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Imidazolinium Salts as Catalysts for the Ring-Opening Alkylation of *meso* Epoxides by Alkylaluminum Complexes

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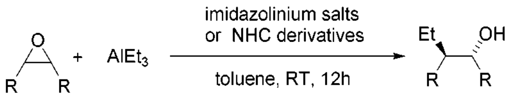
ABSTRACT



Imidazolinium salts and their N-heterocyclic carbene (NHC) derivatives catalyze the alkylation of a variety of *meso* epoxides in the presence of triethylaluminum (yield = 70–90%), under mild conditions. Imidazolinium salts are better catalysts than their NHC derivatives but can lead to dimerization side reactions under extended reaction time. Preformed NHC·AlEt$_3$ complexes and Wanzlick-type olefins, which are dimers of free NHCs, are also catalysts for this reaction.

Due to the prevalence of optically active alcohols as products and intermediates in fine chemical synthesis, substantial research efforts have been devoted to the catalytic synthesis of these versatile synthons.[1] Of the many pathways that have been explored, the desymmetrization of *meso*-epoxides via nucleophilic addition of a carbon nucleophile is particularly attractive due to the simultaneous formation of a carbon−carbon bond. To date, the most common nucleophilic alkylating reagents used in this catalytic addition reaction have been organometallic complexes such as alkyllithium, Grignard reagents, organocopper, and/or alkylaluminum compounds.[2−4] However, the use of alkylithium and Grignard reagents is only of moderate synthetic utility due to facile rearrangements of epoxides.[2] Although organocopper reagents are the best to date for epoxide desymmetrization, their complicated synthesis often limits their laboratory utility.[2] Since trialkylaluminum compounds are readily available commercially and are prepared inexpensively on an industrial scale, they are ideal reagents for the nucleophilic alkylation of epoxides.[5] Furthermore, organoaluminum reagents have been known to give excellent yields of nucleophilic addition products when other carbon nucleophiles fail.[2,6] Thus, any catalyst promoting the utilization of alkylaluminum reagents for epoxide alkylation reactions would greatly expand the current scope of alcohol-forming methodology.

Recently, Schneider et al. reported the high-yield synthesis of alcohols from the ring-opening reaction of epoxides with triethylaluminum using catalytic amounts of Lewis bases such as phosphines.[4] For decades, the use of phosphines as ligands has been ubiquitous in organometallic chemistry.[7−9] More recently N-heterocyclic carbenes (NHC), so-called “phosphine-mimics”, have attracted attention as an alternative to phosphine ligands in homogeneous catalysis.[10] More importantly, NHC are less toxic and can be synthesized in a

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[1] Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361−14384.

[2] Smith, J. G. *Synthesis* **1984**, 629−656.

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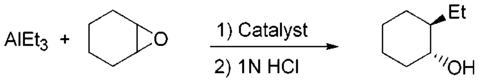
more facile manner compared to phosphine compounds. Recent developments have also shown that NHC closely mimic tertiary phosphines electronically[8] and that these ligands may be interchangeable in homogeneous catalysis. In fact, researchers have utilized members of the NHC ligand family in place of tertiary phosphines in a variety of reactions, such as the palladium-mediated Heck[11] and amination[12] reactions, the rhodium-catalyzed hydrosilylation[13] and hydroformylation[14] of olefins, and the ruthenium-catalyzed olefin metathesis reaction.[15] On the basis of these reports, we hypothesized that NHC may also be useful as catalysts for the addition of triethylaluminum to epoxides (reaction 1).



(1)

We were pleasantly surprised to find that not only do NHC catalyze this reaction but the precursors to NHC, imidazolinium salts, also exhibit very high activity. Herein, we wish to report the catalytic ring-opening desymmetrization of *meso* epoxides using triethylaluminum and catalytic amounts of either an imidazolinium salt or an NHC.

Compounds **1**, **3**, and **4** were synthesized according to literature procedures.[16,17] The imidazolinium salt **2** was synthesized by adapting literature reports of similar compounds.[16] The free carbene **5** can be generated by deprotonation of imidazolinium salt **3** with potassium hydride.[17] This free carbene coordinates to $AlEt_3$ to give **6**, which can be isolated in quantitative yield (Scheme 1, Supporting Information).[18]

Scheme 1. Formation of a Stable Aluminum Carbene Complex

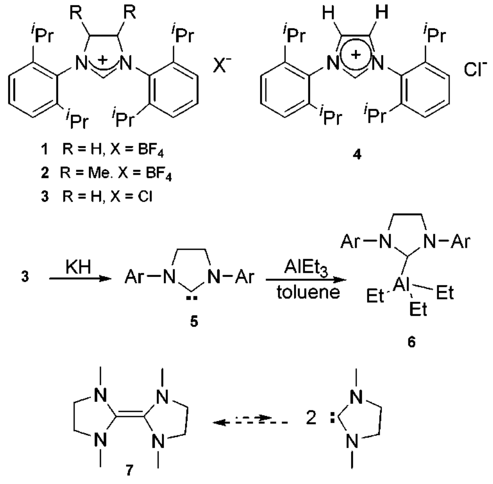
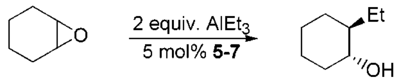


Table 1. $AlEt_3$ Ring Opening of Cyclohexene Oxide[a]



entry	catalyst	time (h)	yield (%)[b]
1	none	24	0
2	**5**	24	28
3	**6**	24	76
4	**7**	24	40

[a] Reaction conditions: $AlEt_3$ (2 equiv), toluene, room temperature. [b] Determined by GC vs internal standard.

As a substrate for the ring-opening addition of triethylaluminum, cyclohexene oxide is unreactive (Table 1, entry 1). However, with the addition of the free carbene **5** (5 mol %), the epoxide can be alkylated at room temperature to form *trans*-2-ethylcyclohexanol in 28% yield after 24 h (Table 1, entry 2). To improve this conversion, we investigated the activity of other nucleophilic carbene catalysts, such as a preformed aluminum carbene complex **6**[18] and the "*Wanzlick-type*" olefin **7** (Figure 1).[19]

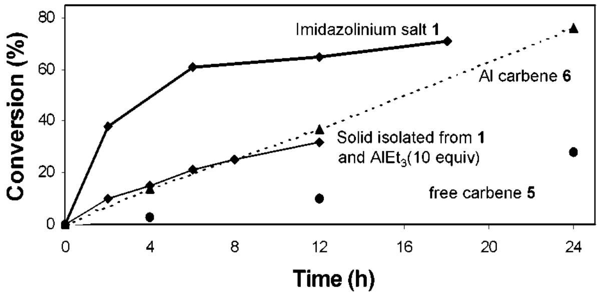


Figure 1. Effect of catalyst generation conditions on the ring opening of cyclohexene oxide.

The aluminum carbene complex **6** demonstrated improved catalytic activity over the free carbene for the ring-opening of cyclohexene oxide (Table 1, entry 3). This is quite surprising when we consider that **6** should form in the free carbene-catalyzed reaction where $AlEt_3$ is used in excess. The ^1H NMR spectrum of **6** and 1 equiv of $AlEt_3$ at room temperature in C_6D_6 shows a broadening of the CH_2 protons of $AlEt_3$; however, no broadening of the CH_2 protons of **6**

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is observed. Interestingly, the Wanzlick-type olefin **7**, which has been reported and debated to exist in equilibrium with free NHC species (Scheme 1),[20−22] also catalyzes reaction 1 (Table 1, entry 4). Presumably, **7** dissociates into the corresponding NHC under our reaction conditions to give an active NHC-type catalyst.

Given the high acidity of the C^1 proton of the imidazolinium salts **1**−**4**, we theorized that the alkyl groups of $AlEt_3$ could be used as Brönsted bases to directly generate the carbene catalyst in situ for reaction 1. Complete deprotanation, if achieved, would be observable by dissolution of the toluene-insoluble imidazolinium salt. Indeed, heterogeneous slurries of **1**−**4** in toluene become homogeneous in the presence of only 1 equiv of $AlEt_3$.

Building upon this result, we employed catalytic amounts of **1**−**4** directly in reaction 1. We noted an increase in catalytic activity during the first 8 h of the reaction. During this initial time, the activity is more than three times that observed for either the free carbene **5** or the preformed aluminum carbene complex **6** (Figure 1). This rate acceleration cannot be attributed to either the BF_4 anion or acidic C^1 protons which result from an incomplete deprotonation of the imidazolinium salt as both NH_4BF_4 and 2,6-lutidinium chloride do not catalyze reaction 1 (Table 2, entries 5 and 6).

Table 2. $AlEt_3$ Ring Opening of Cyclohexene Oxide by Imidazolinium Salts[a]

entry	catalyst	time(h)	yield (%)[b]
1	**1**	12	71
2	**2**	12	93
3	**3**	12	62
4	**4**	12	20
5	NH_4BF_4	24	6
6	lutidine·HCl	24	3

[a] Reaction conditions: $AlEt_3$ (2 equiv), toluene, room temperature. [b] Determined by GC vs internal standard

The rate acceleration observed for the in situ generated catalysts that result from the reaction of **1**−**4** and $AlEt_3$ is specific to the initial generation conditions. The direct reaction between the imidazolinium salt **1** with $AlEt_3$ (10 equiv) in toluene (reaction time = 12 h) yielded a white solid after the removal of all volatile reactants. The ^1H NMR spectrum of this solid is quite complicated and is different from that of the Al(carbene) complex **6**. This solid is not as active as **1**. However, its activity is very similar to that of complex **6** during the first 12 h of the reaction (Figure 1).

When using the imidazolinium salts **1**−**4** as catalysts, prolonging the overall reaction time beyond 18 h leads to formation of *trans*-2-[(*trans*-2-ethylcyclohexyl)oxy]cyclohexanol as the side product and thus a decrease in the overall yield of the desired *trans*-2-ethylcyclohexanol product.

The saturated imidazolinium salts **1**−**3** were found to give higher yields than their unsaturated analogue **4** (Table 2, entries 1−4). Further, complex **1** possessing a noncoordinating BF_4 counterion results in better catalytic activity than **3** which has a Cl counterion (Table 2, entries 1 and 3).

Although the uncatalyzed reaction between terminal epoxides and $AlEt_3$ proceeds at room temperature,[4] cyclic epoxides such as cyclopentene and norbornene oxides are only slightly reactive with triethylaluminum (Table 3, entries 1a and 3a). Using precatalyst **2**, the ring-opening nucleophilic addition of $AlEt_3$ to these substrates was greatly accelerated (Table 3, entries 1b and 3b). In addition to cyclic epoxides, 2,3-butene oxide, an acyclic epoxide that exhibits no reactivity toward triethylaluminum, produced over 50% yield of 3-methylpentan-2-ol under our reaction conditions (Table 3, entries 2a and 2b).

Table 3. $AlEt_3$ Addition to *meso* Epoxides Catalyzed by **2**[a]

entry	substrate	catalyst	time (h)	yield (%)[b]
1a	cyclopentene oxide	none	12	0
1b		**2**	12	77
2a	2,3-butene oxide	none	12	0
2b		**2**	12	53
3a	norbornene oxide	none	4	25[c]
3b		**2**	4	90[c]
4a	2,3-epoxy-2,3-dimethylbutane	none	12	0
4b		**2**	12	15

[a] Reaction conditions: **2** (5 mol %); $AlEt_3$ (2 equiv), toluene, room temperature. [b] Determined by GC vs internal standard. [c] 1 equiv of $AlEt_3$.

In summary, the alkylation of *meso* epoxides with $AlEt_3$ can be successfully accomplished using catalytic amounts of imidazolinium salts, their NHC derivatives, and Wanzlick-type olefins to produce functionalized alcohols. Further mechanistic study of this catalyst system will be reported in due course.

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Supporting Information Available: Synthetic procedures and characterization data for **2** and **6** and experimental and analytical procedures (including a typical GC trace). This material is available free of charge via the Internet at http://pubs.acs.org.

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