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1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) catalyzed Michael reactions

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Abstract—1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD), a bicyclic guanidine base, has been found to be an excellent catalyst for Michael and Michael-type reactions. A wide variety of Michael donors and acceptors can participate in these reactions using 10–20 mol % of TDB. These reactions are mild, fast, easy to perform, produce excellent yields and can occur in several solvents without the need for strictly anhydrous conditions.

Bicyclic guanidine bases[1] such as 1,5,7-triazabicyclo[4.4.0]dec-5-ene (Fig. 1, TBD) and 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine (Fig. 1, 7-methyl-TBD or MTBD) are known as superbases due to their high pK_a values.[2] They have been shown to promote various reactions including the Wittig reaction,[3] nitroaldol (Henry) reaction,[4] dialkyl phosphite addition to carbonyl compounds[4] and the addition of azoles to α,β-unsaturated nitriles and esters.[5]

Stoichiometric amounts of MTBD have also been shown to be moderately active in Baylis–Hillman reactions.[6] Immobilized MTBD, in siliceous MCM-41, can promote the Knoevenagel condensation, epoxidation[7a] and the formation of thioureas.[7b] Polystyryl-supported TBD (PSTBD) can catalyze 1,2-epoxide ring-opening, aldol-type condensation and the Michael addition of nitroethane onto benzylidene acetone.[8a] Nucleophilic ring-opening reactions of 2,2-dialkyl-1,2,3,4-tetrahydro-γ-carbolinium salts with thiols can also be mediated by polymer-supported TBD.[8b] Guanidine bases have also received intense investigations as potential enantioselective catalysts.[9]

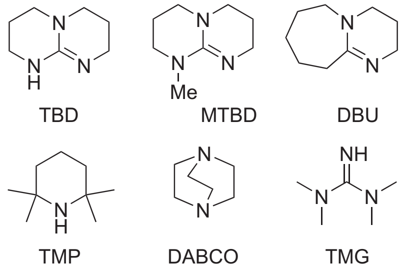

Figure 1. Various organobases.

Carbon–carbon bond formation is central to organic synthesis. Direct Michael addition and Michael-type conjugate reactions are amongst the most simple, efficient and atom-economical ways to achieve this transformation. These reactions are typically performed with stoichiometric amounts of inorganic bases such as sodium ethoxide, potassium *tert*-butoxide, potassium hydroxide, sodium metal, LDA, sodium hydride or *n*-butyllithium.[10] Strong basic conditions can, however, lead to side reactions. Recently, excellent enantioselective Michael reactions have been developed using transition metal catalysts.[11] A quaternary ammonium salt,[12] a proline lithium salt,[13a] L-proline,[13b] cinchona alkaloids[14] and imidazolidine[15] have also been shown to exhibit catalytic activity in several conjugate addition reactions. In contrast, organobases such as DBU[16a,b] (Fig. 1) and TBD[8a,16c] are less well documented as catalysts for Michael reactions. In this letter, we report our survey of the range of substrates and carbon nucleophiles that are suitable for Michael and Michael-type reactions using TBD as the catalyst.

As a reliable starting point, dimethyl malonate was used as the Michael donor to the cyclic enone, 2-cyclopenten-1-one (Scheme 1 and Table 1). With 10 mol % of TBD,

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Keywords: TBD; Michael reaction; Organobase.

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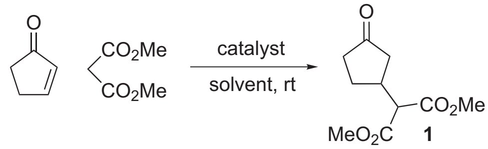


Scheme 1. Organobase catalyzed Michael reaction between 2-cyclopenten-1-one and dimethyl malonate.

Table 1. The influence of different organobases and solvents on the reaction in Scheme 1

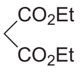
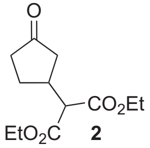
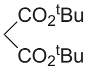
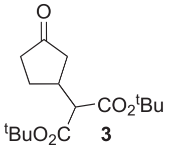
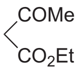
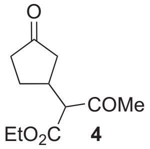
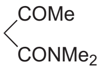
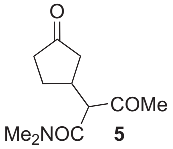
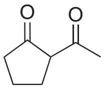
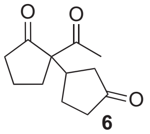
Entry	Catalyst (mol %)	Solvent	Time	Yield[a] (%)
1	TBD (10)	Toluene	5 min	95
2	TBD (5)	Toluene	30 min	95
3	TBD (10)	DMF	15 min	90
4	TBD (10)	MeOH	15 min	90
5	TBD (10)	MeCN	30 min	90
6	TBD (10)	Et_2O	30 min	90
7	TBD (10)	THF	30 min	90
8	TBD (20)	Tol:H_2O (99:1)	30 min	90
9	MTBD (10)	Toluene	6 h	91
10	DBU[b] (10)	Toluene	24 h	93
11	TMG (10)	Toluene	37 h	85[c]

[a] Isolated yield. Conversion estimated to be 100% by TLC. No side products observed.

[b] DBN had a similar reaction profile as DBU.

[c] Reaction did not complete.

Table 2. TBD (10 mol %) catalyzed Michael reaction between various carbon nucleophiles and 2-cyclopenten-1-one in toluene

Entry	Donor	Product	Time	Yield[a] (%)
1		 **2**	30 min	90
2		 **3**	1 h	99
3		 **4**	10 h	99
4		 **5**	6 h	95
5		 **6**	6 h	94[b]

[a] Isolated yield. Conversion estimated to be 100% by TLC. No side products observed.

[b] 20 mol % of catalyst used.

the reaction proceeded smoothly at room temperature (25 °C) with toluene as the solvent. The reaction was complete in 5 min and, after flash chromatography, gave an excellent isolated yield of 95% (Table 1, entry 1). The amount of catalyst could be reduced to 5 mol % (entry 2) without affecting the yield. This protocol is much more convenient and operationally simpler to perform than the reported methodology using sodium methoxide to generate the same product.[17]

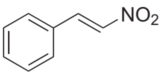
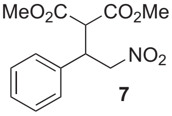
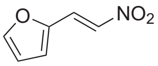
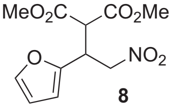
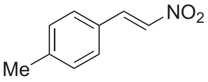
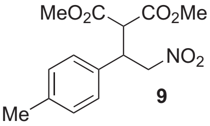
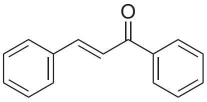
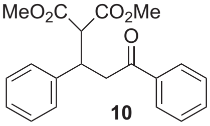
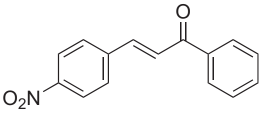
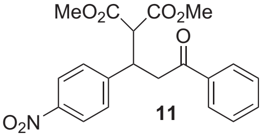
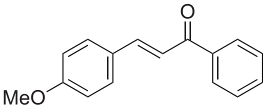
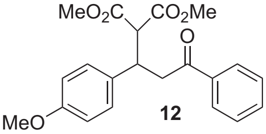
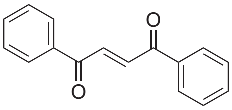
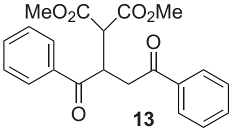
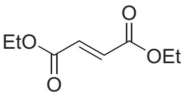
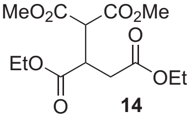
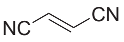
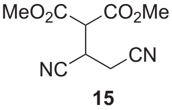
Under the same conditions, a variety of solvents such as DMF (entry 3), methanol (entry 4), acetonitrile (entry 5), diethyl ether (entry 6) and THF (entry 7) were found to be suitable solvents for this reaction. These reactions were typically complete within 15–30 min giving isolated yields of $\geqslant$90%. We also discovered that this reaction was not sensitive to moisture. For example, the reaction in toluene containing 1% water with 20 mol % of the catalyst was complete in 30 min and the yield was 90% (entry 8).

Next, we were keen to find out if it was a general phenomenon for organobases to act as catalysts in Michael reactions. We compared the results obtained with TBD against a variety of organobases such as MTBD, DBU, DBN, 1,1,3,3-tetramethylguanidine (Fig. 1, TMG), tetramethylpiperidine (Fig. 1, TMP), DABCO and diisopropylethylamine (DIPEA). MTBD (entry 9), DBU (entry 10) and DBN were all effective catalysts for this reaction. However, they catalyzed the reaction at a much slower rate than TBD. It is interesting to note the difference in reaction time between TBD and MTBD (entry 9). Such differences were greatly reduced in polar solvents such as MeOH and MeCN. The guanidinium intermediate that is generated when TBD is protonated may play a role as a hydrogen bond donor in the catalytic cycle. This type of interaction would be enhanced in non-polar solvents such as toluene. The TMG catalyzed reaction (entry 11) was not able to reach completion. Other organobases such as TMP, DABCO and DIPEA were ineffective as catalysts for this reaction. No products were observed after 56 h of reaction time. This is not unexpected as the conjugate acids of these bases have relatively low pK_a values.

Subsequently, we investigated the suitability of a range of carbon nucleophiles for this reaction using 2-cyclopenten-1-one as the substrate. Diethyl malonate (Table 2, entry 1), di-*tert*-butyl malonate (entry 2), ethyl acetoacetate (entry 3), *N*,*N*-dimethylacetoacetamide (entry 4) and 2-acetylcyclopentanone (entry 5) were all found to be useful donors. The reactions of all these nucleophiles proceeded smoothly, giving high isolated yields of the Michael adducts. It is interesting to note that the reaction with 2-acetylcyclopentanone generated no side products even though it contained multiple enolizable protons (entry 5). This demonstrates the mildness and chemoselectivity of this reaction. The quaternary carbon of the product was identified using DEPT NMR experiments.

Using dimethyl malonate as the donor, we decided to investigate other suitable Michael acceptors (Table 3). We found that with 10–20 mol % of TBD, a wide range of substrates including various β-nitrostyrenes (Table 3, entries 1–3), various chalcones (entries 4–6), *trans*-1,2-

Table 3. TBD (10 mol %) catalyzed Michael reaction between dimethyl malonate and various substrates in toluene

Entry	Substrate	Product	Time (min)	Yield[a] (%)
1		 **7**	5	96
2		 **8**	5	94
3		 **9**	5	93
4		 **10**	60	92
5		 **11**	5	98
6		 **12**	120	95[b]
7		 **13**	5	96
8		 **14**	30	91[c]
9		 **15**	120	93[b]

[a] Isolated yield. Conversion estimated to be 100% by TLC. No side product observed for all experiments.

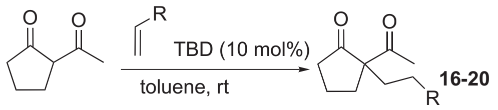
[b] 20 mol % of catalyst used.

[c] 15 mol % of catalyst used.

dibenzoylethylene (entry 7), diethyl fumarate (entry 8) and fumaronitrile (entry 9) were suitable substrates for this reaction (see Supplementary data for more examples). The β-nitrostyrenes were excellent substrates for this reaction, giving high yields within a short reaction time. We realized that electron deficient chalcones were more active substrates and reacted in shorter times. However, the difference in reaction time did not affect the yield of the reactions.

One-step construction of a quaternary carbon is often a difficult task, especially under catalytic conditions and this area has attracted the interest of many chemists.[18] Using our methodology, we therefore focussed on broadening the range of suitable acceptors for the donor 2-acetylcyclopentanone (Scheme 2). We tested various activated terminal alkenes and found several suitable acceptors; for example acrylonitrile (Table 4, entry 1), acrylates (entries 2 and 3), phenyl vinyl sulfone (entry 4) and phenyl vinylsulfonate (entry 5). All reactions were complete within a short reaction time, giving moderate to excellent isolated yields of previously unreported Michael adducts.

In conclusion, we have discovered a mild, catalytic, high yielding and efficient methodology for Michael and



Scheme 2. TBD (10 mol %) catalyzed Michael reactions between 2-acetylcyclopentanone and various activated terminal alkenes.

Table 4. The reaction times and yields of the reactions in Scheme 2

Entry	R	Product	Time	Yield[a] (%)
1	CN	**16**	1 h	83
2	CO_2Me	**17**	30 min	93
3	CO_2Ph	**18**	30 min	97
4	SO_2Ph	**19**	1.5 h	87
5	SO_3Ph	**20**	5 min	85

[a] Isolated yield. Conversion estimated to be 100% by TLC. No side products observed.

Michael-type reactions using TBD. This reaction is easy to perform, is usually fast and the purification protocol is simple. No side products were observed for most reactions. As this reaction is not sensitive to moisture, the solvent used and reaction conditions need not be absolutely anhydrous. This methodology can accommodate a wide range of substrates and donors, making it a useful addition to the chemist's toolbox. Using this protocol, we have synthesized a series of Michael adducts containing quaternary carbon centres that were previously unreported. Moreover, TBD is inexpensive and commercially available. We are currently actively pursuing the asymmetric version of this reaction.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.010. Experimental procedures and spectral data of the products are presented. More examples of suitable substrates and donors for TBD catalyzed Michael reactions are provided. Spectral data of previously unreported products are also presented.

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