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Grignard allylic substitution catalyzed by imidazol-2-ylidene- and imidazol-4-ylidene-magnesium complexes

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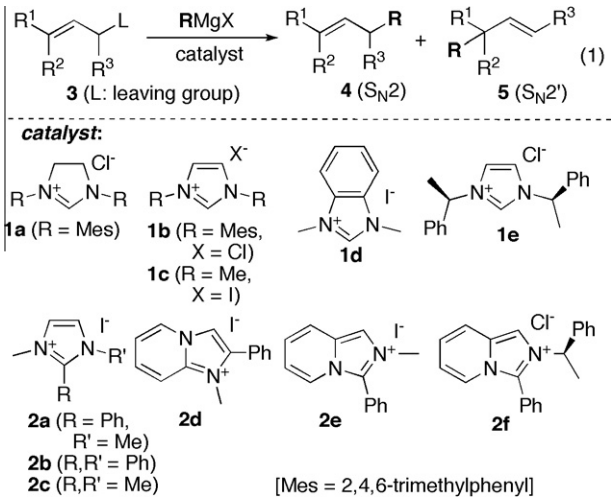
ABSTRACT

In the presence of a catalytic amount of 1,2-disubstituted or 1,2,3-trisubstituted imidazolium salts, γ-substituted allyl chlorides reacted with alkyl Grignard reagents to undergo substitution reactions in an S_N2'-selective fashion, where the magnesium ate complexes [(*N*-heterocyclic carbene-MgR_3)$^-$(MgX)$^+$] of imidazol-2-ylidenes or imidazol-4-ylidenes, generated in situ, were postulated as the active species. It was observed that the reactions with imidazol-4-ylidene catalysts were faster than those with imidazol-2-ylidenes. Enantioselective catalysis using a chiral imidazolium salt was preliminarily investigated.

Controlling the reactivities of nucleophilic organometallic compounds is key to the success of selective bond formation. It is well known that the properties of organometallics R_mMX_n can be altered by the coordination of Lewis-basic solvents or chelating agents and/or by the complexation with other inorganic or organometallic materials such as LiCl and Li(acac).[1] Indeed, the reactivity control achieved in this manner has been accepted as a versatile means for developing and tuning these reactions. However, most of these schemes require a stoichiometric or solvent amount of the controlling reagent.[2]

Catalytic use of Lewis-basic reagents is most efficient for controlling the regiochemical and stereochemical course of a reaction, involving an asymmetric catalysis exemplified by Lewis base-activated aldol[3] and allylation[4] reactions of carbonyl compounds. Recently, Lewis base-catalyzed, Cu-free allylic substitution reactions with organomagnesium and organozinc reagents have been reported. Lee and Hoveyda reported asymmetric allylic alkylation reactions with Grignard reagents using chiral *N*-heterocyclic carbenes[5] (NHCs) as Lewis base catalysts,[6] where, based on the observation that lack of a phenolic OH in the side-chain of the precursor imidazolium salt caused low reactivity and selectivity, magnesium 4,5-dihydroimidazol-2-ylidene alkoxide was postulated as an active catalyst. Kondo and co-workers reported allylic substitution of 4-chloro-2-alkylbutenoates with dialkylzinc reagents in the presence of catalytic phosphazene base (*t*-Bu-P4 base) and LiCl to selectively yield S_N2' products.[7] These findings clearly demonstrate the effects of Lewis base coordination in altering the reactivity of RMgX and R_2Zn reagents. However, the researches have been restricted to the reaction of 4-chloro-2-alkylbutenoates (tiglic acid esters). Herein, we report the γ-selective Grignard allylic substitution reactions of γ-alkyl- or aryl-substituted allylic chlorides and phosphates **3** catalyzed by an NHC catalyst (Eq. 1), involving imidazol-2-ylidenes as well as imidazole-4-ylidenes, which can possibly be generated in situ from the corresponding imidazolium salts such as **1a–c** and **2a–d** (Scheme 1). During this investigation, quite recently, Alexakis and co-worker have reported an improved, efficient asymmetric allylic substitution procedure with use of chiral imidazol-2-ylidenes, which also have a side chain having a phenolic OH as an N-substituent.[8]

First, we investigated the reaction of *trans*-1-chloro-3-nonene (**3a**) with *n*-BuMgCl in the presence of various imidazolium salts illustrated in Scheme 1. The reactions were quenched after 6 h and the results are shown in Table 1. The reaction in the absence of an imidazolium salt was very slow, and yielded only a trace amount of S_N2 product **4a** (data not provided). As observed from



Scheme 1. Grignard allylic substitution in the presence of an imidazolium salt.

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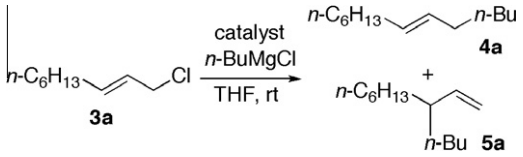
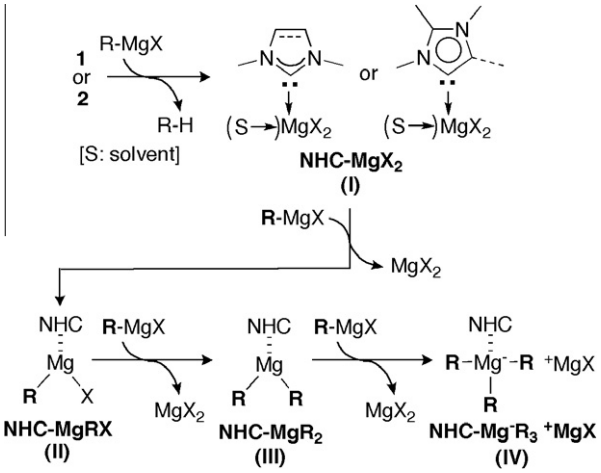
Table 1
Reaction of **3a** with *n*-BuMgCl in the presence of 5 mol % of imidazolium salt **1** or **2**[a]



Run	Catalyst (5 mol %)	Conversion[b] (%)	**4a**:**5a**[b]
1	**1a**	43	1:99
2	**1b**	36	2:98
3	**1c**	99	2:98
4	**1d**	60	48:52
5	**2a**	99	4:96
6	**2b**	96	6:94
7	**2c**	94	5:95
8	**2d**	93	6:94
9	**2e**	93	7:93

[a] Compound **3a** (1.0 mmol), *n*-BuMgCl (1.5 mmol, 0.90 M in THF), **1** or **2** (0.05 mmol), THF (5 mL).
[b] Determined by ^{1}H NMR analysis of the crude mixture using an internal standard.



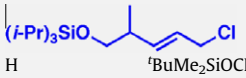
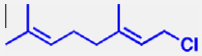
Scheme 2. Postulated organometallic compounds involved in the reaction mixture.

the table, all imidazolium salts employed catalyzed the substitution reaction cleanly to yield a mixture of **4a** and **5a**. In all cases, except for **1d** (run 4), the S_N2' product **5a** was provided highly selectively. The 1,2,3-trisubstituted imidazolium salts **2a**–**e**, which may be deprotonated by the reaction with Grignard reagent to generate imidazol-4-ylidene, effectively catalyzed the reaction to complete within 6 h at room temperature (runs 5–9). Meanwhile, the reactions with 1,2-disubstituted imidazolium salts **1** (except for **1c**), precursors of the corresponding imidazol-2-ylidenes, were relatively slow (runs 1, 2, and 4). Imidazolium salts **1**, except for **1d**, exhibited higher selectivity than **2** did.

Table 2 summarizes the results of the reaction of various allylic substrates with *n*-BuMgCl in the presence of an imidazolium salt **1a** or **2a** (5 mol %) (Eq. 1 in Scheme 1). As observed from runs 1 to 7, the reaction of γ-alkyl-substituted allylic substrates with *E*- or *Z*-geometry proceeded in a highly S_N2'-selective way. Aryl substitution at the γ-position decreased the regioselectivity (runs 8–11). Although carboxylic esters and 2-pyridyl ethers were poor substrates (data not provided), allylic chlorides and phosphates were good substrate, with the former demonstrating better selectivity. For both chlorides and phosphates, **1a** always achieved better regioselectivity than **2a**, although the reaction with **1a** needed longer time. Substitution of secondary allylic chlorides proceeded with a high S_N2' selectivity (run 12), albeit in a low yield of substitution products, as a result of competitive dehalogenative homocoupling through the generation of an allylic anion by the attack of the reagent on the chlorine atom. Due to their steric hindrance (run 13), γ,γ-disubstituted allylic substrates demonstrated low S_N2' selectivity. The reactions in diethyl ether as well as in THF were nearly equivalent (runs 7, 8, and 10). In the reaction labeled run 6, moderate 1,2-diastereoselectivity (75%) was observed for the S_N2' product. Regarding Grignard reagents, the reaction with secondary alkyl-MgX and aryl-MgX, such as, *i*-PrMgCl and PhMgBr, yielded a mixture of **4** and **5** quantitatively but in an S_N2 selective way (for the reactions of **3a** in the presence of **2a**, the ratios **4**:**5** were 58:42 and 85:15, respectively).

We postulated the organometallic compounds involved in the reaction mixture, as illustrated in Scheme 2, where imidazolium

Table 2
Allylic substitution reactions with *n*-BuMgCl catalyzed by **2a** or **1a**[a]

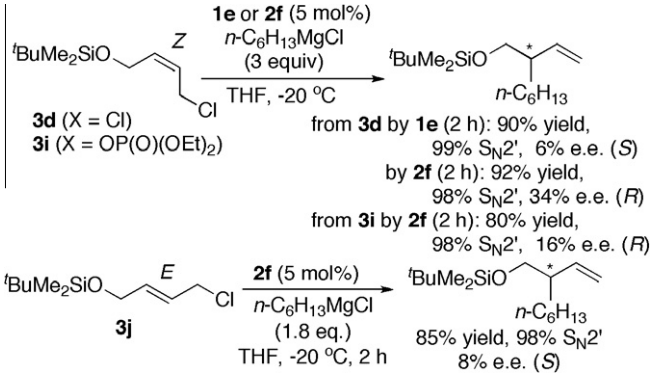
Run	**3**	R^1	R^2	R^3	L	Catalyst	h[b]	S_N2/S_N2' (**4**:**5**)[c]	Yield[d] (%)
1	**3a**	*n*-C_6H_{13}	H	H	Cl	**2a**	6	4:96	99
2	**3a**	*n*-C_6H_{13}	H	H	Cl	**1a**	28	1:99	97
3	**3a′**	*n*-C_6H_{13}	H	H	$OP(O)(OEt)_2$	**2a**	6	18:82	99
4	**3a′**	*n*-C_6H_{13}	H	H	$OP(O)(OEt)_2$	**1a**	25	2:98	97
5	**3b**	*c*-C_6H_{11}	H	H	Cl	**2a**	8	5:95	97
6	**3c**					**2a**	43	11:89 [d.r. 75:25][e]	90
7	**3d**	H	^{t}BuMe$_2$SiOCH$_2$	H	Cl	**2a**	4 (3)[f]	5:95, 3:97 [f]	95 (90) [f]
8	**3e**	Ph	H	H	Cl	**2a**	2 (2) [f]	15:85, 21:79 [f]	92[g] (99) [f]
9	**3e**	Ph	H	H	Cl	**1a**	4	8:92	92[g]
10	**3e′**	Ph	H	H	$OP(O)(OEt)_2$	**2a**	0.5 (0.5) [f]	32:68, 46:54 [f]	99 (99) [f]
11	**3e′**	Ph	H	H	$OP(O)(OEt)_2$	**1a**	0.5	4:96	99
12	**3g**	Ph	H	Me	Cl	**2a**	48	4:96	45[h]
13	**3h**					**2a**	9	37:63	99

[a] Substrate (1.0 mmol), *n*-BuMgCl (1.5 mmol, 0.90 M in THF), **2a** (0.05 mmol) in THF (5 mL) at room temperature.
[b] Reaction time.
[c] Determined by ^{1}H NMR analysis of the crude mixture.
[d] Yield of a mixture of S_N2' and S_N2 products after column chromatography.
[e] Diastereomeric ratio (*anti*:*syn*) of S_N2' product.
[f] The reaction was performed in ether using a Et_2O solution of *n*-BuMgCl.
[g] Dehalogenative homocoupling (8%) products of the substrate were co-produced.
[h] Dehalogenative homocoupling products (37%) of the substrate were co-produced (see footnote [9]). Obtained as a mixture of alkene geometric isomers.

Table 3
Results of the stoichiometric reactions of **3a** with **1b** (2 equiv) and *n*-BuMgCl (3.1–6.7 equiv)[a]

Run	Grignard[b]–(equiv as an anion source)[c]	Reagent types[d] (equiv)	h	Conversion (%) (**4a**:**5a**)[e]
1	3.1 Equiv (1.1 equiv)	**I** (0.9) + **II** (1.1)	44	No reaction
2	4.9 Equiv (2.9 equiv)	**II** (1.1) + **III** (0.9)	44	96 (65:35)
3	6.7 Equiv (4.7 equiv)	**III** (1.3) + **IV** (0.7)	10	97 (27:73)
4	1.5 Equiv with 5 mol % of **1b** [catalytic condition]		28	97% (2:98)

[a] Substrate (1.0 mmol), *n*-BuMgCl (3.1–8.2 mmol, 0.94 M in THF), **1b** (2.0 mmol) in THF (7 mL) at room temperature.
[b] The Grignard reagent was titrated prior to use.
[c] Equivalent for deprotonation of **1b** was deducted.
[d] Postulated considering the reagent stoichiometry and the mechanism depicted in Scheme 2.
[e] Determined by ^{1}H NMR analysis of the crude mixture.



Scheme 3. Preliminary study on asymmetric reactions.

salt **1** or **2** was deprotonated by the reaction with a Grignard reagent to generate the corresponding carbene, imidazol-2-ylidene or imidazol-4-ylidene, respectively, and yield the corresponding NHC-MgX_2 (**I**) complexes. Under catalytic conditions, subsequent substitution and complexation of the resulting NHC-MgX_2 complex with the Grignard reagents might yield NHC-MgRX (**II**), NHC-MgR_2 (**III**),[10] an ate complex $(NHC\text{-}MgR_3)^-(MgX)^+$ (**IV**),[11] and their solvated derivatives.

To confirm the active intermediate(s) among these schemes, the stoichiometric reactions were investigated (Table 3). Thus, to a mixture of imidazolium salt **1b** (2.0 equiv) in THF was added dropwise a THF solution of *n*-BuMgCl (equiv indicated in the table) at 0 °C. After being stirred for 1 h at room temperature, a solution of **3a** (1.0 equiv) in THF was added. An analysis of the hypothetical mechanisms illustrated in Scheme 2 and the reagent stoichiometry suggests that the use of 3.1, 4.8, 6.6, and 8.2 equiv of the Grignard reagent, respectively, would generate the following combinations of the reagents: NHC-MgX_2/NHC-MgXR [**I** (0.9 equiv) + **II** (1.1 equiv)] (run 1), NHC-MgXR/NHC-MgR_2 [**II** (1.1 equiv) + **III** (0.9 equiv)] (run 2), NHC-MgR_2/$[(NHC\text{-}MgR_3)^-(MgX)^+]$ [**III** (1.3 equiv) + **IV** (0.7 equiv)] (run 3), because 2 equiv of the Grignard reagent (1 equiv to **1b**) were consumed in the deprotonation of **1b**. The reaction mixture comprising **I** and **II** did not react with **3a** (run 1). The reaction with reagent **III** (a mixture with **II**) afforded **4a** and **5a** in good yield, but the reaction was slow and yielded S_N2 product **4a** predominantly (run 2). Contrastingly, the reactions involving reagent **IV** proceeded much faster (run 3) and demonstrated S_N2' selectivity. These results suggest that the reaction under catalytic conditions may involve (NHC)(trialkyl)magnesium ate complex $[(NHC\text{-}MgR_3)^-(MgX)^+]$ (**IV**) as a rapid, active species.

The σ-donative nature of the ligating imidazolylidenes in NHC-magnesium complexes might have a significant effect on the reaction rate and selectivity. Recently, efforts have been devoted to the evaluation of the σ-donating ability of NHC ligands.[12] Based on the currently available data for the C2- and C4-bound carbenes (imidazol-2- and -4-ylidenes), the carbenes derived from the corresponding salts **1** and **2** can be classified in the following order of donor strength: **2c** > **2a** > **2b** > **2d** > **2e** ≫ **1c** > **1d** > **1a** > **1b**. This is in good agreement with the order of the rate of the reaction with each salt. Increasing σ-donating ability of NHC might enhance the nucleophilicity of NHC-magnesium complexes.

Scheme 3 depicts the preliminary results of the asymmetric allylic substitution reaction[13] using enantiomerically pure imidazolium salts **1e** and **2f**. The reaction of **3d** with *n*-$C_6H_{13}MgCl$ in the presence of 5 mol % of **2f** at −20 °C afforded the corresponding S_N2' product with a high yield and high regioselectivity, but with moderate enantiomeric excess (34% ee).[14] Ee was reduced with phosphate **3i** or *E* substrate **3j**, the later of which demonstrated an opposite enantioselectivity to *Z* isomer **3d**.

We demonstrated that *N*-heterocyclic carbenes (NHCs), imidazol-2-ylidenes, and imidazolium-4-ylidenes, catalyzed a γ-selective Grignard substitution reaction of γ-substituted allyl chlorides and phosphates, in which magnesium ate complexes $(NHC\text{-}MgR_3)^-(MgX)^+$ were postulated as the active species. It is possible to apply this reaction to an asymmetric reaction catalyzed by a chiral imidazol-4-ylidene. Further investigations, which include improvement of enantioselectivity, are still being conducted.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.067.

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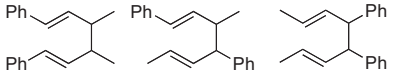
9. Dehalogenative homocoupling products shown below were co-produced.



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