DOI: 10.1002/adsc.201200914

Biomimetic Direct Aldol Reaction of Pyruvate Esters with Chiral Aldehydes

Osama El-Sepelgy[a,*] and Jacek Mlynarski[a,b,*]

[a] Faculty of Chemistry, Jagiellonian University, Ingardena 3, 30-060 Krakow, Poland
E-mail: ozelsepelgy@yahoo.com or jacek.mlynarski@gmail.com
[b] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, Warsaw, Poland

Received: October 19, 2012; Revised: November 16, 2012; Published online: January 16, 2013

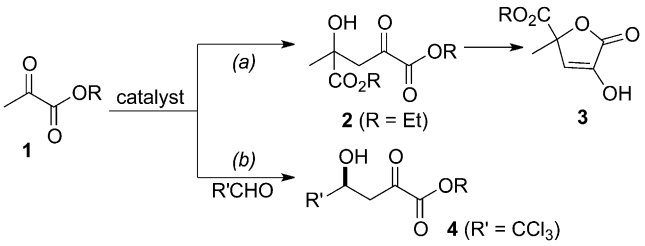
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200914.

Abstract: Direct aldol reactions of pyruvate esters with sugar aldehydes is efficiently promoted by dinuclear metal complexes or chiral *Cinchona* alkaloid organocatalysts. Application of sterically hindered aryl esters enables the to-date problematic aldol reaction of pyruvate donors with *syn*- or *anti*-selectivity *en route* to the short and efficient synthesis of 3-deoxy-2-ulosonic acids.

Keywords: aldol reaction; asymmetric synthesis; carbohydrates; organocatalysis; pyruvates

The aldol reaction, in addition to being an effective method for the formation of carbon-carbon bonds, is also an outstanding example of the inspiration transferred from a biochemical processes to chemical synthesis. While initially the aldol reaction was used for the synthesis of relatively simple organic compounds,[1] now it constitutes an intensively explored tool for the synthesis of complex natural products including monosaccharides.[2] An important way to improve the efficiency of chemical methods for the aldol reaction is the development of a catalytic system where both donor and acceptor substrates are activated simultaneously to perform the direct aldol reaction with high efficiency and stereoselectivity similar to aldolase enzymes.[3]

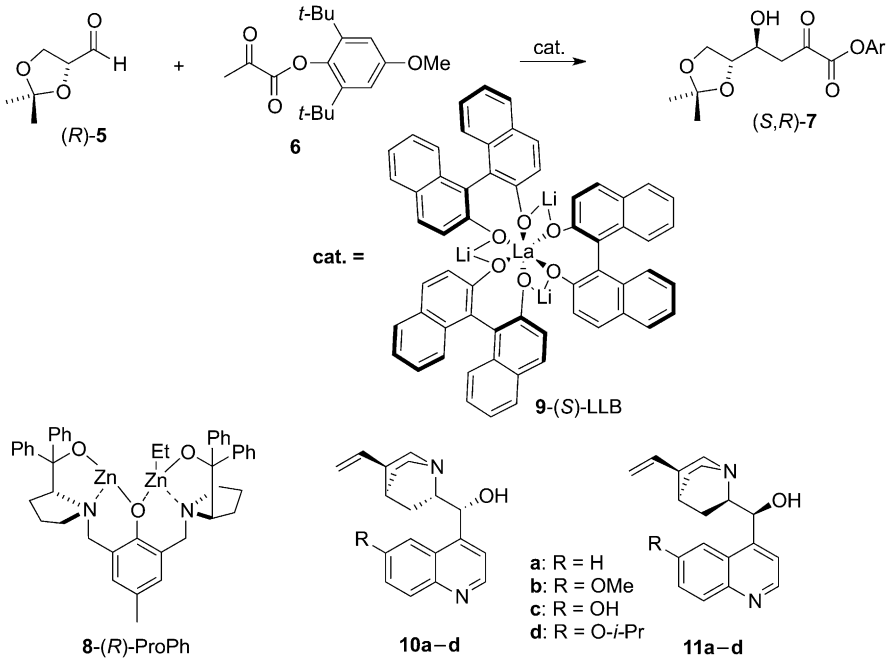
While such a methodology is known for many other asymmetric aldol syntheses, the direct activation of pyruvate esters **1** still remains an elusive goal if not simply a white spot on the aldol reaction map. The state-of-the-art of known methodologies is narrow and strictly limited to the self-condensation of pyruvate donors with pyruvate-type acceptors (Scheme 1, path a) or the cross aldol reaction of active and non-enolizable aldehydes (Scheme 1, path b).



Scheme 1. Homo (a) and cross (b) aldol reactions of pyruvate esters.

Trying to solve the problem, Jørgensen developed a chiral copper-based catalyst for asymmetric homoaldol reaction of ethyl pyruvate leading to diethyl 2-hydroxy-2-methyl-4-oxoglutarate (**2**). This, in turn, was isolated as the more stable isotetronic acid (**3**).[4] A direct catalytic homoaldol reaction of ethyl pyruvate leading to **3** was also performed by Dondoni under pyrrolidine-based organocatalytic control.[5] On the other hand, an organocatalytic cross aldol reaction of pyruvate ester was demonstrated only for highly active chloral hydrate.[6] In spite of many trials, a direct activation of pyruvate donors towards reaction with aliphatic aldehydes was long thought to be confined to the realm of enzymes.[7] Solving this problem is not only important from the conceptual point of view, but also because pyruvate- and phosphoenol pyruvate-dependent aldol reactions are vital in the formation of 3-deoxy-2-ulosonic acids and sialic acids, which are essential sugar units for many biological processes and transformations.[8] As a C_3 building block phosphoenol pyruvate participates also in the biosynthesis of the aromatic core of aryl amino acids in the shikimate pathway.

Now, we postulate that the stability of simple aliphatic pyruvate ester is sufficient for the reaction with fast-reactive electrophiles, while addition to other aldehydes needs the more stable enol form and a disciplined reaction course. In this article we show that the better stability of the pyruvate ester enol



Scheme 2. Direct aldol reaction of the pyruvic ester **6** with glyceraldehyde.

form may result from the bulky ester group attached to the keto ester which allows one to perform the elusive reaction with aliphatic aldehydes eventually following the biomimetic synthesis of ulosonic acids.

Previously Enders[9] and our group[10] had shown that pyruvic derivatives such as those with dimethyl acetal or thiazole ring moieties can be used as chemical equivalents of pyruvic esters in the catalytic reaction with chiral glyceraldehyde. Unfortunately, despite the enormous effort which we put in the activation of pyruvate methyl and ethyl esters by using a broad range of metal catalysts and organic molecules, we could not observe their reactions with aliphatic aldehydes.

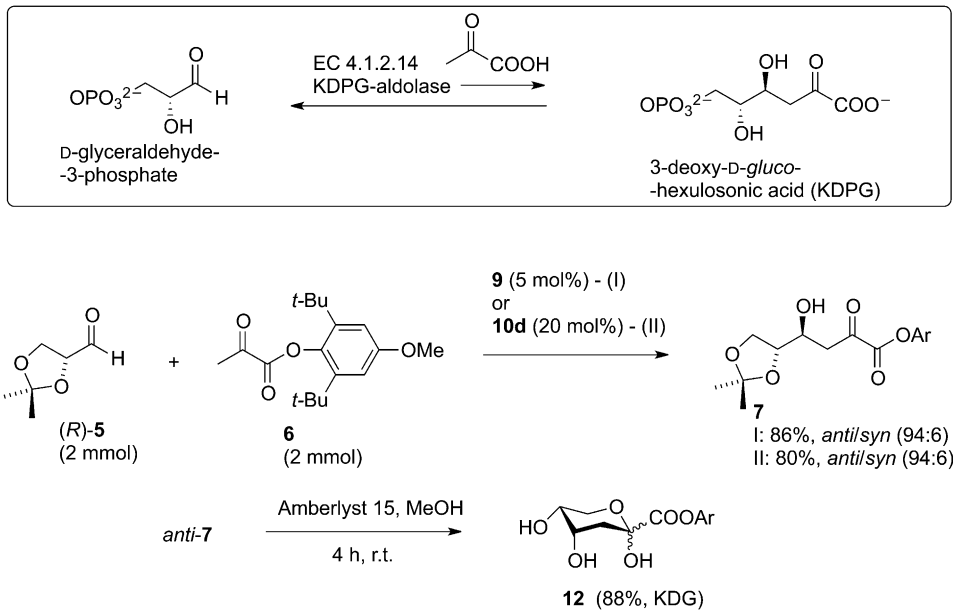
Now, we began our thorough study by considering the catalytic aldol reaction of various pyruvate esters with (*R*)-glyceraldehyde (**5**) promoted by the asymmetric dinuclear zinc catalyst with the ProPh ligand (**8**)[11] and the lanthanium-lithium-BINOL complex (**9**)[12] (Scheme 2). To test our presumption that sterically hindered esters might support enol formation, we tested *tert*-butyl, phenyl, and 4-methoxyphenyl esters. Our initial attempts were, however, unsuccessful and did not result in the formation of desired aldols.

Therefore, we investigated enolization of the more bulky 2,6-di-*tert*-butyl-4-methoxyphenyl ester (**6**) by using (*S*)- and (*R*)-ProPh catalysts (Table 1).[13] To our delight the reaction of ester **6** with (*R*)-glyceraldehyde acetonide promoted by (*R*)-ProPh catalysts resulted in the clean and efficient formation of desired cross aldol product **7** with a very good level of *syn*/*anti* diastereoselectivity favouring *anti* isomer (Table 1, entry 2). The stereoselectivity of the reaction was further improved by using the La-Li-(*S*)-BINOL catalyst and performing the reaction at −20 °C (Table 1, entry 4). The *anti*-configured aldol ester was formed predominantly with high yield (81%) and an excellent *anti/syn* ratio of 16:1. The here elaborated efficient reaction conditions need only a (1:1) ratio of the two substrates. Application of either (*R*)-configured catalyst (entry 3) and (*S*)-glyceraldehyde with (*S*)-config-

Table 1. Direct aldol reaction of the pyruvic ester **6** with glyceraldehyde.[a]

Entry	Catalyst	Solvent	Yield[c] [%]	*anti/syn*[d]
1	(*S*)-**8** (5 mol%)	THF	62	3/1
2	(*R*)-**8** (5 mol%)	THF	62	8/1
3	(*R*)-**9** (5 mol%)	THF	81[b]	4/1
4	**(*S*)-9 (5 mol%)**	**THF**	**81[b]**	**16/1**
5	(*S*)-**9** (5 mol%)	THF	81[b]	2/1[e]
6	**10a** (20 mol%)	$CHCl_3$	31	5/1
7	**11a** (20 mol%)	$CHCl_3$	31	2/1
8	**10b** (20 mol%)	$CHCl_3$	75	7/1
9	**11b** (20 mol%)	$CHCl_3$	61	1/1
10	**10c** (20 mol%)	$CHCl_3$	51	1.5/1
11	**11c** (20 mol%)	$CHCl_3$	62	6/1
12	**10d (20 mol%)**	**$CHCl_3$**	**80**	**16/1**
13	**11d** (20 mol%)	$CHCl_3$	59	1/1.5

[a] Reactions were performed with **5** (0.1 mmol), **6** (0.1 mmol), catalyst (see Table) in THF (12 h) or $CHCl_3$ (48 h) at room temperature.
[b] Reaction was performed at −20 °C.
[c] Yield of isolated product.
[d] Determined by ^{1}H NMR analysis.
[e] The (*S*)-aldehyde was used.



Scheme 3. Efficient diastereoselective synthesis of KDG ester.

ured catalyst (entry 5) resulted in the loss of stereoselectivity as a consequence of the formation of mismatched substrate-catalyst pairs.

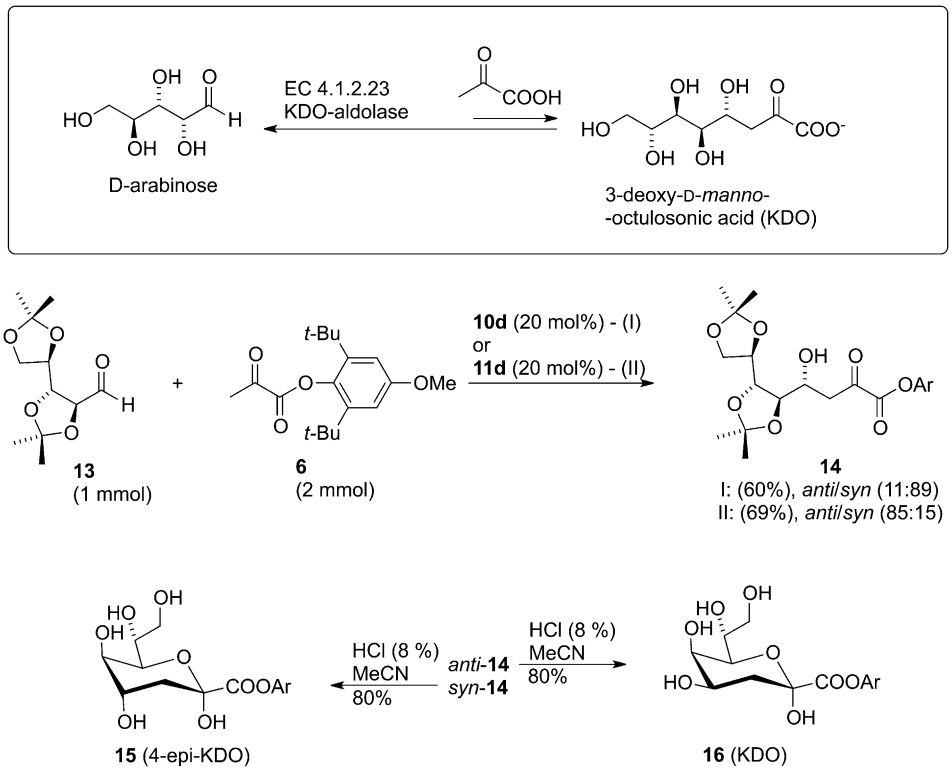
Our results suggest that the remarkable stability of the pyruvate enol esters was attributed to the steric hindrance present in the aryl moiety. This particular feature of the 2,6-di-*tert*-butyl-4-methoxyphenyl derivative was previously observed during the Grignard addition to 1,2-esters.[14]

To explore further this concept of stable hindered enol formation, we tested also the possibility of a parallel organocatalytic protocol for pyruvate ester deprotonation. This was an exciting challenge in the light of unknown protocol for such a substrate activation. After many trials including various organocatalyst structures and modes of activation, we selected tertiary amines of *Cinchona* alkaloids as the most promising candidates for further research.[15] The tertiary amine-based catalysts could act through formation of a tight ion pair followed by aldehyde addition giving an additional evidence for the easy deprotonation and stable enol formation from **6**.

The results collected in Table 1, entries 6–13 highly support our concept. Initial application of cinchonidine (**10a**, **CD**) and cinchonine (**11a**, **CN**) to the elaborated reaction showed promising results while yield and stereoselectivity remained poor (Table 1, entries 6 and 7). The most efficient means turned out to be variation of the *Cinchona* alkaloid scaffold at the C-6′ position of the quinoline core of quinine (**10b**, **QN**) and quinidine (**11b**, **QD**). Further alkylation of the quinine by the bulky isopropyl group delivered an efficient and selective catalyst. To our delight the aldol reaction from Scheme 2 promoted by 20 mol% of **10d** afforded high *anti*-diastereoselectivity (16:1) and high yield (80%) of aldol **7**. It is interesting to mention that application of a quinidine-based catalyst favoured formation of the oposite *syn*-configured aldol albeit with lower diastereoselectivity (entry 13).

This newly elaborated methodology could easily be applied for the synthesis of sugar 3-deoxy-2-keto acids (ulosonic acids), and to prove this concept we scaled up the synthesis and compared results obtained by using both enolization ways (Scheme 3). In recent years, several chemical and enzymatic methodologies have been reported for the synthesis of sialic and ulosonic acids[16] but our attempt seems to be the simplest and more closely related to enzymatic pathway. The *anti*-configured aldol product **7** possesses the configuration of natural 3-deoxy-D-*gluco*-hexulosonic acid (KDG, Scheme 3) and can be easily transformed into this biomolecule. By using the biomimetic concept and following the KDPG-aldolase function the synthesis of **7** can be performed by using metal catalyst (**9**) or organocatalyst (**10d**) in high yield and high stereoselectivity. Thus, the obtained *anti*-aldol **7** was easily deprotected with an acidic ion-exchange resin (Amberlyst 15) in methanol to give the cyclic forms of the desired KDG ester **12** (Scheme 3).[17]

Next, we tested the flexibility of our methodology for the synthesis of a higher, eight-carbon ulosonic acid – KDO ester, starting from arabinose diacetonide **13** and the same pyruvate ester **6** (Scheme 4). Because of the different structure of the chiral aldehyde, application of the metal-based catalyst resulted in a less selective formation of the desired aldol **14**. The most promising catalyst was (*R*)-ProPh yet the unexpected formation of *syn*-configured aldol (*anti/syn*, 1:6, 70%



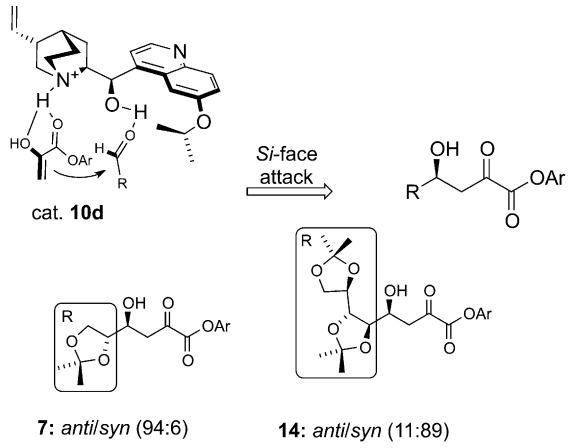
Scheme 4. Synthesis of KDO and 4-epi-KDO esters.

yield) closed this entry to natural 3-deoxy-D-*manno*-octulosonic acid (KDO).

However, the biomimetic synthesis of the desired *anti*-configured aldol **14** was successfully performed by using organocatalyst **11d** (*anti/syn*, 85:15, 69% yield). Interestingly, a parallel synthesis of the *syn*-configured aldol by using organocatalyst **10d** proved to have additional practical advantages of the newly described methodology (*anti/syn*, 11:89, 60% yield). It is also a highly important observation as previously published methodologies based on addition of lithium enolates to chiral aldehydes led to *anti*-configured products only.[18] Now, from both *syn*- and *anti*-configured key intermediates, the syntheses of KDO ester **16** and pharmaceutically important 4-epi-KDO ester **15** were flexibly accomplished by simple deprotection of isopropylidene residues (Scheme 4).

The diastereomeric excesses of the aldols **7** and **14** were determined by high resolution NMR of the reaction mixtures. For both aldol products separation of the diastereomers was easily possible by simple flash chromatography making the elaborated methodology useful for a practical synthesis of natural keto acids and their isomers.

Although the number of possible conformations of *Cinchona* alkaloids in the solution makes it difficult to analyse,[19] the transition state structure of the substrate-catalyst complex can be rationalised by using the model depicted at Scheme 5. While the reaction



Scheme 5. Proposed approximate structure of the substrate-catalyst **10d** complex for the *S*-selective formation of aldols.

of pyruvate ester involves initial deprotonation by the *Cinchona* catalyst **10d** (**CD**, **QN** native configuration) and subsequent attack to the aldehyde, the role of catalyst is also to provide an asymmetric environment to the reaction center through a network of hydrogen bonds. The large substituent in the aldehyde molecule is placed away from the bulky catalyst substituent. The *Re* face of the aldehyde is covered so effectively by the quinolone ring that the pyruvate enol approaches the *Si* face to produce the *S*-configured alcohol **7** or **14**. By using catalyst **11d** (**CN**, **QD** native

configuration) the diastereoisomeric (*R*)-alcohols are formed predominantly.

In conclusion, we showed that both metal-based complexes and chiral tertiary amines can initiate stable enol formation from hindered pyruvate esters which can be further trapped by electrophilic aldehydes. This is the first example of an efficient *catalytic stereoselective* aldol reaction of pyruvate esters with aliphatic aldehydes closely resembling the biomimetic synthesis of ulosonic acids. The elaborated methodology allowed the first catalytic synthesis of 3-deoxy-2-keto esters through a direct aldol reaction of sugar aldehydes with pyruvate esters. The presented protocol provides an attractive and biomimetic approach to ulosonic acids and constitutes another interesting field of application for the powerful Trost and Shibasaki catalysts.

Moreover, we have presented new concept of direct aldol reaction of keto esters promoted by chiral tertiary amines. The described methodology delivers a flexible entry to both *syn*- and *anti*-configured aldols while *syn*-selectivity was not achievable previously by using stoichiometrically generated lithium enolates. Although obtaining better diastereoselectivity in the aldol reaction of hindered keto esters is troublesome and constitutes a general problem,[20] our further efforts will be direct to designing even more efficient and stereoselective catalysts for the elaborated direct aldol reaction of pyruvate esters.

Experimental Section

Direct Aldol Reaction of Aryl Pyruvate with Glyceraldehyde

(1) Using catalyst 9: A solution of water in THF (0.01 mmol, 10 μL, 1 M) was added to a solution of potassium bis(trimethylsilyl)amide (KHMDS) in toluene (0.0045 mmol, 9 μL, 0.5 M) at 0 °C. After stirring for 15 min a solution of LLB in THF (0.005 mmol, 0.1 mL, 0.05 M) was added and the stirring was continued at 0 °C for 30 min. The catalyst solution was cooled to −20 °C and a mixture of aldehyde **5** (13 mg, 0.1 mmol) and aryl pyruvate **6** (31 mg, 0.1 mmol) in 0.5 mL THF was added to the solution. The reaction mixture was stirred for 12 h at −20 °C, then quenched with ammonium chloride, extracted with ethyl acetate, dried with magnesium sulfate and purified on silica gel using 0–2% methanolic dichloromethane as eluent to give aldol adduct **7**; yield: 35.5 mg (81%).

(2) Using Cinchona catalyst 10d: A mixture of aldehyde **5** (260 mg, 2 mmole), aryl pyruvate **6** (613 mg, 2 mmol) and catalyst **10d**[21] (141 mg, 0.4 mmol) in 10 mL of chloroform was stirred for 48 h at room temperature. The reaction mixture was purified on silica gel using 0–2% methanolic dichloromethane as eluent to give aldol adduct **7**; yield: 698 mg (80%).

Acknowledgements

This project was operated within the Foundation for Polish Science TEAM and MPD Programmes co-financed by the EU European Regional Development Fund. The research was carried out with the equipment purchased thanks to the financial support of the European Regional Development Fund in the framework of the Polish Innovation Economy Operational Program (contract no. POIG.02.01.00-12-023/08).

References

[1] R. Mahrwald, (Ed.), *Modern Aldol Reactions*, Wiley-VCH, Weinheim, **2004**.
[2] a) D. Enders, A. A. Narine, *J. Org. Chem.* **2008**, *73*, 7858; b) M. Markert, R. Mahrwald, *Chem. Eur. J.* **2008**, *14*, 48; c) N. Mase, C. F. Barbas III, *Org. Biomol. Chem.* **2010**, *8*, 4043; d) J. Mlynarski, B. Gut, *Chem. Soc. Rev.* **2012**, 41, 587.
[3] B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, *39*, 1600.
[4] N. Gathergood, K. Juhl, T. B. Poulsen, K. Thordrup, K. A. Jørgensen, *Org. Biomol. Chem.* **2004**, *2*, 1077.
[5] a) P. Dambruoso, A. Massi, A. Dondoni, *Org. Lett.* **2005**, *7*, 4657; for synthesis of isotetronic acid derivatives, see b) D. Lee, S. G. Newman, M. S. Taylor, *Org. Lett.* **2009**, *11*, 5486; c) Y. Sun, H. Chen, Z. Li, Q. Wang, F. Tao, *Synthesis* **2008**, 589; d) J.-M. Vincent, C. Margottin, M. Berlande, D. Cavagnat, T. Buffeteau, Y. Landais, *Chem. Commun.* **2007**, 4782.
[6] H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983.
[7] S. M. Dean, W. A. Greenberg, C.-H. Wong, *Adv. Synth. Catal.* **2007**, *349*, 1308.
[8] B. Lindberg, *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 279.
[9] a) D. Enders, T. Gasperi, *Chem. Commun.* **2007**, 88; see also: b) S. Luo, H. Xu, L. Chen, J.-P. Cheng, *Org. Lett.* **2008**, *10*, 1775.
[10] O. El-Sepelgy, D. Schwarzer, P. Oskwarek, J. Mlynarski, *Eur. J. Org. Chem.* **2012**, 2724.
[11] B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003.
[12] N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168.
[13] 2,6-Di-*tert*-butyl-4-methoxyphenyl ester was used by Enders for the synthesis of hindered SAMP-hydrazone: a) D. Enders, H. Dyker, G. Raabe, *Angew. Chem.* **1992**, *104*, 649; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 618; b) D. Enders, H. Dyker, G. Raabe, *Angew. Chem.* **1993**, *105*, 420; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 421.
[14] O. J.-C. Nicaise, D. M. Mans, A. D. Morrow, E. Villa Hefti, E. M. Palkovacs, R. K. Singh, M. A. Zukowska, M. D. Morin, *Tetrahedron* **2003**, *59*, 6433.
[15] For non-asymmetric examples of *syn*-selective reactions of keto esters with cyclopent-2-enone catalyzed by the tertiary amine of DBU, see: a) M. Shi, W. Zhang, *Tetrahedron* **2005**, *61*, 11887. For *syn*-selective reactions of hydroxy- and dihydroxyacetone see: b) M. Market, M. Mulzer, B. Schetter, R. Mahrwald, *J. Am. Chem. Soc.*

2007, *129*, 7258; c) J. Paradowska, M. Rogozińska, J. Mlynarski, *Tetrahedron Lett.* **2009**, *50*, 1639.
[16] a) A. Banaszek, J. Mlynarski, *Stud. Nat. Prod. Chem.* **2005**, *30*, 419; b) I. Hemeon, A. J. Benet, *Synthesis* **2007**, 1899.
[17] For the detailed experimental procedure see the Supporting Information.
[18] A. Dondoni, P. Merino, *J. Org. Chem.* **1991**, *56*, 5294.
[19] T. Marcelli, H. Hiemstra, *Adv. Synth. Catal.* **2010**, *352*, 1229.
[20] C. H. Heathcoock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, D. VanDerveer, *J. Org. Chem.* **1980**, *45*, 3846.
[21] A. Berkessel, M. Guixà, F. Schmidt, J. M. Neudőrfl, J. Lex, *Chem. Eur. J.* **2007**, *13*, 4483.

