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An efficient $Yb(OTf)_3$ catalyzed alkylation of 1,3-dicarbonyl compounds using alcohols as substrates

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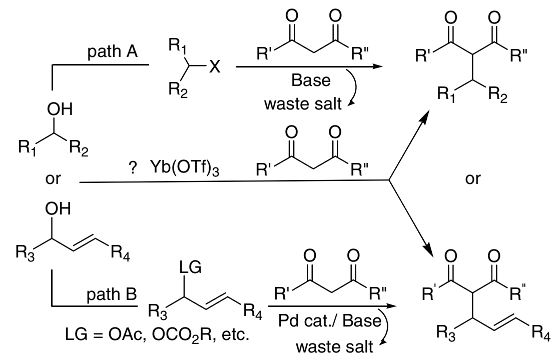
Abstract—A highly efficient and environmentally friendly method for catalytic benzylation/allylation of 1,3-dicarbonyl compounds with alcohols has been developed by using $Yb(OTf)_3$ as a catalyst. The reactions proceed smoothly to give the desired products in moderate to excellent yields, mostly at room temperature. The catalyst can be recovered and reused at least six times without visible loss of catalytic activity for such reactions.

1. Introduction

The alkylation of 1,3-dicarbonyl compounds is a useful tool for the formation of C–C bonds in organic synthesis. Among the numerous works devoted to this reaction, those on development of new electrophiles are very topical.[1–6] The major goal is to prepare complex compounds with required structures and/or to meet several requirements including the cheap and readily available starting materials, atom-economy, mild reaction conditions, simple manipulation, and environmentally friendly catalysts. Among a variety of approaches for the alkylation of 1,3-dicarbonyl compounds, alcohols are arguably one of the most ideal substrates that are receiving increased attention.[2–8] Nevertheless, nucleophilic substitution of the hydroxy group in alcohols is generally difficult due to its poor leaving ability. As a result, hydroxy groups usually require pre-activation through transformation into good leaving groups such as halides, carboxylates, carbonates, and phosphonates before the treatment with 1,3-dicarbonyl compounds (Scheme 1, paths A and B).[9] However, such a process inevitably produces salt waste, which would set limits for the industrial application and for the scope of substrates. Very recently, several Lewis acids and Brønsted acids catalytic systems have been proved successful for the alkylation of 1,3-dicarbonyl compounds using alcohols as electrophiles directly.[2–6] Compared to other known alkylation reactions, this new methodology offers several potential advantages, such as the wide availability of the starting materials and the generation of H_2O as the only side product. Despite significant recent advances in this area, there remains room for improvement, such as increase of catalyst stability, lowering reaction temperature, and increase of yields. In particular, the recovery and reuse of Lewis acid catalysts remain a significant challenge and have not been explored so far. Therefore, development of a general, efficient, conveniently reusable, and readily available



Scheme 1.

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catalyst for this highly valuable but challenging transformation is highly desirable.

Rare earth triflates, RE(OTf)$_3$ (Tf = trifluoromethanesulfonyl), are versatile Lewis acids in organic synthesis and are easily prepared in 50% TfOH aqueous media. Unlike other Lewis acids such as $BF_3 \cdot Et_2O$, $SnCl_4$, and $AlCl_3$, rare earth triflates are stable in air and water, and act as Lewis acids even in the presence of water.[10] In seeking to broaden the scope of Lewis acid catalysts for the alkylation of 1,3-dicarbonyl compounds with alcohols, we became interested in establishing whether lanthanide triflates could be used as catalysts for such reaction. Moreover, we are also interested to recycle the Lewis acid catalyst in alkylation of 1,3-dicarbonyl compounds with alcohols. Preliminary results are described here.

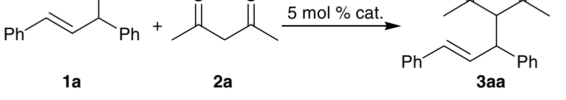
2. Results and discussion

As the first attempt, the reaction of allylic alcohol **1a** with 2,4-pentadione **2a** in the presence of 5 mol % Yb(OTf)$_3$ was selected as a model reaction to develop the optimum reaction conditions. The results are summarized in Table 1.[13] The choice of solvents has a significant impact on the activation of the catalyst. The reaction of 2,4-pentadione **2a** with **1a** in dichloroethane, toluene, and tetrahydrofuran afforded the product only in moderate yields (Table 1, entries 1–3). However, the corresponding product was obtained in high yields after 1 h when acetonitrile or dioxane was used as solvent (Table 1, entries 4 and 5). The best result was achieved in nitromethane, affording the desired product **3aa** in 93% yield within 30 min at room temperature (Table 1, entry 6). However, no product was determined in the absence of Yb(OTf)$_3$ after 12 h (Table 1, entry 7).

With the optimum reaction conditions in hand, we subsequently explored the scope of the reaction to various alcohols and 1,3-dicarbonyl compounds. As shown in Table 2, various 1,3-dicarbonyl compounds were efficiently allylated by allylic alcohols to give the corresponding products in moderate to excellent yields under the current reaction conditions. It is noted that diethyl malonate **2b**, which has lower acidity (enolizable ability), also displayed a high reactivity and reacted quickly with **1a** and **1b** to give the desired products in 87% and 90% yields, respectively (Table 2, entries 1 and 3). Although a few Lewis acid catalyzed allylations of active methylenes with allylic alcohols have been reported previously,[2,3] all those methods required a longer reaction time and higher temperature compared with the present method. Interestingly, **1c** and **1d** reacted with diketone **2a** (or keto ester **2c**) to give the same products, with similar yields and regioselectivity (Table 2, entries 4–7). These features suggest the same allylic cation as intermediate for both allylic alcohols. Namely, the positive charge is delocalized on the resultant allyl units, and 2,4-pentadione attacks regioselectively the sterically less hindered carbon atom of the allylic functionality. However, in the *p*-toluenesulfonic acid catalytic system the reaction of allylic alcohols **1c** and **1d** with 2,4-pentadione afforded the product as a mixture of regioisomers.[6] Moreover, it was found that primary allylic alcohol **1e** was also a suitable substrate for the allylation of dibenzoylmethane **2d**, but the products were a mixture of regioisomers (Table 2, entry 8). It is worth mentioning that aliphatic allylic alcohol shows low activity, perhaps due to the instability of the resultant allylic intermediate under the same conditions. The reaction of **1f** with **2d** gave the product only in moderate yield even with reaction longer time (Table 2, entry 9).

The reported examples of Lewis acid catalyzed alkylation of 1,3-dicarbonyl compounds with alcohols as substrates are very rare.[2,3] Alternatively, although palladium-catalyzed allylations of 1,3-dicarbonyl compounds using allylic alcohols, via a redox mechanism have been intensively studied, in most cases the Lewis acid additive such as BF_3 or $Ti(O^iPr)_4$ is required to activate the hydroxy.[11] Moreover, it has been found that benzylic alcohols are not suitable substrates in the palladium-catalytic system.[11,12] To explore the generality of the Yb(OTf)$_3$-catalyzed alkylation of 1,3-dicarbonyl compounds, we also examined the reaction of 1,3-dicarbonyl compounds with benzylic alcohols. The results indicate that Yb(OTf)$_3$ is also highly effective in the catalytic benzylation of 1,3-dicarbonyl compounds using benzylic alcohols as substrates. The reaction of benzhydrol **1g** with various 1,3-dicarbonyl compounds at 60 °C proceeded smoothly to give the corresponding benzylation products in high yields (Table 2, entries 10–12). However, when these reactions were carried out at room temperature, the dimeric ethers were obtained as the main products instead of the desired C–C coupled products. Furthermore, treatment of 2,4-pentadione **2a** with simple 1-phenylethanol **1h** also afforded the corresponding benzylation product (Table 2, entry 13). It is worth noting that the reaction of **1h** with more reactive **2d** could also proceed at room temperature to afford the desired product in 87% yield after 12 h (Table 2, entry 15). Keto ester **2f** is also a suitable substrate for the benzylation reaction (Table 2, entry 16). The presence of the electron-donating substituent in *para*-position of benzene

Table 1. The alkylation of 2,4-pentadione **2a** with allylic alcohol **1a** under various conditions[a]

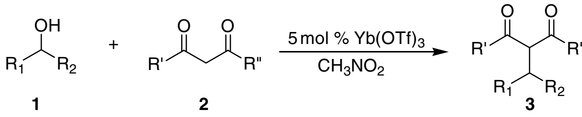


Entry	Catalyst (5 mol %)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	Yb(OTf)$_3$	DCE	rt	6	87
2	Yb(OTf)$_3$	Tol	rt	24	78
3	Yb(OTf)$_3$	THF	rt	6	75
4	Yb(OTf)$_3$	Dioxane	rt	1	90
5	Yb(OTf)$_3$	CH_3CN	rt	1	91
6	Yb(OTf)$_3$	CH_3NO_2	rt	0.5	93
7	None	CH_3NO_2	rt	12	—

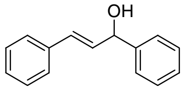
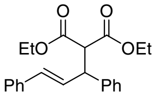
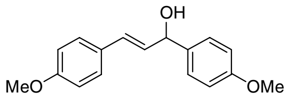
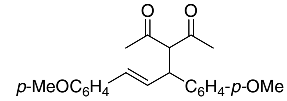
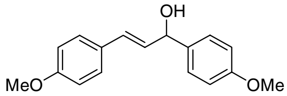
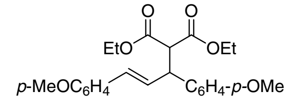
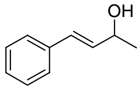
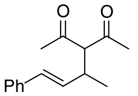
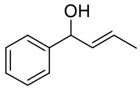
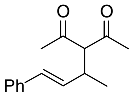
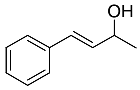
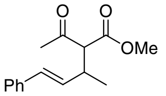
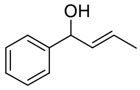
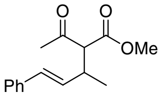
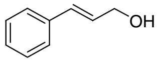
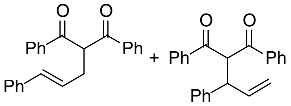
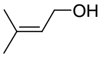
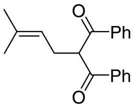
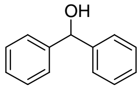
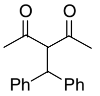
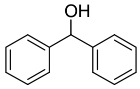
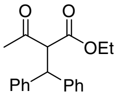
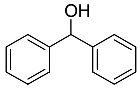
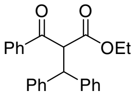
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol, 1.5 equiv), catalyst (0.015 mmol, 5 mol %), solvent (2 mL).

[b] GC–MS yield.

Table 2. Yb(OTf)$_3$ catalyzed alkylation of 1,3-dicarbonyl compounds under the optimum conditions[a]

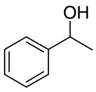
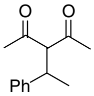
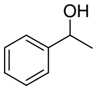
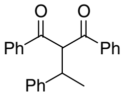
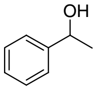
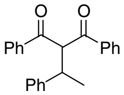
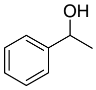
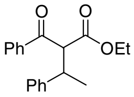
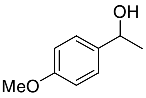
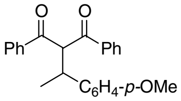
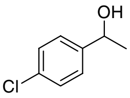
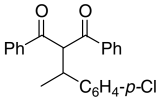


R' = R" = Me, **2a**; R' = Me, R" = OMe, **2c**
R' = R" = OEt, **2b**; R' = Me, R" = OEt, **2e**
R' = R" = Ph, **2d**; R' = Ph, R" = OEt, **2f**

Entry		Alcohol	Nu–H	Time (h)	Product		Yield[b] (%)
1	**1a**		**2b**	3		**3ab**	87
2	**1b**		**2a**	0.5		**3ba**	92
3	**1b**		**2b**	2		**3bb**	90
4	**1c**		**2a**	0.75		**3ca**	92
5	**1d**		**2a**	0.5		**3ca**	90
6[c]	**1c**		**2c**	3		**3cc**	85
7[c]	**1d**		**2c**	3		**3cc**	83
8	**1e**		**2d**	12	 (70 : 30)	**3ed**	72
9[d]	**1f**		**2d**	24		**3fd**	51
10[e]	**1g**		**2a**	1		**3ga**	96
11[e]	**1g**		**2e**	6		**3ge**	80
12[e]	**1g**		**2f**	6		**3gf**	92

(*continued on next page*)

Table 2 (*continued*)

Entry	Alcohol		Nu–H	Time (h)	Product		Yield[b] (%)
13[e]	**1h**		**2a**	1		**3ha**	93
14[e]	**1h**		**2d**	1		**3hd**	90
15	**1h**		**2d**	12		**3hd**	87
16[c,e]	**1h**		**2f**	12		**3hf**	52
17	**1i**		**2d**	10		**3id**	92
18	**1j**		**2d**	12		**3jd**	85

[a] Reaction conditions: alcohols **1** (0.3 mmol), 1.5 equiv 1,3-dicarbonyl compounds **2**, 5 mol % $Yb(OTf)_3$ at room temperature.
[b] Isolated yields base on the starting alcohol.
[c] 1:1 Mixture of diastereoisomers.
[d] 15% Diallylation product was obtained.
[e] The reaction was carried out at 60 °C.

ring can increase the reactivity of benzylic alcohol, while the electron-withdrawing substituent in *para*-position of benzene ring seems to have a negative effect on benzylation reaction (Table 2, entries 17 and 18).

Finally, we checked the reusability of the $Yb(OTf)_3$ catalyst in the reaction of alcohol **1a** with 2,4-pentadione **2a** in nitromethane at room temperature. After the first experiment, the reaction mixture was diluted with water and extracted with ether. The catalyst that remained in the aqueous layer can be recovered by removing the water and then drying under vacuum at 200 °C for 4 h for the next use.[14] The results of six runs showed that the recovered catalyst remains almost consistent in yields and rates (93%, 92%, 95%, 94%, 90%, 92%, 90%, respectively) (Fig. 1).

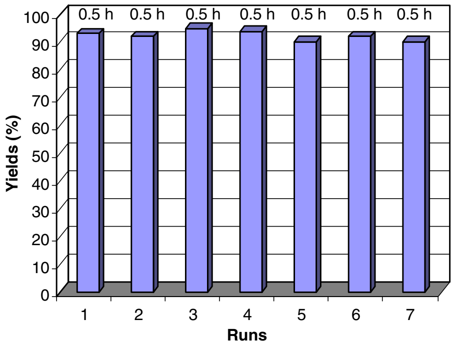


Figure 1. Recycling results for the reaction of **1a** with 2,4-pentadione (**2a**) catalyzed by $Yb(OTf)_3$. First run: 1 mmol allylic alcohols (**1a**), 1.5 mmol 2,4-pentadione (**2a**), 5 mol % $Yb(OTf)_3$ in 10 mL nitromethane at room temperature.

3. Conclusion

In summary, a general and highly efficient $Yb(OTf)_3$-catalyzed alkylation of diketo, keto esters, and even lower acidic diethyl malonate compounds using allylic and benzylic alcohols as electrophiles has been developed. The corresponding alkylation products were obtained in moderate to high yields, mostly at room temperature. Furthermore, the present catalyst could be recovered and reused at least six times for such reaction without visible loss of catalytic activity. The present work provides a clean, environmentally friendly and synthetically competitive alternative to the already established use of metal complexes. Further development on this methodology is currently under way in our laboratory.

Acknowledgments

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References and notes

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13. *General experimental procedure for the* $Yb(OTf)_3$*-catalyzed alkylation of 1,3-dicarbonyl compounds*: To a mixture of alcohols **1** (0.3 mmol) and 1.5 equiv of 1,3-dicarbonyl compounds in 2 mL nitromethane was added 5 mol % $Yb(OTf)_3$ (9.7 mg, 0.015 mmol) and then the reaction mixture was stirred at room temperature or the corresponding conditions mentioned in the text. After completion of the reaction that was monitored by GC–MS or TLC, the solvent was removed under reduced pressure. The residue was purified by a short column chromatography using hexane/ethyl acetate as the eluent. Selected data: *3-[(E)-1,3-bis(4-methoxyphenyl)prop-2-enyl]pentane-2,4-dione* (**3ba**): ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 1.92 (s, 3H), 2.23 (s, 3H), 3.77–3.79 (m, 7H), 4.25–4.27 (m, 1H), 6.02–6.08 (dd, $J = 8.2$, 15.7 Hz, 1H), 6.32 (d, $J = 15.7$ Hz, 1H), 6.80 (d, $J = 8.7$ Hz, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 7.16 (d, $J = 8.6$ Hz, 2H), 7.22 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ 203.07, 202.95, 159.26, 158.60, 132.28, 130.73, 129.41, 128.90, 127.49, 127.36, 114.35, 113.92, 74.85, 55.27, 55.22, 48.40, 30.00, 29.70. EI-MS: *m*/*z* (relative intensity): 352 (M^+, 3%), 253 (100). *Diethyl [(E)-1,3-bis(4-methoxyphenyl)prop-2-enyl]malonate* (**3bb**): ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 1.03 (t, $J = 7.0$ Hz, 3H), 1.20 (t, $J = 7.0$ Hz, 3H), 3.77 (s, 6H), 3.84 (d, $J = 10.8$ Hz, 1H), 3.96–3.99 (m, 2H), 4.13–4.18 (m, 3H), 6.16 (dd, $J = 8.5$, 15.7 Hz, 1H), 6.38 (d, $J = 15.7$ Hz, 1H), 6.80 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 7.20 (d, $J = 8.7$ Hz, 2H), 7.24 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ 167.91, 167.51, 159.09, 158.52, 132.59, 130.74, 129.73, 128.97, 127.46, 127.32, 113.97, 113.85, 61.45, 61.27, 58.08, 55.21, 55.16, 48.41, 14.12, 13.82. EI-MS: *m*/*z* (relative intensity): 412 (M^+, 10%), 253 (100). *2-(1-(4-Methoxyphenyl)ethyl)-1,3-diphenylpropane-1,3-dione* (**3id**): ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ 1.22 (d, $J = 6.8$ Hz, 3H), 3.57 (s, 3H), 3.93–3.98 (m, 1H), 5.50 (d, $J = 10.0$ Hz, 1H), 6.60 (d, $J = 8.8$ Hz, 2H), 7.08 (d, $J = 8.8$ Hz, 2H), 7.15–7.19 (m, 2H), 7.28–7.34 (m, 3H), 7.41–7.45 (m, 1H), 7.65 (d, $J = 7.2$ Hz, 2H), 7.93 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ 195.03, 194.76, 158.16, 137.18, 136.95, 135.84, 133.52, 133.02, 128.84, 128.80, 128.71, 128.51, 128.46, 113.78, 65.08, 55.13, 40.47, 20.41. EI-MS: *m*/*z* (relative intensity): 358 (M^+, 10%), 253 (100).
14. *Typical experimental procedure for the reuse of catalyst*: After the reaction was completed, the mixture of reaction was diluted with water, and then the organic species were extracted with ether. The catalyst remaining in the aqueous layer can be recovered by removing water and then drying under vacuum at 200 °C for 4 h for the next use.