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Installation of the imidazole ring on chiral substrates via allylic substitution

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ABSTRACT

Allylic substitution of chiral allylic picolinate (1 equiv) with the copper reagents derived from 2-lithio-1-alkylimidazoles (2 equiv), $CuBr \cdot Me_2S$ (1 equiv) and $MgBr_2$ (3 equiv) afforded imidazole derivatives possessing a chiral allylic chain at the C2 position stereo- and regioselectively. The chiral imidazoles thus produced were transformed into $[\text{chiral imidazolium}]^+[NTf_2]^-$ in good yields. Similarly, the 2-pyridyl derivative with a chiral side chain was synthesized.

1. Introduction

Imidazole derivatives and imidazolium salts possessing one or more chiral chains have attracted much attention as new chiral catalysts and materials.[1] Such chiral compounds have been frequently synthesized by N-alkylation of imidazole or *N*-alkyl imidazoles using alkyl halides possessing a chiral center[2] and by condensation of a chiral amine, glyoxal, ammonia and formaldehyde.[2e,3,4] Conversely, chiral imidazoles, in which the C2 carbon is connected to a chiral carbon residue (Fig. 1, types I and II), have been synthesized by various methods.[5] However, only a few methods appear to be universal and highly selective. To establish a method that produces type III imidazole derivatives, we focused on the substitution of secondary carbon electrophiles with the imidazole C2 anions.

The C2 acidic carbon[6,7] of 1-alkyl imidazoles has been sacrificed for addition to carbonyl compounds and their derivatives,[5b,c,8] alkylation with alkyl halides,[8b,c,e,9] coupling with aryl and allylic halides,[10] and conversion to 2-halo-imidazoles followed by coupling with organometallics,[9h,11] thus successfully furnishing the C2-substituted imidazoles.[5h,12] However, the production of chiral imidazoles has only been reported for the diastereoselective addition to chiral imines.[5c] With regard to alkylation, the reportedly low nucleophilicity of the C2 anion toward *primary* alkyl bromides[13] suggests difficulty with *secondary* alkyl halides. We have published the substitution of secondary allylic picolinates with copper reagents derived from RMgBr and $CuBr \cdot Me_2S$ to afford *anti* S_N2' products with high stereoselectivity and regioselectivity.[14] The picolinoxy leaving group is responsible for the high efficiency in selectivity and reactivity. The substitution was expanded with copper reagents derived from aryl lithiums[15] and alkynyl lithiums.[16] Furthermore, the allylic substitution was utilized to create quaternary carbon centers.[17] These variations have been successfully applied to the synthesis of biologically active compounds.[18] Substitution with furyl and thienyl copper reagents was also successful,[15b] despite quite low nucleophilicity of the reagents toward 1,4-addition to enones.[19] As such, substitution of chiral picolinates **3** with 1-alkylimidazol-2-yl copper reagents **2** was envisaged to afford imidazole derivatives **4** (Scheme 1), although a recent publication describing allylic substitution with oxazole and oxadiazole anions mentions that the method is not applicable to imidazole derivatives.[20] Herein, we present the results of this investigation.

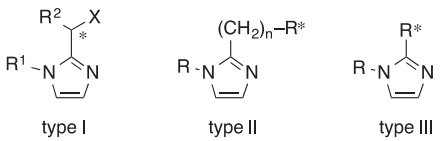

Fig. 1. Imidazole derivatives with chiral alkyl residues.

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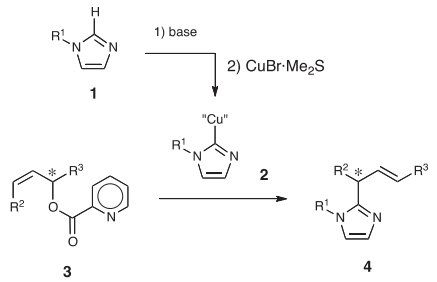
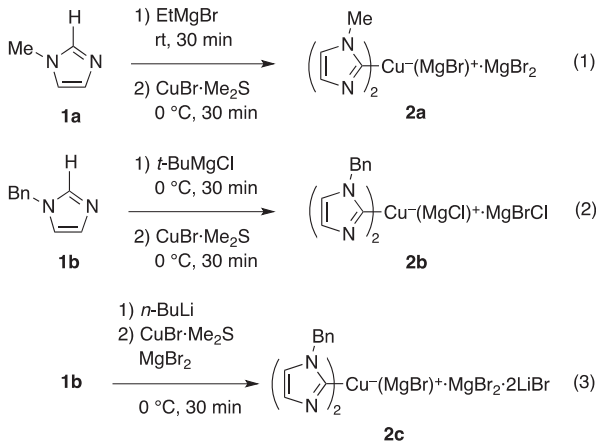


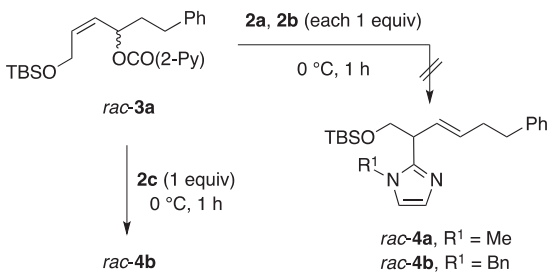
Scheme 1. Synthesis of chiral imidazoles and imidazolium salts through allylic substitution.

2. Results and discussion

First, 1-methylimidazole (**1a**) was treated with EtMgBr in THF at room temperature for 30 min to obtain the magnesium anion as a white precipitate (Scheme 2, Eq. 1). The anion was mixed with $CuBr\cdot Me_2S$ in a 2:1 ratio at 0 °C for 30 min and the supposed copper reagent **2a** (1 equiv) was subjected to reaction with the racemic picolinate *rac*-**3a** (1 equiv) under the conditions established for $Ph_2Cu(MgBr)\cdot MgBr_2$ (0 °C, 1 h) (Scheme 3). Unfortunately, most of *rac*-**3a** was unreacted and recovered. Conversely, the reaction of 1-benzylimidazole (**1b**) with *t*-BuMgCl afforded the magnesium anion, which was soluble in THF. However, the derived copper reagent **2b** did not show any reactivity for the substitution.



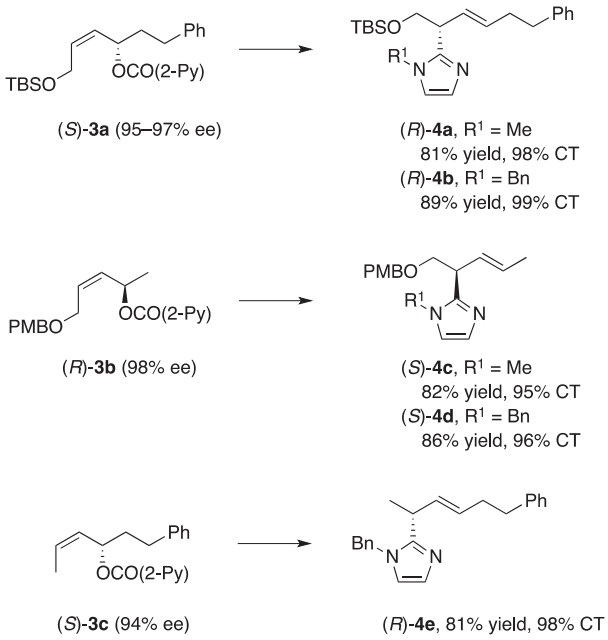
Scheme 2. Preparation of copper reagents.



Scheme 3. Preliminary results of allylic substitution.

The lithium version was also applied to the present study. Thus, $CuBr\cdot Me_2S$ (1 equiv) and freshly prepared $MgBr_2$ (3 equiv) were added to a solution of the anion derived from **1b** and *n*-BuLi at 0 °C to form copper reagent **2c** (Scheme 2, Eq. 3), which was subjected to reaction with *rac*-**3a** (0 °C, 1 h) to produce *rac*-**4b** with >98% regioselectivity (Scheme 3). Exclusive formation of the *trans* olefin in the product was confirmed by ^1H NMR spectroscopy (J_{H-H}=16 Hz). This result clearly demonstrates the higher performance of the lithium version over the magnesium version.

To assess the stereoselectivity of the substitution by chirality transfer (CT),[21] the substitution was repeated with optically active picolinate (*S*)-**3a** (95% ee) to afford (*R*)-**4b**[22] with 94% ee by chiral HPLC analysis of the derived alcohol and 99% CT (Scheme 4). Similarly, substitution of (*S*)-**3a** with the anion from **1a** afforded (*R*)-**4a** in 81% yield with 98% CT and >98% regioselectivity. Picolinates (*R*)-**3b** (98% ee) and (*S*)-**3c** (94% ee) were then examined and found to form (*S*)-**4c**, -**4d**, and (*R*)-**4e** in good yields with >95% CT and >98% regioselectivity.



Scheme 4. Synthesis of optically active imidazole derivatives.[a,b]
[a] Regioselectivity of the products were >98% by ^1H NMR spectroscopy. [b] CT: Chirality transfer.

The products were then converted to imidazolium salts. Briefly, *N*-alkylation of (*R*)-**4a** with MeI (2 equiv) in CH_2Cl_2 at 30 °C overnight afforded solids **5a** as a solid with mp 97–98 °C, as shown in Scheme 5. Furthermore, anion exchange of **5a** with $LiNTf_2$ in CH_2Cl_2/H_2O (1:1)[23] proceeded smoothly at room temperature (monitored by TLC) to afford **6a** as an oily compound in 85% yield. *N*-Alkylation of (*R*)-**4b** with BnBr (4 equiv) proceeded slowly to afford **5b** as an oil after two days. Anion exchange of **5b** with $LiNTf_2$ afforded **6b** as an oil. Likewise, (*S*)-**4c** and -**4d** were converted to the imidazolium salts **6c** and **6d** in good yields without any problems.

The present method was also applied to a pyridyl copper reagent. As shown in Scheme 6, the requisite lithium anion **7** (2 equiv), which was derived from 2-bromopyridine[24] (2.1 equiv) and *t*-BuLi (4 equiv) in Et_2O at −78 °C for 30 min, was treated with $CuBr\cdot Me_2S$ (1 equiv) and $MgBr_2$ (5 equiv) in THF (0 °C, 30 min) to afford the copper reagent. The quantity of $MgBr_2$ used was calculated on the basis of the guideline established for the lithium version of allylic substitution ($MgBr_2$>LiBr).[15] Substitution of (*S*)-**3a** with the pyridyl copper reagent was completed within 1 h at 0 °C, affording **8** in 86% yield with >99% regioselectivity by ^1H NMR spectroscopy and with >99% CT by chiral HPLC analysis. In addition, pyridine derivative **8** was converted to pyridinium salt **10** in good yield by *N*-methylation with MeI followed by anion exchange with $LiNTf_2$. Our method is complementary to the Zincke reaction with chiral amines[25] and *N*-alkylation of pyridine with alkyl derivatives[26] in the synthesis of chiral pyridinium salts.[27]