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Triethylborane triggered intermolecular domino Michael–aldol three-component coupling reactions☆

S. Chandrasekhar,* Ch. Narsihmulu, N. Ramakrishna Reddy and M. Srinivasa Reddy

Indian Institute of Chemical Technology, Hyderabad 500 007, India

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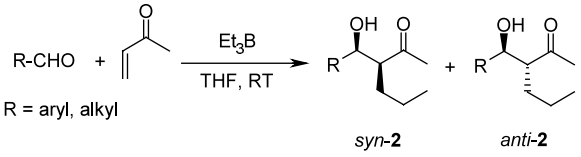
Abstract—The triethylborane triggered intermolecular domino Michael–aldol reaction is described. Initial triethylborane addition in a Michael fashion to methyl vinyl ketone resulted in a vinylborane which further reacted with an aldehyde to give the aldol product in a one-pot process.

There has been great demand to develop 'one-pot' procedures for successive reactions for the formation of several C–C bonds.[1] The minimization of steps involved in multistep synthesis not only allows the reduction of waste but also results in the diminution of costs. The word 'domino' has been coined and extensively used by Tietze et al., for such classes of reactions.[2] Of several such transformations described to date, most reactions concern radical or anionic processes and involve intramolecular reactions resulting in the formation of carbocycles.[3] Metal catalysts[4] are extensively used for these transformations. Three-component couplings involving the successive formation of two bonds preferably C–C bonds using a single catalyst are being seriously studied in several laboratories and Lewis acids are often used for this purpose. The most common Lewis acids include lanthanum and scandium triflate, $BiCl_3$ and others but most involve one C–C and one C–X bond where 'X' is a heteroatom.[5,6] Installation of two carbon chains in the α- and β-positions in enones has been studied to some extent using base[7] or $Cu(OTf)_2$ and a chiral ligand.[8] While exploring this multicomponent 'domino' reaction, we have discovered serendipitously that no additional catalyst is required for the domino Michael–aldol reaction if the carbon nucleophile for Michael initiation is obtained from Et_3B. In this paper, the results pertaining to this very useful Michael–aldol reaction are reported. In the design of the present protocol the following aspects were considered. (a) Can one of the reagents add in a Michael fashion onto the enone without external catalysis? (b) Are functional groups tolerated? (c) What is the role of substituents in the aldol reaction once the Michael reaction has been triggered? (d) Can metal contamination be avoided?

Much to our satisfaction, we observed that the Michael addition of Et_3B onto methyl vinyl ketone and the subsequent aldol reaction between the α-carbon of the methyl vinyl ketone and aryl/alkyl aldehyde were very facile (Scheme 1). Accordingly when Et_3B (2 equiv.) was added to methyl vinyl ketone (1 equiv.) and benzaldehyde **1a** (entry 1, Table 1) in THF under an argon atmosphere, the clean formation of 3-(hydroxyphenylmethyl)-hexan-2-one **2a** was observed in 82% isolated yield as a *syn–anti* mixture (20:80).[9]

To check the generality of the aldol reaction, the same experiment was repeated in the presence of *p*-methyl benzaldehyde **1b** (entry 2) as the aldol partner and the requisite product **2b** was obtained in a 54:46 *syn*:*anti* ratio in a 72% isolated yield. When the electrophilicity of the aldehyde group was reduced by substitution on the aryl ring in *p*-methoxybenzaldehyde **1c** (entry 3), the β-hydroxymethyl ketone **2c** was obtained in a better yield (85%) and better diastereoselectivity (20:80 *syn*/



Scheme 1.

Keywords: domino Michael–aldol reaction; triethylborane; three-component coupling.

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* Corresponding author. Tel.: +91-40-7193434; fax: +91-40-7160512; e-mail: srivaric@iict.ap.nic.in

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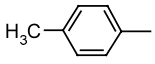
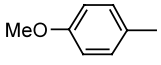
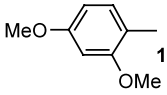
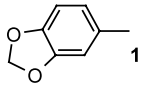
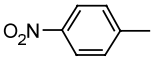
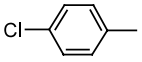
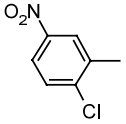
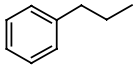
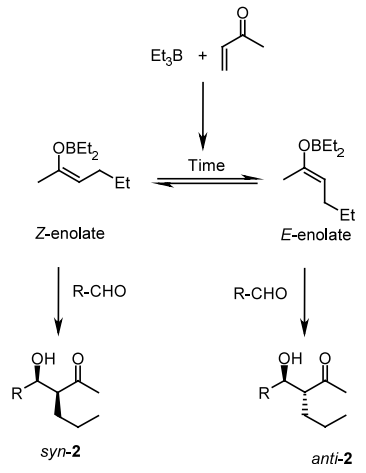
Table 1. Triethylborane triggered domino Michael–aldol reactions

Entry	R	Time (h)	Product[b] *syn* : *anti*	Yield[a] (%)
1	 **1a**	6	20 : 80 **2a**	82
2	 **1b**	6	54 : 46 **2b**	72
3	 **1c**	8	20 : 80 **2c**	85
4	 **1d**	8	40 : 60 **2d**	81
5	 **1e**	8	34 : 66 **2e**	73
6	 **1f**	4	70 : 30 **2f**	85
7	 **1g**	4	65 : 35 **2g**	82
8	 **1h**	4	45 : 55 **2h**	90
9	 **1i**	8	66 : 34 **2i**	65
10	 **1j**	8	58 : 42 **2j**	90

[a] All products were characterised by ^{1}H NMR and mass spectrometry.

[b] The *syn*/*anti* ratio was calculated by ^{1}H NMR and the diastereoisomers were separated by column chromatography.

anti). This observation prompted us to study 2,4-dimethoxybenzaldehyde **1d** (entry 4) as a substrate for the aldol reaction. However, the *syn*/*anti* ratio was only reasonable at 40:60 although the yield of **2d** was 81%. 3,4-Methylenedioxybenzaldehyde **1e** (entry 5) also gave a similar result with a *syn*/*anti* ratio of 34:66 and the aldol product **2e** in a 73% yield. To ascertain the role of the electrophilicity of the –CHO group, *p*-nitrobenzaldehyde **1f** (entry 6) was chosen as the third component in the three-component coupling reaction and to our pleasant surprise the *syn*/*anti* ratio was reversed to 70:30 and the overall yield of **2f** was 82% 4-Chlorobenzaldehyde **1g** (entry 7) behaved as expected with the *syn* product as the major isomer. 2-Chloro-5-nitrobenzaldehyde **1h** (entry 8) gave product **2h** with a *syn*:*anti* ratio



Scheme 2.

of 45:55, where the presence of the chlorine atom at the *ortho* position showed only a minor effect. The only aliphatic example, 3-phenylpropanal **1i** (entry 9) studied gave a 66:34 mixture of *syn*/*anti* products in a lower yield (**2i**, 65%). Furfuraldehyde **1j** (entry 10) gave a 58:42 mixture of the *syn*/*anti* products **2j** in a 90% overall yield which indicated its slightly less electrophilic nature compared to benzaldehyde.

It is a well understood phenomenon that the stereochemistry of aldol products is dependent on the geometry of the enolate intermediates and that *Z*-enolates preferably result in the *syn* products, with *E*-enolates producing *anti* products.

The more reactive *p*-nitrobenzaldehyde would appear to react readily with the initially formed *Z*-enolate and a preference for the *syn* product was observed. However, in the case of the less reactive *p*-methoxybenzaldehyde, the initially formed *Z*/*E* enolate isomerises to the more stable *E*-enolate giving the *anti*-aldol product selectively, see Scheme 2.

The relative diastereoselectivity was confirmed by exhaustive ^{1}H NMR.[10]

As far as we understand, this methodology represents the first non-metal mediated tandem Michael–aldol reaction for the synthesis of α-alkyl-β-hydroxy ketone derivatives.

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References

1. Hall, N. *Science* **1994**, *32*, 266.
2. Reviews: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**,

32, 131–164; recent examples: (c) De Meijere, A.; Nuske, H.; Es-Sayed, M.; Laban, T.; Schroen, M.; Brase, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3669–3672; (d) Paulsen, H.; Antons, S.; Brandes, A.; Logers, M.; Muller, S. N.; Naab, P.; Schmeck, C.; Schneider, S.; Stoltefuß, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3373–3375; (e) Knolker, H. J.; Baum, E.; Graf, R.; Spieß, O. *Angew. Chem., Int. Ed.* **1999**, *38*, 2603–2606; (f) Breit, B.; Zahn S. K. *Angew. Chem., Int. Ed.* **1999**, *38*, 969–971.

3. (a) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207–222; (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167–176; (c) Lautens, M.; Fillion, E. *J. Org. Chem.* **1997**, *62*, 4418–4427; (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338; (e) Neuschutz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227–255.
4. (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38; (b) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323; (c) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813; (d) Grigg, R. *J. Heterocyclic Chem.* **1994**, *31*, 631; (e) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379; (f) Negishi, E.; Coperet, C.; Ma, S.; Liou, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365; (g) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. *Chem. Rev.* **1996**, *96*, 635; (h) Grigg, R.; Sridharan *J. Organomet. Chem.* **1999**, *576*, 65; (i) De Meijere, A.; Brase, S. *J. Organomet. Chem.* **1999**, *576*, 88.
5. (a) Qi, X.; Montgomery, J. *J. Org. Chem.* **1999**, *64*, 9310–9313; (b) Ikeda, S.; Cui, D. M.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4712–4713; (c) Ikeda, I.; Kondo, K.; Sato, Y. *Chem. Lett.* **1999**, 1227–1228; (d) Fukuta, Y.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* **1999**, *40*, 4703–4706; (e) Mascarenhas, C. M.; Duffey, M. O.; Liu, S. Y.; Morken, J. P. *Org. Lett.* **1999**, *1*, 1427–1429; (f) Loh, T. P.; Wei, L. W. *Tetrahedron Lett.* **1998**, *39*, 323–326; (g) Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 1083–1086; (h) Ghosh, A. K.; Kwahama, R.; Wink, D. *Tetrahedron Lett.* **2000**, *41*, 8425–8429; (i) Shimizu, M.; Morita, A.; Kaga, T. *Tetrahedron Lett.* **1999**, *40*, 8401–8405.
6. (a) Kobayashi, S.; Ishitani, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1379; (b) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773–5776; (c) Kobayashi, S.; Akiyama, R.; Kawamura, M.; Ishitani, H. *Chem. Lett.* **1997**, 1039–1040; (d) Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115–116; (e) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 19–20; (f) Qian, C.; Huang, T. *J. Org. Chem.* **1998**, *63*, 4125–4128; (g) Akiyama, T.; Iwai, J. *Synlett* **1998**, 273–274; (h) Annunzita, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *J. Org. Chem.* **1996**, *61*, 8293–8296; (i) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *Chem. Commun.* **1999**, *651*, 652; (j) Heaney, H.; Simcox, M. T.; Slawin, A. M. Z.; Giles, R. G. *Synlett* **1998**, 640–642; (k) Cozzi, P. G.; Di Simone, B.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 1691–1695.
7. (a) Takesu, K.; Ueno, M.; Ihara, M. *J. Org. Chem.* **2001**, 4667; (b) Takesu, K.; Misawa, K.; Yamada, M.; Furuta, Y.; Taniguchi, T.; Ihara, M. *J. Chem. Soc., Chem. Commun.* **2000**, 1739.
8. Feringa, B. L.; Pineshi, M.; Arnold, L. A.; Imbos, R.; De Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623.
9. **Typical experimental procedure**: To a solution of the aldehyde (2 mmol) and methyl vinyl ketone (2 mmol) in THF (10 mL) was added triethylborane (4 mmol, 1 M solution in THF) and the mixture stirred at rt. After completion of the reaction (monitored by TLC) the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (3×10 mL). The organic extracts were washed with brine, dried (Na_2SO_4), concentrated in vacuo and purified by chromatography to give the aldol products.
10. Spectroscopic data[11] for compound **2c** *syn*: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (d, J=8.7 Hz, 2H), 6.78 (d, J=8.7 Hz, 2H), 4.72 (d, J=6.4 Hz, 1H), 3.76 (s, 3H), 2.88–2.74 (m, 1H), 2.50 (bs, 1H), 1.92 (s, 3H), 1.72–1.03 (m, 4H), 0.81 (t, J=7.5 Hz, 3H); EIMS: m/z 236 (M^+), 220, 178, 138, 110, 71, 43; ^{13}C NMR (200 MHz, $CDCl_3$) δ 212.79, 159.02, 134.24, 127.35, 113.73, 73.89, 59.80, 55.15, 31.63, 29.90, 20.92, 14.19; FTIR (KBr), 3425, 2958, 1704, 1247 cm^{-1}.
Compound **2c** *anti*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J=8.5 Hz, 2H), 6.83 (d, J=8.2 Hz, 2H), 4.63 (d, J=6.4 Hz, 1H), 3.76 (s, 3H), 2.79–2.64 (m, 1H), 2.50 (bs, 1H), 2.14 (s, 3H), 1.78–1.60 (m, 2H), 1.38–1.10 (m, 2H) 0.90 (t, J=6.9 Hz, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 213.41, 159.21, 134.69, 127.56, 113.82, 75.52, 59.30, 55.10, 31.74, 31.49, 20.38, 14.10; FTIR (KBr), 3460, 2958, 1706, 1248 cm^{-1}.
Compound **2f** *syn*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J=8.6 Hz, 2H), 7.52 (d, J=9.0 Hz, 2H), 5.04 (s, 1H), 3.20 (bs, 1H), 2.88–276 (m, 1H), 2.08 (s, 3H), 1.76–1.58 (m, 1H), 1.40–1.24 (m, 2H), 1.20–1.02 (m, 1H), 0.85 (t, J=7.1 Hz, 3H); m/z 208 (M^+– 43), 152, 100, 71, 43; ^{13}C NMR (200 MHz, $CDCl_3$) δ 212.86, 149.38, 147.12, 126.89, 123.36, 72.53, 58.34, 31.38, 28.54, 20.90, 14.04; FTIR (KBr), 3410, 2915, 1699, 1517 cm^{-1}.
Compound **2f** *anti*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J=9.06 Hz, 2H), 7.50 (d, J=8.6 Hz, 2H), 4.82 (s, 1H), 3.20 (bs, 1H), 2.94–2.86 (m, 1H), 2.14 (s, 3H), 1.64–1.23 (m, 4H), 0.89 (t, J=7.1 Hz, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 213.12, 149.98, 147.33, 127.12, 123.52, 74.46, 58.49, 31.80, 31.28, 20.27, 13.88; FTIR (KBr), 3389, 2966, 1714, 1525, 1346 cm^{-1}.
Compound **2h** *syn*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J=2.6 Hz, 1H), 8.10 (d, J=8.6 Hz, 1H), 7.50 (d, J=8.6 Hz, 1H), 5.31 (d, J=2.5 Hz, 1H), 3.63 (d, J=1.9 Hz, 1H), 3.03 (d, J=7.5 Hz, 1H), 2.36 (s, 3H), 1.75–1.64 (m, 1H), 1.40–1.20 (m, 2H), 1.15–1.02 (m, 1H), 0.82 (t, J=7.1 Hz, 3H); EIMS: m/z 185 (M^+–99), 100, 71, 43; ^{13}C NMR (200 MHz, $CDCl_3$) δ 213.56, 146.81, 140.92, 137.61, 130.31, 123.70, 23.29, 69.13, 53.74, 31.00, 26.77, 20.44, 13.99; FTIR (KBr), 3370, 2953, 1689, 1531, 1347 cm^{-1}.
Compound **2h** *anti*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J=2.8 Hz, 1H), 8.08 (d, J=2.8 Hz, 1H), 7.51 (d, J=8.6 Hz, 2H), 5.22 (s, 1H), 3.86 (d, J=7.6 Hz, 1H), 3.05 (d, J=7.0 Hz, 1H), 2.03 (s, 3H), 1.75–1.65 (m, 1H), 1.60–1.46 (m, 1H), 1.45–1.24 (m, 2H), 0.90 (t, J=7.3Hz, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 213.34, 146.86, 140.92, 138.44, 130.29, 123.58, 123.28, 69.05, 53.84, 31.71, 31.13, 26.66, 20.34, 13.86; FTIR (KBr), 3483, 2962, 1709, 1525, 1346 cm^{-1}.
11. Spectroscopic data is taken after separation of the isomers. However, the ratio of isomers is determined based on the spectral data of the unseparated mixture.