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One-pot synthesis of aromatic homoallylic alcohols from aldehydes and Grignard reagents promoted by Titanium(IV) tetraisopropanolate

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ABSTRACT

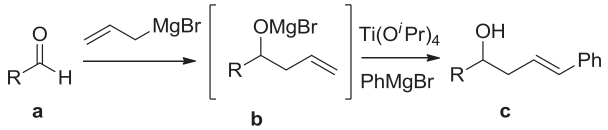
An efficient method of Titanium(IV) mediated one-pot reaction approaching aromatic homoallylic alcohols from aldehydes and dual Grignard reagents was developed with good isolated yields. This method could use aromatic-, heteroaromatic-, or aliphatic-aldehydes as starting materials. However, electron-riched benzaldehyde or cinnamaldehyde tended to precede further hydroxyl eliminations to give all conjugated structures as demonstrated.

1. Introduction

Homoallylic alcohols are important intermediates for the synthesis of natural products, pharmaceuticals, pesticides, fluorescent probes, *etc.*[1] Recent years, direct arylation of its terminal olefin has attracted chemists' attention that applied transition metal, mainly Pd, catalyzed coupling methods between aryl boronic acids and homoallylic alcohols or between vinylsilane and aryl halides to obtain the desired products.[2] Alternatively, starting with allylic diindiums or homopropargylic alcohols could achieve the similar outcomes.[3] Instead of traditionally used Pd catalyst, researchers utilized Titanium(IV) tetraisopropanolate to promote an oxidative arylation between homoallylic alcohols and aryl Grignards recently.[4] Organotitanium compounds have already showed its unique catalytic properties as well as its environmental friendly since 1950s.[5] Therefore, in this work, an effective one-pot synthesis method approach aromatic homoallylic alcohols from aldehydes and dual Grignard reagents will be reported.

2. Results/discussion

Considering the magnesium alkoxide was the product from Grignards addition and the starting material for the oxidative arylation of homoallylic alcohols, one-pot synthesis procedure was designed (Scheme 1) to minimize the separation process attributed to the loss of important intermediates as well as to maximize the production yields.[6]



Scheme 1. Proposed reaction sequence.

Therefore, the model reactions were conducted with Ti(O^{i}Pr)$_4$ mediated benzaldehyde, allylmagnesium bromide and phenylmagnesium bromide.[6] The testing results were summarized in Table 1. It was quite obvious that THF was not a suitable solvent that gave out a mixed products even after flash column (Verified by NMR). If Et$_2$O acted as solvent, it give moderate yield of 41% (entry 3). It seems that Ti(O^{i}Pr)$_4$ worked well in DCM, giving a higher yield of 86%. Further investigation on the loading amount of phenylmagnesium bromide suggested that 3.0 equiv would be better. If less amount of Ti(O^{i}Pr)$_4$ was used, the reaction proceeded to give around 70% yield (entries 9–10). At the same time, it needed to be added at −78 °C to prevent side reactions.

Under the optimized condition, different types of aldehydes were applied to test its scope.[8] It can be seen from Table 2 that all

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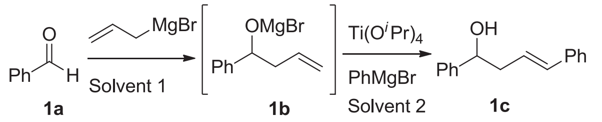
Table 1
Optimization of reaction conditions[a]

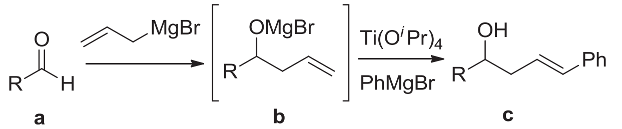


Entry	Solvent 1	Solvent 2	PhMgBr (equiv.)	Yield (%)[b]
1	THF	THF	3.0	Mixture
2	Et_2O	THF	3.0	Mixture
3	Et_2O	Et_2O	3.0	41
4	Et_2O	CH_2Cl_2	3.0	75
5	CH_2Cl_2	CH_2Cl_2	3.0	86
6	CH_2Cl_2	CH_2Cl_2	1.0	0
7	CH_2Cl_2	CH_2Cl_2	2.0	54
8	CH_2Cl_2	CH_2Cl_2	4.0	72
9	CH_2Cl_2	CH_2Cl_2	3.0	70[c]
10	CH_2Cl_2	CH_2Cl_2	3.0	76[d]

[a] Reaction conditions: benzaldehyde (5.0 mmol), allyl magnesium bromide (6.0 mL, 1.0 M in Et_2O), $Ti(O^iPr)_4$ (10.0 mmol), phenylmagnesium bromide (3.0 M in Et_2O) and solvents (5.0 mL).
[b] Isolated yield.
[c] $Ti(O^iPr)_4$ (5.0 mmol) was used.
[d] $Ti(O^iPr)_4$ (7.5 mmol) was used.

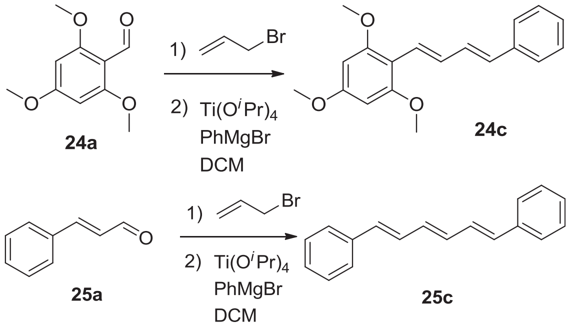
these reactions gave desired products in good yields. If the electron-donating group merged on the benzene ring, it gave excellent yields up to 90% (Table 2, entries 2–5). However, if the aromatic ring substituted with halogen like Cl or Br, the yields were slightly decreased as the further cross coupling between products and phenyl-magnesium bromide were detected in the reaction mixture (Table 2, entries 6–8 and 19–23). In addition, phenolic hydroxyl group was tolerated as it only consumed one additional mole of allylmagnesium bromide and was freed upon final quenching (Table 2 entries 10–11). The aliphatic aldehyde also performed well in the present reactions (Table 2, entries 12–17) while the consumption of $Ti(O^iPr)_4$ and phenylmagnesium bromide need to be doubled when α,β-unsaturated aldehyde was used (Table 2, entry 18). The results demonstrated the hetroaromatic aldehyde could proceed well to give desired products (Table 2, entries 19–23). Additional investigation on substrates scope found that electron-riched benzaldehyde or highly conjugated cinnamaldehyde tended to precede further hydroxyl eliminations (Scheme 2).

Table 2
Scope of different substrates[a]



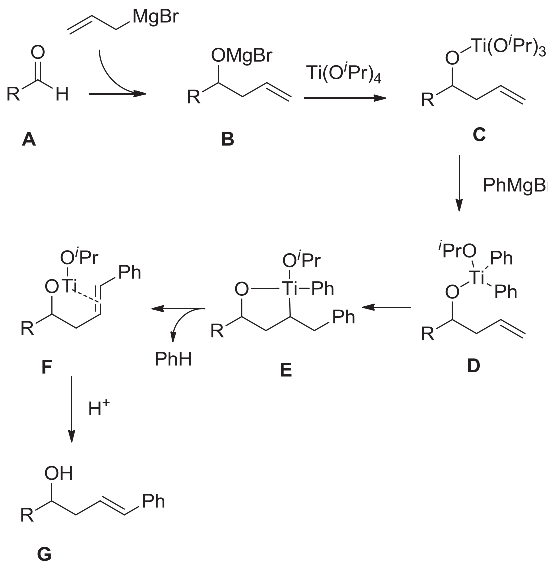
Entry	Substrate	R	Product	Yield (%)[b]
1	**1a**	Phenyl	**1c**	86
2	**2a**	4-Methoxyphenyl	**2c**	88
3	**3a**	3-Methoxyphenyl	**3c**	90
4	**4a**	3,4-Dimethoxyphenyl	**4c**	89
5	**5a**	Piperonyl	**5c**	90
6	**6a**	4-Chlorphenyl	**6c**	82
7	**7a**	3-Bromophenyl	**7c**	80
8	**8a**	2-Bromophenyl	**8c**	82
9	**9a**	2-Bromopiperonyl	**9c**	80
10[c]	**10a**	3-Hydroxyphenyl	**10c**	89
11[c]	**11a**	4-Hydroxy-3-Methoxyphenyl	**11c**	85
12	**12a**	Benzylmethyl	**12c**	87
13	**13a**	Benzylethyl	**13c**	85
14	**14a**	Ethyl	**14c**	82
15	**15a**	*n*-Propyl	**15c**	93
16	**16a**	Neopentyl	**16c**	87
17	**17a**	*n*-Pentyl	**17c**	86
18[d]	**18a**	1-Allyl	**18c**	86
19	**19a**	3-Bromo-5-pyridyl	**19c**	82
20	**20a**	5-Bromo-2-pyridyl	**20c**	80
21	**21a**	4-Bromo-3-thiophenyl	**21c**	82
22	**22a**	2-Chloro-3-quinolinyl	**22c**	83
23	**23a**	2-Chloro-8-methyl-3-Quinolinyl	**23c**	84

[a] Unless otherwise stated, all reactions were performed using substrates (5.0 mmol), allylmagnesium bromide (6.0 mL, 1.0 M in Et_2O), $Ti(O^iPr)_4$ (10.0 mmol), phenylmagnesium bromide (5.0 mL, 3.0 M in Et_2O) in DCM (5.0 mL).
[b] Isolated yield.
[c] Allylmagnesium bromide (11.0 mL, 1.0 M in Et_2O) was used.
[d] The reaction was performed using substrates (5.0 mmol), allylmagnesium bromide (6.0 mL, 1.0 M in Et_2O), $Ti(O^iPr)_4$ (20.0 mmol), phenylmagnesium bromide (10.0 mL, 3.0 M in Et_2O) in DCM (5.0 mL).



Scheme 2. Two reaction exceptions.

Based on the experimental results and pervious literature,[4,8] the following reaction mechanism was proposed. Aldehyde firstly reacted with allylmagnesium bromide to give **B**. The addition of $Ti(O^iPr)_4$ and then phenylmagnesium bromide produced intermediate **D**, which passed through double bond activation and insertion to give **E**. The following β-hydride elimination give out benzene and **F**, which quenched with acid to provide the final product (Scheme 3).



Scheme 3. Proposed reaction mechanism.

3. Conclusion

In conclusion, an one-pot synthesis of aromatic homoallylic alcohols from aldehydes and Grignard reagents promoted by