortho* positions prevents delocalization of the anion into the more hindered ring, increasing electron density and reactivity at the nearer nitrogen atom, despite its more



Scheme 2 Alternative synthesis of the alcohols **5a** and **5b**.



Scheme 3 Regioselective methylation of the urea complex **6**.

crowded environment. The presumption is supported by our observation that *N*,*N*′-dimesitylformamidine **1a** is far more active than *N*,*N*′-bis(2-^{i}Prphenyl)formamidine **1b** at 25 °C (Table 1, entries 1 and 2). In the case of **1g** having two disubstituted arene rings, the N atom near the less hindered mesityl ring attacked the (*R*)-styrene oxide, offering the major product (*S*)-**4d-OTf**, while the minor product (*S*)-**4e-OTf** resulted from the nucleophilic attack of the N atom near the more hindered diisopropylphenyl ring. The regiochemistry was confirmed by the X-ray crystal structure of (*S*)-**4d-I** (Fig. S4, see ESI†), obtained by treatment of (*S*)-**4d-OTf** with excess NaI (p. S41, see ESI†).

In conclusion, we have established a facile and versatile method for the preparation of various imidazolinium salts. Noticeably, this novel synthetic strategy for the preparation of chiral backbone-monosubstituted imidazolinium salts is more straightforward, and does not involve any transition-metal catalyzed reaction compared to the previously reported methods.

Financial support from the Shanghai Municipal Committee of Science and Technology (08dj1400100-2), National Basic Research Program of China (973)-2010CB833302, Shanghai Pujiang Talent Program (11PJ1402500), and the National Natural Science Foundation of China for financial support (21171056, 21072206, 20472096, 20872162, 20672127, 20821002 and 20732008) is greatly acknowledged.

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