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Regioselective propargylation of aldehydes using potassium allenyltrifluoroborate promoted by tonsil

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ABSTRACT

The propargylation of aldehydes using potassium allenyltrifluoroborate promoted by tonsil, an inexpensive and readily available clay, in a chemo- and regioselective way is described. The method is simple and avoids the use of air and moisture sensitive organometallics and products were obtained in good to moderate yields.

The most used method for the formation of new C–C bonds is based on the addition of organometallic reagents to carbonyl compounds.[1] In this context, the propargylation reaction plays an important role due to the high density of functional groups in the resulting products.[2] However, there are two major issues associated with the propargylation reaction, both intrinsically related: the use of propargyl of allenyl organometallics and the regioselectivity of the obtained products.

It is know that some propargyl and allenyl organometallics can undergo metallotropic rearrangements during reactions with carbonyl compounds to give the corresponding products in low regioselectivity.[3] For propargyl magnesium bromide, for example, the regioselectivity of the reaction can be improved by $HgCl_2$[4] or $ZnCl_2$[5] poisoning, however, the high Lewis base character[6] of propargyl magnesium bromide makes the search for more stable and selective reagents to achieve the propargylation reaction a subject of the great interest.

The regioselectivity of reactions involving the less reactive tin, silicon and boron allenyl- or propargyl organometallics, generally proceed through a S_E2' mechanism by the direct addition of the organometallic to a carbonyl compound catalyzed by a Lewis acid or base,[6] so the use of an allenyl organometallic generally yields the corresponding propargyl alcohol and vice versa.[7]

In this work, we report the use of tonsil, an inexpensive and easily available commercial clay, to promote the addition of allenyl-boron compounds to aldehydes.

In the course of developing milder reaction conditions, first the type of boron compound and the appropriate reagent to promote the propargylation reaction was examined. Thus, allenylboronic acid pinacol ester, **1a** or potassium allenyltrifluoroborate, **1b** (1.5 mmol) and 3-nitro-benzaldehyde, **2a** (1 mmol) were treated at room temperature with different reagents using CH_2Cl_2 as the reaction solvent. The results are presented in Table 1.

When the reaction was performed using **1a**, a commercially available reagent, without the use of any promoter, the corresponding product **3a** was not observed after 48 h (Table 1, entry 1). The change of boron reagent to potassium allenyltrifluoroborate, **1b**, gave **3a** in only 30% conversion after 12 h (Table 1, entry 2). A dramatic effect was observed when different clays were used to promote the reaction where higher conversions were observed in all cases (Table 1, entries 3–6). Shorter reaction times were observed when tonsil clay was used as the reaction promoter, however, the reaction using **1b** proved to be more regioselective (Table 1, entries 3 and 4). The use of montmorillonite K-10[8] and KSF also gave **3a** in a regioselective way, but both reactions required longer reaction times for completion (Table 1, entries 5 and 6). This result is probably due to the higher superficial area of tonsil clay when compared to montmorillonites tested.[9]

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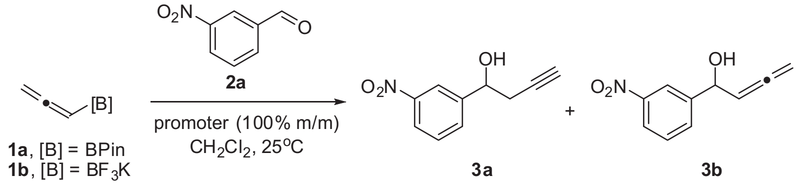
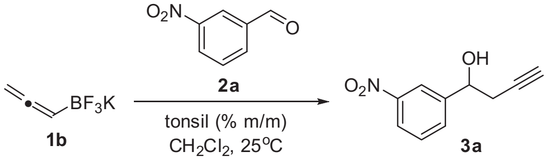
Table 1
Effect of promoter in the propargylation of 3-nitro-benzaldehyde **2a** by allenyl-boron compounds[a]



Entry	1	Promoter	Time (h)	**3a**:**3b**[b]	Conv.[c] (%)
1	**1a**	–	48.0	–	–
2	**1b**	–	12.0	100:0	30
3	**1a**	Tonsil	12.0	70:30	87
4	**1b**	Tonsil	4.0	100:0	99
5	**1b**	Montmorillonite K-10	6.0	100:0	99
6	**1b**	Montmorillonite KSF	6.5	100:0	99

[a] Reaction conditions: Reactions were performed with **2a** (1 mmol), **1a**–**b** (1.5 mmol) in CH_2Cl_2 (5 mL) at 25 °C for the time indicated.
[b] Determined by ^1H NMR.
[c] The conversion was determined by GC with respect to **1a**.

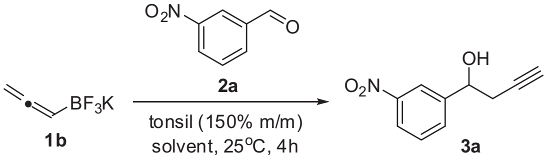
Table 2
Effect of the amount of tonsil on the propargylation of 3-nitro-benzaldehyde **2a** by potassium allenyltrifluoroborate **1b**[a]



Entry	Tonsil (% m/m)	Time (h)	Conv.[b] (%)
1	25	48	94
2	50	24	97
3	100	4	91
4	150	3.5	99
5	200	3.15	98

[a] Reaction conditions: Reactions were performed with **2a** (1 mmol), **1b** (1.5 mmol) in CH_2Cl_2 (5 mL) using different amounts of tonsil (% m/m) at 25 °C for the time indicated.
[b] The conversion was determined by GC with respect to **2a**.

Table 3
Effect of different solvents on the propargylation of 3-nitro-benzaldehyde **2a** by potassium allenyltrifluoroborate **1b**[a]



Entry	Solvent	Conv.[b] (%)
1	CH_2Cl_2	99
2	CH_2Cl_2/H_2O (1:1)	52
3	EtOH	46
4	H_2O	75
5	Et_2O	80

[a] Reaction conditions: Reactions were performed with **2a** (1 mmol), **1b** (1.5 mmol) in the appropriate solvent (5 mL) using tonsil (150% m/m) at 25 °C for 4 h.
[b] The conversion was determined by GC with respect to **2a**.

The above results demonstrated the viability of potassium allenyltrifluoroborate, **1b** as air and moisture stable reagent for the regioselective propargylation of aldehydes.

Next we investigated the effect of the amount of tonsil on the reaction yield. The load of tonsil was varied from 25% to 200% m/m (Table 2). Higher conversions of **2a** into **3a** were observed in all cases. However, by increasing the amount of tonsil shorter reaction times were required (Table 2, entries 2–5). No significant changes were observed by using 150% or 200% m/m of tonsil (Table 2, entries 4 and 5).

Finally, the solvent potentially suitable for the propargylation reaction was investigated. Accordingly, good conversions of **2a** into **3a** were observed when dichloromethane was used as the reaction solvent (Table 3, entry 1). When a 1:1 mixture of dichloromethane and water was used as the reaction medium, lower conversions into the desired product **3a** were observed (Table 3, entry 2).

A similar result was observed when ethanol was used as the reaction solvent, where only moderate conversions were observed (Table 3, entry 3). Surprisingly, when water was used as the reaction solvent, a moderate conversion was observed together with some decomposition of potassium allenyltrifluoroborate, **1b** (Table 3, entry 4). Lastly, the use of diethyl ether also gave moderate conversions (Table 3, entry 5).

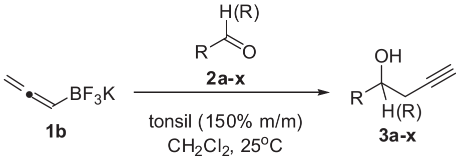
The optimized reaction conditions were then applied to a variety of aldehydes and the results are described in Table 4.[10] The reaction tolerates a wide range of functional groups, for example, aldehydes containing functionalities such as halides, ester, and nitrile were chemoselectively propargylated using the developed reaction conditions.

The reaction seemed to be more sensitive to steric than electronic effects. For example, when 2-nitrobenzaldehyde (Table 4, entry 3), 2-methyl-benzaldehyde (Table 4, entry 8) and 2-fluorobenzaldehyde (Table 4, entry 19) were used, the corresponding products were obtained in good yields but the reactions required longer periods of time for completion. Noteworthy, it is known that the addition of organometallic reagents to compounds functionalized with the nitro group is sometimes difficult, while this group is sensitive to reduction by metals.[11] Under the developed reaction conditions the reduction of the nitro group was not observed (Table 4, entries 1–3).

The chemoselectivity of the reaction was evaluated using ethyl 4-formylbenzoate, **2d** and 4-cyano-benzaldehyde, **2e**. In both cases, the only product observed was that derived from the addition into the aldehyde moiety (Table 4, entries 4 and 5).

Other aromatic aldehydes such as β-naphthaldehyde **2f** (Table 4, entry 6), benzaldehyde **2g** (Table 4, entry 7) and electron-rich

Table 4
Propargylation of compounds **2a–v** by potassium allenyltrifluoroborate **1b** promoted by tonsil[a]



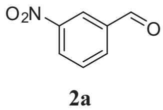
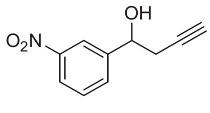
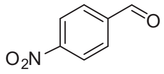
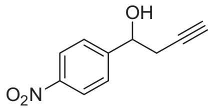
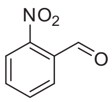
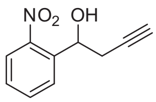
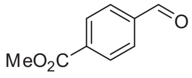
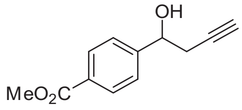
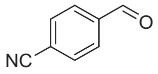
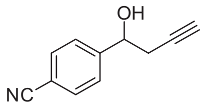
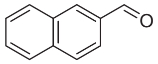
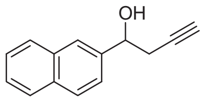
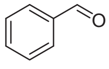
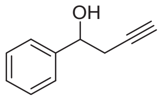
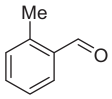
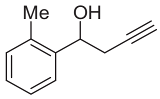
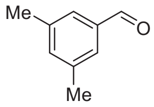
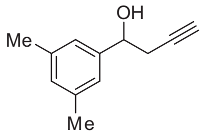
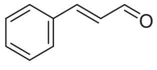
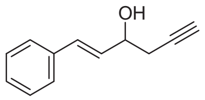
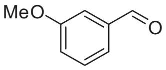
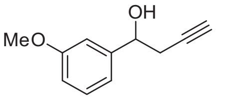
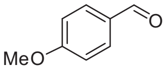
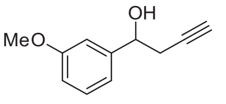
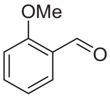
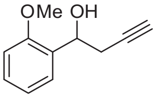
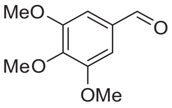
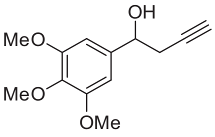
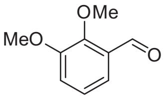
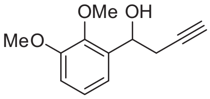
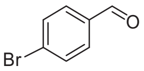
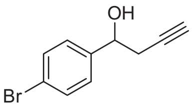
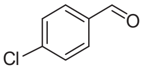
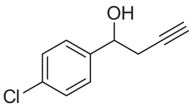
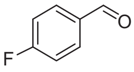
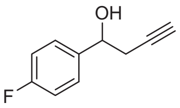
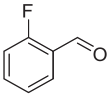
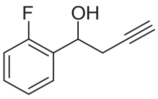
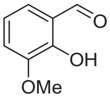
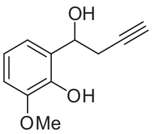
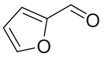
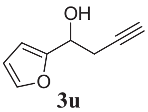
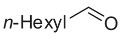
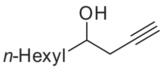
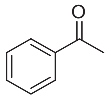
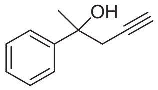
Entry	2	3	Time(h)	%[b]
1	 **2a**	 **3a**	4.0	84
2	 **2b**	 **3b**	3.5	93
3	 **2c**	 **3c**	7.0	91
4	 **2d**	 **3d**	6.0	89
5	 **2e**	 **3e**	6.0	90
6	 **2f**	 **3f**	6.0	73
7	 **2g**	 **3g**	4.0	72
8	 **2h**	 **3h**	7.0	85
9	 **2i**	 **3i**	7.0	70
10	 **2j**	 **3j**	3.0	83

Table 4 (*continued*)

Entry	**2**	**3**	Time(h)	%[b]
11	 **2k**	 **3k**	6.0	93
12	 **2l**	 **3l**	6.0	96
13	 **2m**	 **3m**	7.0	93
14	 **2n**	 **3n**	8.0	92
15	 **2o**	 **3o**	5.0	90
16	 **2p**	 **3p**	7.0	75
17	 **2q**	 **3q**	6.0	66
18	 **2r**	 **3r**	7.0	89
19	 **2s**	 **3s**	7.0	70
20	 **2t**	 **3t**	5.0	70
21	 **2u**	 **3u**	3.0	78
22	 **2v**	 **3v**	6.0	60

(*continued on next page*)

Table 4 (*continued*)

Entry	2	3	Time(h)	%[b]
23	 **2x**	 **3x**	7.0	–[c]

[a] Reaction conditions: Reactions were performed with **2a–v** (1 mmol), **1b** (1.5 mmol) in CH_2Cl_2 (5 mL) using tonsil (150% m/m) at 25 °C for the time indicated.

[b] Isolated yield.

[c] No product was observed after 7 h.

aldehydes (Table 4, entries 11–15) also gave the corresponding homopropargylic alcohols in moderate to excellent yields. When the α,β-unsaturated aldehyde **2j** was used as substrate, only the 1,2-addition product **3j** was observed (Table 4, entry 10).

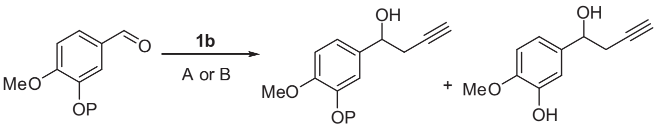
Other aldehydes containing electronegative atoms such as 4-bromo-benzaldehyde, 4-chloro-benzaldehyde, and 2- and 4-fluoro-benzaldehyde also gave similar yields (Table 4, entries 16–19). Aldehydes containing acidic functionalities such as 3-methoxysalicylaldehyde **2t** gave the corresponding product **3t** in 70% yield after 5 h (Table 1, entry 20). Furfuraldehyde **2u** reacted under the optimized conditions, to give the corresponding homopropargylic alcohol **3u** in 78% yield (Table 4, entry 21).

For aliphatic aldehydes, the tonsil-promoted propargylation exhibited moderate efficiency, since **3v** was obtained in 60% yield after 6 h (Table 4, entry 22). Noteworthy that when the reaction conditions were applied to acetophenone, **2x** only unreacted starting material was recovered indicating that the reaction is selective or specific for aldehydes (Table 4, entry 23).

A major concern in the development of new methods for the formation of C–C bonds is their application in the synthesis of complex natural products and therefore its ability to tolerate the presence of protective groups. Recently, our group developed a regio- and chemoselective method for propargylation of aldehydes using Amberlyst A-31, an acidic resin, to promote the reaction.[12] Thus, in order to compare which of the methods would be the most effective in maintaining protecting groups vanillin was converted into the corresponding THP and TBS derivatives **2y** and **2z**, respectively, and these compounds were submitted to propargylation reactions. The results are described in Table 5.

When **2y** was used as the starting material the desired product **3y** and the product correspondent to the removal of THP group **4** were obtained as major products together with a complex mixture of other compounds regardless of the method used (Table 5, entries 1 and 2). Better conversions were observed when **2z** was used as the starting material, however, the tonsil-promoted propargylation gave the desired product **3z** in higher yield and purity (Table 5, entries 3 and 4).

Table 5
Propargylation of protected aldehydes by potassium allenyltrifluoroborate **1b** using different conditions



2y, P = THP
2z, P = TBS
3y-z
4

Entry	Condition[a]	Aldehyde	Ratio (**3**:**4**)[b]	Conv.[c] (%)
1	A	**2y**	1:2	30[d]
2	B	**2y**	1:27	15[d]
3	A	**2z**	2.5:1	53[d]
4	B	**2z**	99:1	75

[a] Condition A: **2y** or **2z** (1 mmol), **1b** (1.5 mmol), CH_2Cl_2 (5 mL), Amberlyst A-31 (200% m/m), 25 °C, 7 h; Condition B: **2y** or **2z** (1 mmol), **1b** (1.5 mmol), CH_2Cl_2 (5 mL), tonsil (150% m/m), 25 °C, 7 h.

[b] The ratio was determined by GC.

[c] The conversion was determined by GC with respect to **2y** or **2z**;

[d] A complex mixture of products was obtained.

In summary, we have demonstrated that tonsil, an inexpensive and readily available clay, can efficiently promote the propargylation of aldehydes in a chemo- and regioselective way using potassium allenyltrifluoroborate.

The method is simple and avoids the use of air and moisture sensitive organometallics. The application of the method in the propargylation of more complex molecules toward the synthesis of natural products is undergoing in our laboratories.

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Supplementary data

Supplementary data (experimental procedures and spectroscopic characterization data, as well as ^{1}H, ^{13}C, ^{19}F and ^{11}B NMR spectra for all synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.017. These data include MOL files and InChiKeys of the most important compounds described in this article.

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10. *Typical experimental procedure:* In a flask containing the appropriate aldehyde **2a**–**z** (1.0 mmol) in CH_2Cl_2 (5.0 mL) at 25 °C was added tonsil (150% m/m) followed by the potassium allenyltrifluoroborate, **1b** (1.50 mmol, 218 mg). The mixture was stirred for the time indicated in Table 4 and at then diluted with CH_2Cl_2 (5.0 mL) and filtered. The filtrate was washed with water (2 × 15 mL), the organic phase was separated and dried over anhydrous $MgSO_4$. The solution was again filtered and the solvent was removed in vacuo to yield **3a**–**z**.
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