Stereoselective Synthesis of Highly Functionalized α-Diazo-β-ketoalkanoates via Catalytic One-Pot Mukaiyama-Aldol Reactions

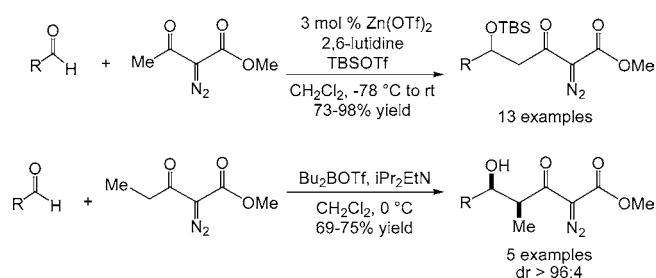**Lei Zhou and Michael P. Doyle***

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ABSTRACT

Methyl diazoacetoacetate undergoes zinc triflate catalyzed condensation with a broad selection of aldehydes to produce δ-siloxy-α-diazo-β-ketoalkanoates in good yield, and δ-hydroxy-α-diazo-β-ketoalkanoates are formed with high diastereoselectivity in reactions with α-diazo-β-ketopentanoate promoted by dibutylboron triflate.

Diazoacetoacetate derivatives are among the most commonly used substrates in catalytic diazo decomposition reactions.[1,2] Their relative stability compared to diazoacetates or vinyldiazoacetates, and their enhanced reaction selectivities compared to diazoacetates, are among their advantages for organic synthesis.[1] Traditionally these diazo compounds have been prepared by multistep synthesis involving diazo transfer as the final step.[3,4] Alternative methods that involve base-mediated condensation of diazo compounds with various electrophiles[5,6] have not been generalizable because they require stoichiometric amounts of base and often occur under relatively harsh reaction conditions.

(1) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons: New York, 1998.

(2) Reviews: (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.*, DOI: 10.1021/cr900239n. (b) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137–1156. (c) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2904. (d) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1–326. (e) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50–61. (f) Doyle, M. P. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; John Wiley & Sons: New York, 2000. (g) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797–1815. (h) Maas, G. *Top. Curr. Chem.* **1987**, *137*, 77–253. (i) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361–475.

(3) Review :Regitz, M.; Maas, G. *Diazo Compounds; Properties and Synthesis*; Academic Press: Orlando, FL, 1986.

(4) (a) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669–8680. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958–964. (c) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431–2435. (d) Clark, J. S.; Middleton, M. D. *Org. Lett.* **2002**, *4*, 765–768.

(5) Review: Zhao, Y.; Wang, J. *Synlett* **2005**, 2886–2892.

(6) (a) Wenkert, E.; McPherson, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 8084–8090. (b) Moody, C. J.; Morfitt, C. N. *Synthesis* **1998**, 1039–1042. (c) Kanemasa, S.; Araki, T.; Kanai, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5059–5062. (d) Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285–1287. (e) Sa, M. M.; Silveira, G. P.; Bortoluzzi, A. J.; Padwa, A. *Tetrahedron* **2003**, *59*, 5441–5447. (f) Erhunmwunse, M. O.; Steel, P. G. *J. Org. Chem.* **2008**, *73*, 8675–8677. (g) Dong, C.; Mo, F.; Wang, J. *J. Org. Chem.* **2008**, *73*, 1971–1974.

We have reported an efficient Mukaiyama-aldol reaction between methyl 2-diazo-3-(trialkylsilanoxy)-3-butenoate and both aromatic and aliphatic aldehydes catalyzed by scandium(III) triflate,[7] and more recently, a process improvement in this reaction using zinc triflate has been described.[8] Although methyl 2-diazo-3-(trialkylsilanoxy)-3-butenoate is produced directly from methyl diazoacetoacetate under a standard set of conditions (R₃SiOTf, Et₃N),[9] we set out to examine if the Mukaiyama-aldol reactions between aldehydes and readily accessible diazoacetoacetates, rather than methyl 2-diazo-3-(trialkylsilanoxy)-3-butenoate, using catalytic amounts of Lewis acid under mild conditions could be achieved. Calter and Zhu previously described a stoichiometric version in which ethyl diazoacetoacetate underwent condensation with aldehydes in the presence of stoichiometric amounts of TiCl₄ at −78 °C,[10] and they also showed that this condensation could be performed in a two-step process from ethyl diazoacetoacetate (i: TMSOTf, Et₃N in CH₂Cl₂, −78 °C; ii: ArCHO, BF₃·OEt₂, −78 °C). We now report a more efficient and general Lewis acid catalyzed one-pot Mukaiyama-aldol reaction between diazoacetoacetates and aldehydes with low catalyst loading of inexpensive zinc triflate. On the basis of the same strategy but not indicated in prior reports, we also report a highly diastereoselective boron-mediated Mukaiyama-aldol reaction with the use of α-diazo-β-ketopentanoate.

Scheme 1
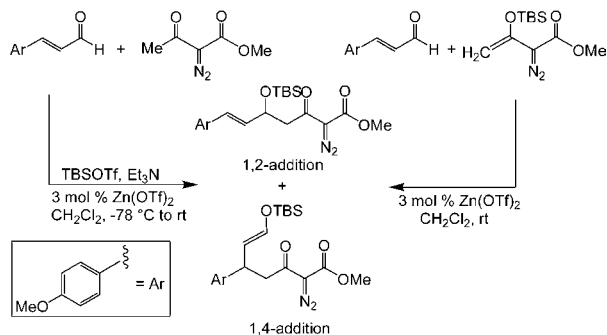
We first screened reaction conditions for the one-pot Mukaiyama-aldol reaction. Reaction between methyl diazoacetoacetate (**2**) and *trans-p*-methoxycinnamaldehyde in the presence of a catalytic amount of zinc triflate, triethylamine (3.0 equiv), and TBS triflate (1.2 equiv) at −78 °C yielded both 1,2- and 1,4-addition products in a 5:1 molar ratio (Scheme 1). This result is identical to that obtained from the reaction of methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate and *trans*-4-methoxycinnamaldehyde in

the presence of zinc triflate (3 mol %) at room temperature (Scheme 1).

Recognizing that the regioselectivity for addition might be dependent on the base employed, a weaker base, 2,6-lutidine,[11] was used in place of triethylamine for the reaction with methyl diazoacetoacetate outlined in Scheme 1. Under these conditions, the one-pot Mukaiyama-aldol reaction proceeded to produce the 1,2-addition product in 90% isolated yield to the virtual exclusion of the 1,4-addition product. Reactions performed at 0 °C or room temperature, however, produced up to 20% of the 1,4-addition product.

Table 1. One-Pot Mukaiyama-Aldol Reactions between Methyl Diazoacetoacetate and α,β-Unsaturated Aldehydes[a]
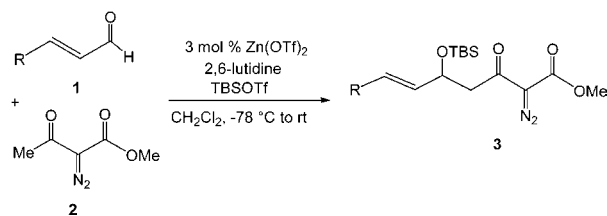
entry	aldehyde 1	3	yield, %[b]
a			73[c]
b			90[c]
c			94[c]
d			98
e			95
f			92
g			89[c]

[a] Methyl diazoacetoacetate **2** (1.0 mmol), 2,6-lutidine (3.3 equiv), and aldehyde (1.1 equiv) were added sequentially to zinc triflate (3 mol %) in 5 mL of dry DCM. After cooling to −78 °C, TBSOTf (1.25 equiv) was added dropwise. The mixture was stirred at −78 °C then warmed to room temperature over 16 h. [b] Yields were obtained by mass following flash column chromatography. [c] Trace amounts of 1,4-addition product were observed.

Examination of the scope of the reaction with a variety of α,β-unsaturated aldehydes (**1**), the results for which are presented in Table 1, showed the production of 1,2-addition

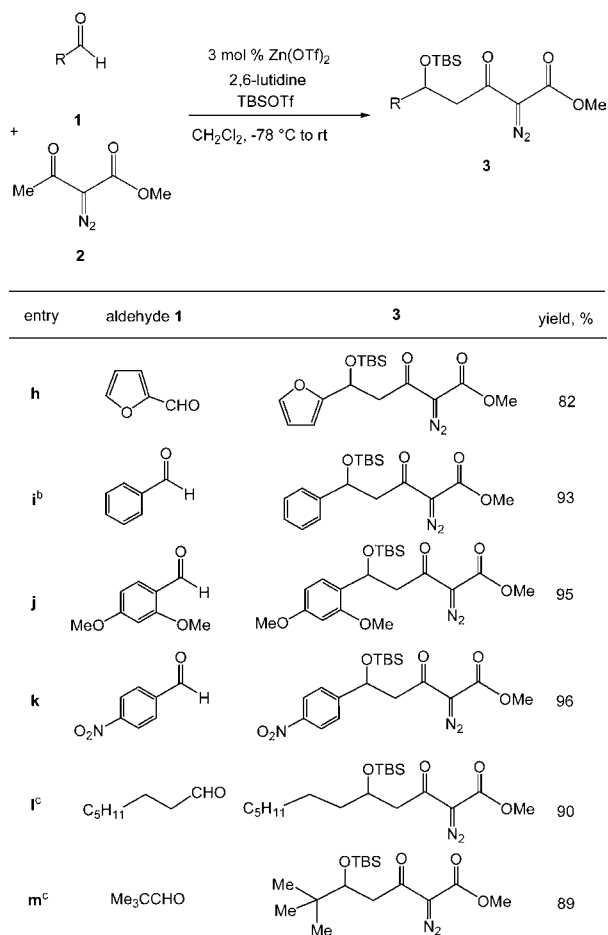(7) Doyle, M. P.; Kundu, K.; Russell, A. E. *Org. Lett.* **2005**, *7*, 5171–5174.

(8) Liu, Y.; Zhang, Y.; Jee, N.; Doyle, M. P. *Org. Lett.* **2008**, *10*, 1605–1608.

(9) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774–10780.

(10) (a) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tetrahedron Lett.* **1997**, *38*, 3837–3840. (b) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415–1419.

(11) For prior use of 2,6-lutidine, see: Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706–8707.

products in very good yields (Table 1). α,β-Unsaturated ketones do not react with methyl diazoacetoacetate under the same conditions and, with substrates such as 2-cyclohexenone, undergo preferential silyl enolization. That methyl diazoacetoacetate reacted with TBS triflate in the presence of 2,6-lutidine at low temperature to yield the vinyl ether, methyl 3-*tert*-butyl-dimethylsilanyloxy-2-diazobut-3-enoate, was confirmed by observing the transformation at low temperature by ^{1}H NMR (see Supporting Information for details).

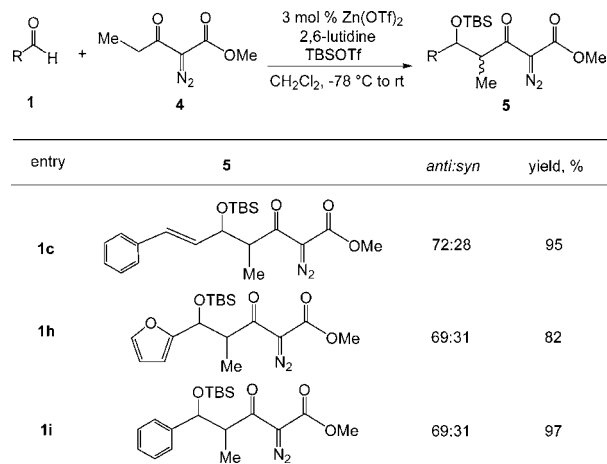**Table 2.** One-Pot Mukaiyama-Aldol Reactions between Methyl Diazoacetoacetate and Aromatic/Aliphatic Aldehydes[a]

entry	aldehyde 1	3	yield, %
h	furfural (2-furaldehyde)	OTBS product	82
i[b]	benzaldehyde	OTBS product	93
j	2,4-dimethoxybenzaldehyde	OTBS product	95
k	4-nitrobenzaldehyde	OTBS product	96
l[c]	C₅H₁₁CHO	OTBS product	90
m[c]	Me₃CCHO	OTBS product	89

[a] Reactions were performed as described in Table 1. [b] Reaction catalyzed by 1 mol % of Zn(OTf)₂ gave the product **3i** in 91% yield. [c] Sc(OTf)₃ (3 mol %) and triethylamine (1.5 equiv) were used.

This methodology was extended to aromatic and aliphatic aldehydes. As shown in Table 2, reactions between methyl diazoacetoacetate and aromatic aldehydes afforded the addition products in excellent yields and suggest the overall generality of this protocol. Product yields were at least as high as those reported for scandium(III) triflate catalyzed reactions of some of these same aldehydes with methyl 2-diazo-3-(trialkylsilanoxy)-3-butenoate that were previously reported by our group.[7] Using 1.0 mol % zinc triflate with

entry **1i** resulted in the production of **3i** in nearly the same yield (91% versus 93%) as when 3 mol % zinc triflate was used. For the aliphatic aldehydes (**1l** and **1m**), the standard conditions (zinc triflate and 2,6-lutidine or zinc triflate and triethylamine) led to less than full conversions over 16 h, so scandium(III) triflate (3.0 mol %) and triethylamine (1.5 equiv) were used and resulted in complete conversion, providing the desired products in good yields (Table 2). Even the enolizable aldehyde (**1l**) underwent this reaction protocol with excellent results.

Table 3. One-Pot Mukaiyama-Aldol Reaction between Methyl 2-Diazo-3-oxo-pentanoate and Aromatic/Vinyl Aldehydes[a]

entry	5	anti:syn	yield, %
1c	cinnamaldehyde product	72:28	95
1h	furyl product	69:31	82
1i	phenyl product	69:31	97

[a] Reactions were performed as described in Table 1.

Diastereocontrol in Mukaiyama-aldol reactions is a universal problem whose solutions have been the subject of numerous investigations.[12] Using the Mukaiyama-aldol protocol with methyl 2-diazo-3-oxo-pentanoate (**4**) under the same conditions as those reported in Tables 1 and 2, we discovered that the condensation products were produced as a mixture of two diastereomers (*anti/syn* ~ 2:1)[13] in good yields (Table 3). Similar results were obtained with the use of stoichiometric TiCl₄ (80% yield, *syn:anti* = 77:23). Although a number of approaches have been used to increase
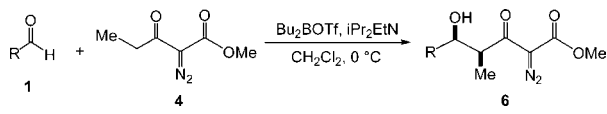
(12) Representative examples: (a) Ollevier, T.; Bouchard, J.-E.; Desyroy, V. *J. Org. Chem.* **2008**, *73*, 331–334. (b) Jankowska, J.; Paradowska, J.; Rakiel, B.; Mlynarski, J. *J. Org. Chem.* **2007**, *72*, 2228–2231. (c) Boeckman, R. K., Jr.; Pero, J. E.; Boehmier, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 11032–11033. (d) Kong, K.; Romo, D. *Org. Lett.* **2006**, *8*, 2909–2912. (e) Jankowska, J.; Mlynarski, J. *J. Org. Chem.* **2006**, *71*, 1317–1321. (f) Jung, M. E.; van den Heuvel, A. *Org. Lett.* **2003**, *5*, 4507–4707. (g) Hassfield, J.; Christmann, M.; Kalesse, M. *Org. Lett.* **2001**, *3*, 3561–3564.
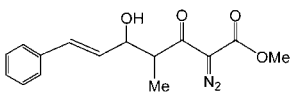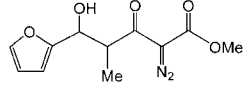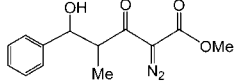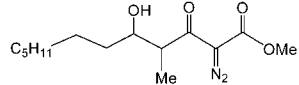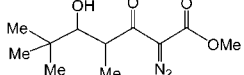
(13) The diastereomeric ratio was determined from ^{1}H NMR integration of the tertiary C−H bonded directly to the OTBS group. The coupling constant *J* of the tertiary C−H: *anti* (threo) *J* = 8.8−9.6 Hz, *syn* (erythro) *J* = 6.4−7.6 Hz.

(14) (a) Ghosh, A. K.; Shevlin, M. *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 63−125. (b) Markert, M.; Scheffler, U.; Mahrwald, R. *J. Am. Chem. Soc.* **2009**, *131*, 16642–16643. (c) Han, S. B.; Hassan, A.; Krische, M. J. *Synthesis* **2008**, *17*, 2669–2679. (d) Nishiyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105–137. (e) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857–7870. (f) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308. (g) Bertelsen, S.; Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189.

diastereoselectivity in aldol reactions,[12,14] we selected di-*n*-butylboryl triflate and diisopropylethylamine because of their demonstrated ability to effect enolization at low temperature[15] and because of the success of Evans and co-workers[16] in using this combination to generate mainly *Z*-enol boronates that subsequently react with aldehyde to afford *syn*-aldol products.[17]

Table 4. Boron-Mediated Aldol Reaction between Methyl 2-Diazo-3-oxo-pentanoate and Aldehydes[a]


entry	6	*syn:anti*[b]	yield, %[c]
1c		99:1	73
1h		99:1	71
1i		96:4	75
1l		97:3	69
1m		97:3	69

[a] Methyl 2-diazo-3-oxo-pentanoate **4** (2.0 mmol), *N,N*-diisopropylethylamine (2.0 equiv), and di-*n*-butylboron triflate (1.1 equiv) were added sequentially to 5 mL of dry DCM. After stirring at 0 °C for 15 min, aldehyde (1.0 equiv) was added. The mixture was stirred at 0 °C for 3 h. [b] The diastereomer ratio was determined by the integral ratio by ^{1}H NMR of the tertiary C−H bonded to the OH group and/or the integral ratio of ^{1}H NMR signals for the methyl group. [c] Yields were obtained by mass following flash column chromatography.

To enhance the diastereoselectivity, a boron-mediated Mukaiyama-aldol reaction was performed. As shown in Table 4, the reaction between methyl 2-diazo-3-oxo-pentanoate (**4**), (*n*-Bu)$_2$BOTf (1.1 equiv), Hunig's base (2.0 equiv), and aromatic/vinyl/aliphatic aldehydes (1.0 equiv) at 0 °C afforded the *syn*-aldol product in good yields with very high diastereoselectivity (Table 4). For the investigated aldehydes, the *syn/anti* is above 96:4. For the reaction with benzaldehyde, the same yield and diastereoselectivity were obtained when the reaction was performed at 0 °C as when the reaction was performed at −78 °C. With triethylamine used in place of Hunig's base with entries **1c**, **1i**, and **1 m**, **6c**, **6i**, and **6m** were obtained in lower yields (**6c** 60%, **6i** 59%, **6m** 51%) but with nearly the same diastereoselectivities (**6c**, 99:1; **6i**, 99:1; **6 m**, 93:7).

Scheme 2
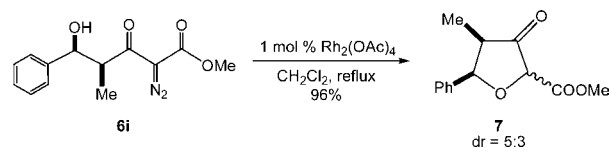
Consistent with the prior report of Calter and Zhu,[10b] rhodium acetate catalyzed diazo decomposition produces the corresponding O−H insertion product in excellent yield. This reaction was explored with Mukaiyama-aldol adduct **6i** (Scheme 2). The tetrahydrofuran derivative **7** was formed as a ~5:3 diastereomeric mixture with the isomer having the methylcarboxylate group trans to the benzene ring predominating.

In summary, we have developed an efficient one-pot aldol reaction between diazoacetoacetate with a wide spectrum of aldehydes using catalytic amounts of zinc triflate, and we also report a highly diastereoselective di-*n*-butylboryl-mediated aldol reaction with the use of substituted diazoacetoacetate. This methodology can be used for the efficient construction of highly substituted diazo compounds. The synthetic utility of the Mukaiyama aldol adduct has been demonstrated with the diazo decomposition/O−H insertion reaction, and we anticipate additional uses of this methodology with the synthesis of more complex α-diazo-β-ketoalkanoates than previously possible. Efforts are continuing to develop the full synthetic potential of this methodology.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.

(16) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.

(17) (a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441–3442. (b) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387–395.