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Divergent Stereocontrol of Acid Catalyzed Intramolecular Aldol Reactions of 2,3,7-Triketoesters: Synthesis of Highly Functionalized Cyclopentanones

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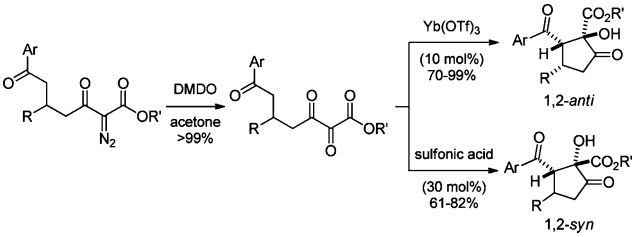
ABSTRACT



The intramolecular acid catalyzed aldol cyclization of 2,3,7-triketoesters formed from ζ-keto-α-diazo-β-ketoesters provides highly functionalized cyclopentanones with good diastereoselectivity in high overall yields via kinetically controlled and stereodivergent catalytic processes. Lewis acid catalysis gives high selectivity for the 1,2-*anti* tetrasubstituted cyclopentanones, whereas Brønsted acid catalysis produces the corresponding 1,2-*syn* diastereomer.

New strategies for the synthesis and application of complex diazo compounds have proven fruitful in the preparation of carbocyclic and heterocyclic ring systems due to the proven utility of selective diazo decomposition reactions in complex environments.[1] A longstanding interest in our research group has been the application of enol diazoacetates of type **1** toward the synthesis of more complex diazo compounds by developing methods that take advantage of the remarkable stability of the diazo-β-ketoester functional group (Scheme 1).[2] To that end, we have recently reported the Mukaiyama–aldol reactions of **1** to give δ-hydroxy diazo-β-ketoesters **2**[2a] as well as a Mukaiyama–Michael variant with enones to provide ζ-keto-α-diazo-β-ketoesters **3** (Scheme 1).[2b] These new methods have provided access to highly functionalized diazo compounds that have allowed us to study increasingly complex materials by way of transition metal catalyzed dinitrogen extrusion reactions.[1]

We have also been intrigued by the umpolung in reactivity provided by the conversion of the diazo functional group to the keto functional group that has been made possible through the use of DMDO.[5] In general, conversion of a diazo functionality **4** to a carbonyl functionality **5** causes a reversal in the polarity of carbon (Scheme 2).

(1) (a) 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. Reviews: (b) Doyle, M. P.; Duffy, R.; Ratnikov, M. O.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704–724. (c) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137–1156. (d) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2904. (e) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1–326. (f) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50–61.

(2) (a) Doyle, M. P.; Kundu, K.; Russell, A. E. *Org. Lett.* **2005**, *7*, 5171–5174. (b) Liu, Y.; Zhang, Y.; Jee, N.; Doyle, M. P. *Org. Lett.* **2008**, *10*, 1605–1608. (c) Truong, P.; Xu, X.; Doyle, M. P. *Tetrahedron Lett.* **2011**, *52*, 2093–2096. (d) Zhou, L; Doyle, M. P. *Org. Lett.* **2010**, *12*, 796–799. (e) Xu, X.; Hu, W.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 6392–6395. (f) Xu, X.; Ratnikov, M. O.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2011**, *13*, 6122–6125.

(3) (a) Xu, G.; Hou, A.; Zheng, Y.; Zhao, Y.; Li, X.; Peng, L.; Zhao, Q. *Org. Lett.* **2007**, *9*, 291–293. (b) Zheng, J.; Xie, X.; Zhao, C.; He, Y.; Zheng, H.; Yang, Z.; She, X. *Org. Lett.* **2011**, 173–175. (c) Zhu, X.; Xiang, K.; Zhang, F.; Tu, Y. *J. Org. Chem.* **2011**, *76*, 6918–6924.

(4) (a) Goessinger, E. *Prog. Chem. Org. Nat. Prod.* **2010**, *93*, 71–210. (b) Trost, B.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131–6141. (c) Trost, B.; Krische, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 233–234.

(5) Saba, A. *Synth. Commun.* **1994**, *24*, 695–699.

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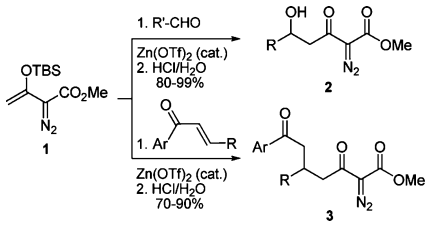
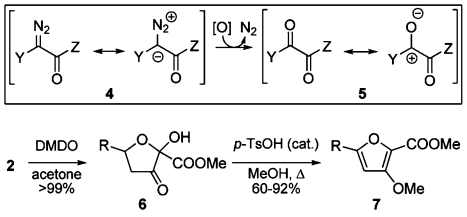
Scheme 1. Mukaiyama Reactions of Silyl Ketene Diazoacetates



Upon reaction of DMDO with δ-hydroxy-α-diazoacetoacetate **2** (Scheme 2), the polarity inversion causes an intramolecular nucleophilic attack from the remote hydroxyl group into the newly formed carbonyl unit to generate hemiketal **6**.[2c] Hemiketal **6** was then further manipulated to provide 3-alkoxyfuran derivatives such as **7** by acid catalyzed dehydration/methanolysis.

Scheme 2. Oxidation of δ-Hydroxy-α-diazoacetoacetates as a Route to Furanones and Furans

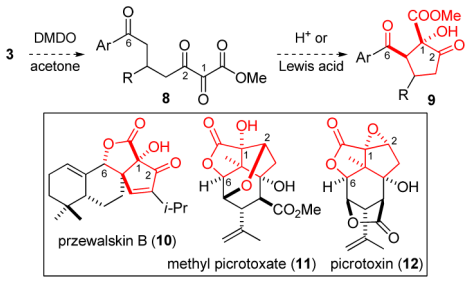


With the success of these early studies, we directed our attention to the application of this umpolung strategy to the previously reported[2b] Mukaiyama–Michael adducts **3** (Scheme 3). Our hypothesis was that oxidation of this class of diazo compounds would provide tetracarbonyl compounds (**8**), which we envisioned as candidates for intramolecular aldol reactions for the construction of the highly functionalized cyclopentanones **9**. Our interest in this strategy was piqued by the knowledge that a number of biologically active natural products such as prezawlskin B (**10**)[3] and the picrotoxanes (e.g., **11**–**12**)[4] share a similarly functionalized cyclopentanone system to which the proposed methodology may allow access.

Our investigation began by first preparing a family of tetracarbonyl compounds, which were available via a two-step sequence involving the intermolecular Mukaiyama–Michael reaction of enol diazoacetate **1** followed by oxidation of the diazoacetoacetate with DMDO (Table 1).[2b] Yields from the two-step process ranged from 69 to 92%.[5,2c] It should be noted that the oxidation step in all

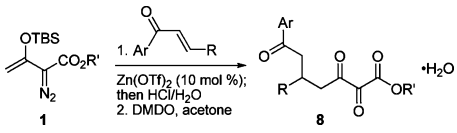
(6) Typical product mixtures were ~9:1 hydrate/ketone and were used without dehydration for subsequent chemistry. If desired, however, the products can be dehydrated by heating at 100 °C under a high vacuum for 2 h. For other examples, see: (a) Rubin, M. B.; Gleiter, R. *Chem. Rev.* **2000**, *100*, 1121–1164. (b) Wasserman, H. H.; Parr, J. *Acc. Chem. Res.* **2004**, *37*, 687–701.

Scheme 3. Diazo-umpolung Route to Cyclopentanones



cases proceeded in virtually quantitative yields, and the products were isolated as hydrates.[6] Thus yields of **8** reflect limitations in the Mukaiyama–Michael reaction.

Table 1. Synthesis of 2,3,7-Triketoesters[a]



8	Ar	R	R′	yield (%)[b,c]
a	C_6H_5	H	Me	80
b	2-naphthyl	H	Me	83
c	4-$MeOC_6H_4$	H	Me	92
d	4-ClC_6H_4	H	Me	83
e	9-anthryl	H	Me	71
f	mesityl	H	Me	69
g	4-$CF_3C_6H_4$	H	Me	81
h	4-$CF_3C_6H_4$	H	Bn	73
i	C_6H_5	Ph	Me	90

[a] See Supporting Information for procedural details. [b] Isolated yield following purification via column chromatography. [c] Overall yields are reported starting from **1** and the respective enone used.

The capabilities of Lewis acids to catalyze aldol condensation reactions with high stereocontrol is well-known;[7] however, application to vicinal tricarbonyl compounds has not been reported. Copper(II), scandium(III), and ytterbium(III) triflates are reported to be effective for aldol condensation reactions,[8] and tin(II) triflate has also been described.[9] These catalysts were evaluated for their effectiveness in mediating carbocyclization of **8a** in

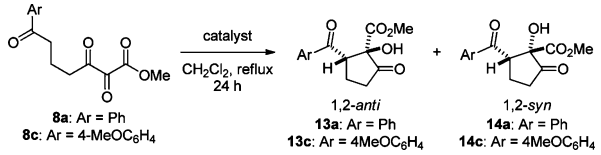
(7) (a) Kurteva, V. B.; Afonso, C. A. M. *Chem. Rev.* **2009**, *109*, 6809. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187–2210. (d) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227.

(8) (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335. (b) Le, J.; Pagenkopf, B. *Org. Lett.* **2004**, *6*, 4097–4099. (c) Lefebvre, O.; Brigaud, T.; Portella, C. *J. Org. Chem.* **2001**, *66*, 1941–1946. (d) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209–217. (e) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. *Chem. Rev.* **2002**, *102*, 2227–2302. Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 12236–12237.

(9) (a) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1992**, *57*, 1325–1327. (b) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron.* **1993**, *49*, 1761–1772. (c) Evans, D.; MacMillan, D.; Campos, K. *J. Am. Chem. Soc.* **1997**, *119*, 10859–10860.

refluxing dichloromethane (Table 2, entries 1−7). Each of these catalysts exhibited a high degree of diastereocontrol, but $Yb(OTf)_3$ provided the highest level of diastereoselectivity. Alternative catalysts such as $La(OTf)_3$,[9c,11] $Zn(OTf)_2$,[9a,3,4] $Ni(OTf)_2$,[12] and $Mg(OTf)_2$[13] showed little or no activity for this transformation under the reaction conditions.

Table 2. Optimization of the Intramolecular Aldol Reaction of 2,3,7-Triketoester **8a**

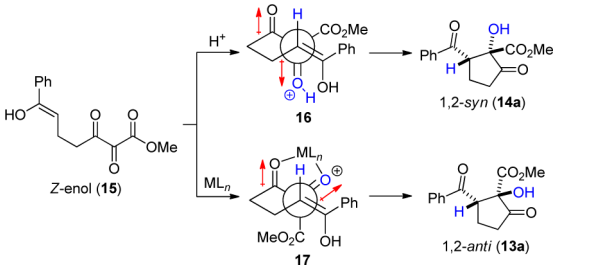


entry[a]	catalyst[b]	*anti*/*syn*[c]	% conversion[c]
1	$Yb(OTf)_3$[d]	N.D.	<5
2	$Yb(OTf)_3$[e]	95:5	65
3	$Yb(OTf)_3$[f]	95:5	>95
4	$Yb(OTf)_3$	95:5	>95
5	$Sn(OTf)_2$	85:15	93
6	$Sc(OTf)_3$	87:13	>95
7	$Cu(OTf)_2$	89:11	>95
8	H_2PO_4[g]	25:75	75
9	*p*-TsOH	32:68	84
10	Mes-SO_3H	30:70	90
11	Mes-SO_3H[h]	30:70	>95
12[i]	$Yb(OTf)_3$	93:7	>95

[a] Reaction performed substrate **8a**. [b] Reaction performed with 10 mol % catalyst. [c] Determined by ^1H NMR spectroscopy (see Supporting Information). [d] 10 mol % catalyst at room temp for 24 h. [e] 5 mol % catalyst. [f] 20 mol % catalyst. [g] 4 equiv of acid used. [h] 30 mol % of the acid used. [i] The stereochemistry of the process was confirmed by a reaction with **8c** using 10 mol % $Yb(OTf)_3$, and product **13c** was analyzed by X-ray (see Supporting Information).

We were surprised to find a significant divergence in stereocontrol between Lewis acid and Brønsted acid catalysts. The use of a Lewis acid gave the 1,2-*anti* product **13a** predominantly, whereas Brønsted acids greatly favored formation of the 1,2-*syn* product **14a**. Furthermore, given the prevalence of *syn*-selective aldol reactions of 1,*n*-dicarbonyl compounds under both Brønsted and Lewis acid catalyzed conditions,[7] the fact that the *anti*-aldol product **13** is formed with high selectivity is notable. Our initial thought regarding the observation that Lewis and Brønsted acids provided divergent reactivity was that we had simply discovered conditions for both the kinetically and thermodynamically controlled processes; however extensive investigations have revealed that the aldol adducts themselves are resistant to equilibration between their *syn*- and *anti*-forms under any of the optimized reaction conditions. When either purified **13a** or **14a** was resubjected to the standard reaction conditions (Table 2, entries 4 and 11), no interconversion of these products was observed. Interconversion was only observed after 7 days in refluxing $CDCl_3$; however, interconversion under these more forcing conditions was accompanied by a significant amount of byproduct formation (>30% relative to **13a** and **14b** based on ^1H NMR). The absence of product interconversion under the standard reaction conditions suggests that this unique stereochemical divergence between Lewis and Brønsted acid catalysis is the result of a kinetically controlled process. In this scenario Lewis acids alter the course of the reaction to give the less common *anti*-aldol product. We believe that the stereochemical outcomes of the Brønsted and Lewis acid catalyzed aldol reactions can be rationalized by analyzing the conformational intermediates en route to the respective products (Scheme 4). Activation of the central carbonyl by a Brønsted acid presumably results in the dipole minimized orientation of the 1,2-diketo unit, which can then be attacked by the tethered *Z*-enol via the lower energy intermediate **16** thus providing **14a**. Lewis acid activation, however, has the ability to coordinate the 1,2-diketo unit thus locking the carbonyls in a *syn*-orientation. The *Z*-enol then reacts with the central carbonyl *via* intermediate **17** to give **13a**.

Scheme 4. Stereochemical Rationale for the Diastereoselectivity of Lewis and Brønsted Acids



Expanding on these initial results, we applied the optimized conditions for the Lewis and Brønsted acid catalyzed processes to representative substrates (Table 3). Both electron-withdrawing and -donating aromatic rings were tolerated, as were sterically demanding aromatic substituents. In the case of the *o*,*o*-disubstitued substrates **13e** and **13f** (Table 3, entries 5 and 6), however, a significant deterioration in *anti*/*syn* selectivity was observed under Lewis acid catalyzed conditions. In fact, in the mesityl example (Table 3, entry 6) selectivity was inverted, and the *syn*-diastereomer was formed preferentially. This anomaly seems to highlight the fact that the *anti*-transition state is inherently more sterically demanding; thus, when the steric

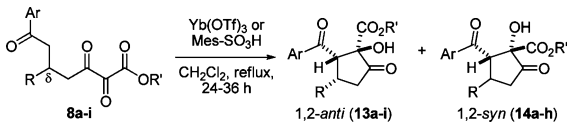
(10) (a) Evans, D.; Downey, W. C.; Hubbs, J. *J. Am. Chem. Soc.* **2003**, *125*, 8706–8707. (b) Fossey, J.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Inorg. Chem.* **2008**, *47*, 781–783.

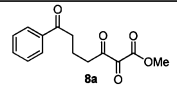
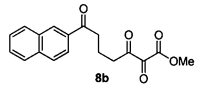
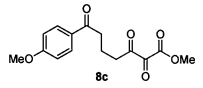
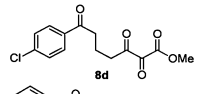
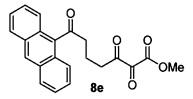
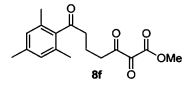
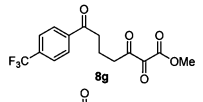
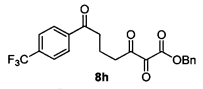
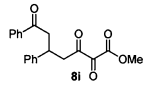
(11) (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807–6810. (b) Ji, J.; Barnes, D.; Zhang, J.; King, S.; Wittenberger, S.; Morton, H. *J. Am. Chem. Soc.* **1999**, *121*, 10215–10216.

(12) (a) Jung, M. E.; Johnson, T. W. *J. Am. Chem. Soc.* **1997**, *119*, 12412–12413. (b) Bouillon, J. P.; Portella, C. *Eur. J. Org. Chem.* **1999**, 1571–1580. (c) Bouillon, J. P.; Portella, C.; Bouquant, J.; Humbel, S. *J. Org. Chem.* **2000**, *65*, 5823–5830. Baik, T. G.; Luis, A. L.; Wang, J. C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112–5113.

(13) The stereochemistry of **13i** was determined by X-ray crystallography (Supporting Information).

Table 3. Scope and Limitations



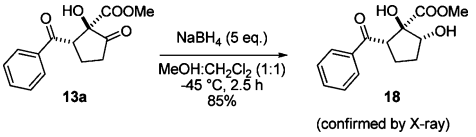
Entry	Substrates	Method	Yield (%)[a]	*anti*:*syn* ratio[b]
1	 8a	A[c]	98	95:5
		B[d]	81	24:76
2	 8b	A	92	95:5
		B	80	33:67
3	 8c	A	94	93:7
		B	67	25:75
4	 8d	A	96	95:5
		B	75	43:57
5	 8e	A	70	57:43
		B	82	10:90
6	 8f	D[f]	51	30:70
		B	61	5:95
7	 8g	A	96	94:6
		B	75	16:84
8	 8h	A	92	93:7
		B	77	23:77
9	 8i	C[e]	92	93:7
		-	-	-

[a] Isolated yield. [b] Diastereomeric ratios determined by ^{1}H NMR spectroscopy. [c] Method A: Reaction was performed with 10 mol % Yb(OTf)$_3$. [d] Method B: Reaction was performed with 30 mol % mesitylenesulfonic acid (Mes-SO$_3$H). [e] Method C: Reaction was performed with 10 mol % Sn(OTf)$_2$. [f] Method D: Reaction was performed with 10 mol % Sc(OTf)$_3$.

demand is too high, an alternative acid coordination such as that in **16** is favored due to the fewer number of Gauche interactions. We were also interested in studying the effect of a δ-substituent on the stereochemical course of the reaction (Table 3, entry 9). To that end, when **8i** was subjected to standard Lewis acid catalyzed conditions the reaction provided **13i** as the major product (*dr* = 93:7) with the usual 1,2-*anti* geometry where the 3-phenyl substituent is positioned *syn* to the aryl ketone moiety, which further exemplifies the stereocontrol predicted by **17**.[13]

With the cyclopentanone system bearing two ketone groups we next queried whether these carbonyl groups could be orthogonally reacted, thus enhancing the synthetic utility of these novel cyclopentanone products. We found that reduction of the cyclic ketone could be performed with high chemo- and stereoselectivity to give the diol **18** in 85% yield as only one diastereomer (Scheme 5).[14] The stereochemistry of **18** was confirmed by X-ray crystallography to be the 1,2-*anti* diol resulting from a chelation controlled delivery of the hydride.

Scheme 5. Chemo- and Stereoselective Reduction of Dione **13a**[a]



[a] No trace of the aryl ketone reduction product under these conditions.

In conclusion, the Mukaiyama–Michael reaction of silyl enoldiazoacetates was exploited to prepare a series of highly functionalized ξ-keto-α-diazo-β-ketoesters. The diazo groups of these compounds were oxidized with DMDO to generate 2,3,7-triketoesters in virtually quantitative yields, which set up highly stereoselective intramolecular aldol reactions to provide usefully functionalized cyclopentanones. Lewis acid catalysts provided high degrees of 1,2-*anti* diastereoselectivity, while Brønsted acids selectively provided the 1,2-*syn* diastereomer, a fact that we believe makes this methodology even more synthetically attractive. The prospect of using chiral acid catalysts to achieve an asymmetric variant of this reaction, and application of the overall strategy toward natural product synthesis are currently being explored.

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Supporting Information Available. General experimental procedures, the X-ray structures of **13c**, **13i**, and **18**, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Tsubuki, M.; Matsuo, S.; Honda, T. *Tetrahedron Lett.* **2008**, *49*, 229–232.

The authors declare no competing financial interest.