



## Grignard allylic substitution reaction catalyzed by 1,2,3-triazol-5-ylidene magnesium complexes

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### ABSTRACT

Allylic chlorides and phosphates reacted with alkyl-Grignard reagent in an  $S_N2'$ -selective manner in the presence of a catalytic amount of 1,2,3-triazol-5-ylidenes to provide  $\alpha$ -branched alkenes.

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Controlling the reactivities and selectivities of nucleophilic organometallic compounds,  $R_mMX_n$ , is key to the success of selective bond formation. The electronic and/or steric nature of these compounds can be altered by the coordination of Lewis-basic solvents or chelating agents and/or by complexation with other inorganic or organometallic materials such as LiCl and Li(acac).<sup>1</sup> Such reactivity control is accepted as a versatile means of developing and tuning these reactions. However, most of these schemes require stoichiometric or solvent quantities of the controlling reagent.<sup>2</sup> Catalytic use of Lewis-basic reagents is most efficient for controlling the regiochemical and stereochemical course of a reaction, as exemplified by asymmetric catalyses developed for the Lewis-base-activated aldol<sup>3</sup> and allylation<sup>4</sup> 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 that in asymmetric allylic alkylation reactions with Grignard reagents using chiral N-heterocyclic carbenes<sup>5</sup> (NHCs) as Lewis-base catalysts,<sup>6</sup> magnesium 4,5-dihydroimidazol-2-ylidene alkoxide was postulated as an active catalyst. This was based on the observation that the lack of a phenolic OH in the side-chain of the precursor imidazolium salt caused low reactivity and selectivity. Kondo et al. reported that the allylic substitution of 4-chloro-2-alkylbutenoates with dialkylzinc reagents in the presence of catalytic phosphazene base (*t*-Bu-P4 base) and LiCl selectively yields  $S_N2'$  products.<sup>7</sup> However, these

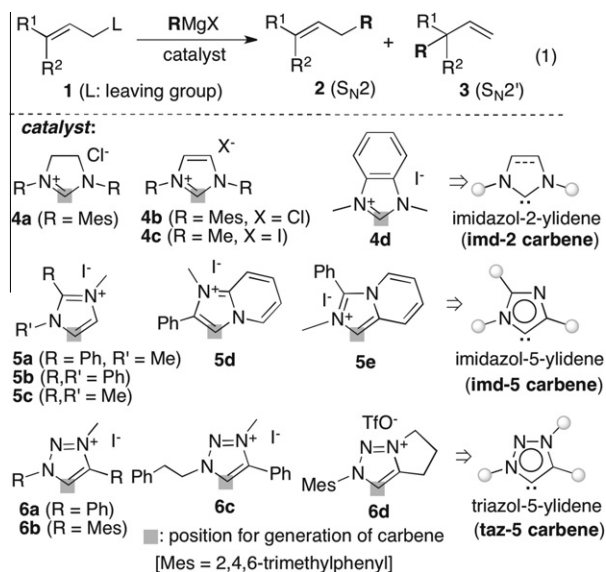
investigations have been restricted to the reaction of 4-chloro-2-alkylbutenoates (tiglic acid esters). Alexakis and co-workers have reported an improved, efficient asymmetric allylic substitution procedure based on chiral imidazol-2-ylidenes with a side-chain bearing a phenolic OH as an N-substituent.<sup>8</sup> These findings clearly demonstrate the effects of Lewis-base coordination in altering the reactivity of  $RMgX$  and  $R_2Zn$  reagents. Recently, we have developed  $\gamma$ -selective Grignard allylic substitution reactions of  $\gamma$ -alkyl- or -aryl-substituted allylic chlorides and phosphates, **1** catalyzed by imidazol-2-ylidenes (**imd-2** carbenes) as well as imidazole-5-ylidenes (**imd-5** carbenes) (Eq. 1), which can be possibly generated in situ from the corresponding imidazolium salts such as **4a-d** and **5a-e** (Scheme 1).<sup>9</sup>

It has been observed that the reactions with imidazol-2-ylidene (**imd-2**) were generally slower and more selective while those with imidazol-5-ylidene (**imd-5**) were faster and less selective.

Herein we report the  $\gamma$ -selective Grignard substitution reactions of allylic chlorides and phosphates **1** catalyzed by 1,2,3-triazol-5-ylidenes (**taz-5** carbenes),<sup>10</sup> which may be generated in situ from the corresponding triazolium salts **6a-d** (Scheme 1). It was found that, in comparison to catalysis with **imd-2** or **imd-5**, reactions with **taz-5** were reasonably rapid with a higher  $S_N2'$ -( $\gamma$ )-selectivity, which enables the construction of a quaternary carbon center from 3,3-disubstituted allylic chlorides. It has been reported that 1,2,3-triazol-5-ylidenes were coordinated to various metals and their donor properties were estimated to be compatible with the most basic 2-imidazolylidenes, albeit being slightly less basic than other abnormal carbenes.<sup>11</sup> This report presents the first example of catalytic use of 1,2,3-triazol-5-ylidene magnesium

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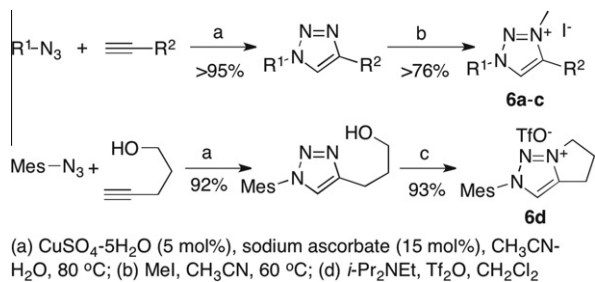


**Scheme 1.** N-heterocyclic carbene-catalyzed allylic Grignard substitution.

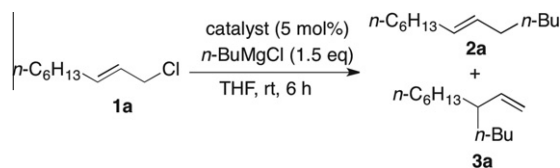
complexes in organic transformation and comparison of their reactivity with that of imidazol-2-ylidene and imidazole-5-ylidene complexes.

Trisubstituted 1,2,3-triazolium salts **6a–d** were synthesized by the copper-catalyzed azide-alkyne [3+2] cycloaddition (Huisgen reaction)<sup>12</sup> followed by inter- or intra-molecular N-alkylation reaction (Scheme 2).<sup>13</sup>

Initially, we investigated the reaction of *trans*-1-chloro-3-nonene (**1a**) with *n*-BuMgCl in the presence of various imidazolium salts, **4a,b** or **5a,b** or triazolium salts **6a–d** to compare their catalytic activity and selectivity (Scheme 3). The reactions were quenched after 6 h and the results are shown in Table 1. The reaction in the absence of an imidazolium or triazolium salt was very slow and yielded only a trace amount of the  $S_N2$  product **2a** (data not provided). As shown in the table, all imidazolium and triazolium salts cleanly catalyzed the substitution reaction to yield a mixture of **2a** and **3a**. In all cases, the  $S_N2'$  product **3a** was obtained with high selectivity. The 1,2,3-trisubstituted imidazolium salts **5a,b** and 1,3,4-trisubstituted 1,2,3-triazolium salts **6a–d**, which may be deprotonated by the reaction with a Grignard reagent to respectively generate **imd-5** or **taz-5** carbenes, effectively catalyzed the reaction to complete in <6 h at room temperature (runs 3–8). Meanwhile, the reactions with 1,3-disubstituted imidazolium salts **4a** and **4b**—precursors of the corresponding **imd-2** carbenes—were relatively slow (runs 1 and 2), when the reaction for 6 h did not complete and over 55% of the substrate **1a** was recovered. Since **4a** (or **4b**) and **6b** have the same substituents (mesityl) at the carbene-carbon  $\beta$ , the observed difference of reactivity may



**Scheme 2.** Preparation of 1,2,3-triazolium salts **6a–d**.



**Scheme 3.** Reaction of **1a** with *n*-BuMgCl.

**Table 1**

Reaction of **1a** with *n*-BuMgCl in the presence of 5 mol % of an imidazolium salt, **4a–d** or **5a–e** or triazolium salt **6a–d**<sup>a</sup>

Run	Catalyst (5 mol %)	Conversion <sup>b</sup>	<b>2a</b> : <b>3a</b> <sup>b</sup> ( $\alpha$ : $\gamma$ )
1 <sup>c</sup>	<b>4a</b>	43	1:99
2 <sup>c</sup>	<b>4b</b>	36	2:98
3 <sup>c</sup>	<b>5a</b>	99	4:96
4 <sup>c</sup>	<b>5b</b>	96	6:94
5	<b>6a</b>	96	1:99
6	<b>6b</b>	99	2:98
7	<b>6c</b>	93	1:99
8	<b>6d</b>	98	5:95

<sup>a</sup> Compound **1a** (1.0 mmol), *n*-BuMgCl (1.5 mmol, 0.90 M in THF), **4**, **5**, or **6** (0.05 mmol), THF (5 mL).

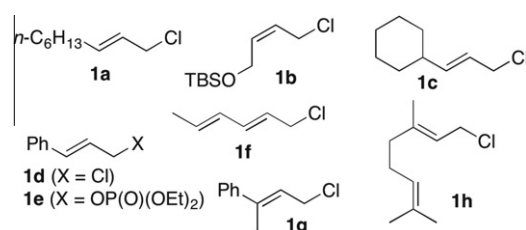
<sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude mixture using an internal standard.

<sup>c</sup> Previous results (see Ref. 9).

mainly attribute to an electronic reason (runs 1, 2, and 6). The TLC analyses of the reaction mixtures indicated that the reaction with **5a** was faster than that with **6b**. Overall, 1,2,3-triazol-5-ylidenes (**taz-5** carbenes) was able to combine both high reactivity and  $S_N2'$ -selectivity.

With these results in hand, we further studied the reaction of various allylic substrates **1** illustrated in Figure 1 and several Grignard reagents in the presence of 5 mol % of the representative salts of **4a** (or **4b**), **5a**, or **6b** (Table 2).<sup>14</sup> For comparison, **4a**, **4b**, and **6b** having the same substituents at the carbene-carbon  $\beta$  were chosen.

For the reaction of a secondary Grignard reagent (*i*-PrMgCl) (runs 1–3), only **taz-5** carbene from **6b** gave satisfactory yield and selectivity (run 3). The **4b**- and **5b**-catalyzed reactions showed much lower selectivity. Meanwhile, the reaction with the aryl-Grignard reagent (PhMgCl) resulted in a low selectivity to predominantly give the  $\alpha$ -substituted product (runs 4 and 5). The **6b**-catalyzed reactions with silyloxymethyl- and secondary alkyl-substituted substrates, **1b** and **1c**, also proceeded very selectively (runs 6 and 7). The **imd-2** or **taz-5** carbene from **4a** or **6b**, respectively, selectively catalyzed the reaction of cinnamyl chloride (**1d**) and phosphate **1e** to afford the corresponding  $S_N2'$  product **3d** in excellent yield (runs 8, 10, 11, and 13) but the reactions with **imd-5** carbene from **5a** showed relatively low selectivity (runs 9 and 12). All **4b**-, **5a**-, **6b**- and IMes-CuCl-catalyzed reactions of the conjugated diene substrate **1f** produced a mixture of  $S_N2'$  ( $\alpha$ -) and  $S_N2'$  ( $\gamma$ -) products **2f** and **3f**, but the  $\epsilon$ -substituted



**Figure 1.** Allylic substrates.

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