

# Strain-Driven Direct Cross-Aldol and -Ketol Reactions of Four-Membered Heterocyclic Ketones

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**(5)** Supporting Information

**ABSTRACT:** Owing to the ring strain and  $\alpha$ -heteroatom effect, the four-membered heterocyclic ketones can undergo direct cross-aldol and -ketol reactions without the need for preformed enol or "enolate-like" intermediates. Besides the organocatalyzed cross-ketol addition onto their highly active carbonyl group, their ability to act as a nucleophilic donor has also been explored. As a result, a number of discrete aldol



adducts were synthesized and the distinct reactivities were successfully combined into a double-aldol one-pot reaction.

In recent years, four-membered heterocycles have emerged as prominent building blocks in drug discovery and development.<sup>1</sup> By including these structural motifs in drug candidates, several pharmacological properties could be significantly altered, among the most important of these was the capacity to improve physicochemical and pharmacokinetic parameters.<sup>2</sup> As a result, there is a current drive to explore and broaden the synthetic accessibility to this important class of molecules.<sup>3</sup>

While several strategies have been developed for the synthesis of four-membered heterocycles, their construction remains far from straightforward and facile, especially for medicinal chemistry development. To circumvent this barrier, Carreira, Rogers-Evans, Müller and co-workers have recently introduced **1a,b** azetidin-3-ones and oxetan-3-one (**1c**) into the synthetic practice of medicinal chemistry as versatile synthetic modules that can be easily attached onto molecular scaffolds or transformed into new classes of spirocyclic ring systems.<sup>1a,d,4</sup>

Intrigued by the potential of four-membered heterocyclic ketones 1a-d as practical synthetic modules in medicinal chemistry, a study was initiated to investigate their organocatalytic aldol reactivity with a parallel purpose of generating discrete building blocks. These inherently bifunctional molecules 1a-d were also envisaged as a linchpin element that can be grown by aldol chemistry in two directions to form rigid "polyketide-like" or "sugar-analog" fragments.<sup>5</sup> The results of these efforts are presented in this communication.

In most cases, the aldol reaction<sup>6</sup> of nonequivalent aldehydes and/or ketones is a formidable synthetic challenge on account of (a) the need for preformed enolate or enolate-like species to achieve selectivity, (b) undesired reactivity of aldehydes to polymerize under basic conditions, (c) dehydration of the aldol products, and (d) the equilibriums of ketol formation being generally shifted toward the starting materials. Nevertheless, the angle strain in 1a-d (Figure 1) was conceived to serve as a handle to attain organocatalytic direct cross-aldol and -ketol reactions. Prior studies on the carbocyclic analog have established the enhanced reactivity of cyclobutanone in carbonyl additions owing to the relief of strain during conversion of an sp<sup>2</sup>hybridized carbonyl carbon to an sp<sup>3</sup>-hybridized carbon.<sup>7</sup>





However, the effect of the ring strain on the chemical reactivity is not versal as illustrated by the general base-catalyzed enolization of cyclobutanone.<sup>8</sup> The ring strain had only a negligible effect on the rate constant of the enolization, as it was similar to the value determined for acetone. Finally, the aldol donor reactivity of 1a-d was expected to be further complicated by the known effect of the  $\alpha$ -heteroatom on carbonyl enolization.<sup>9</sup>

First, experiments were performed to ascertain if these strained ketones are suitable electrophilic partners in selective cross-ketol reactions. As an initial trial, the reaction of the 1-diphenylmethylazetidin-3-one (1a) with acetone was probed in the presence of secondary amine catalysts (Table 1). Gratifyingly, the desired cross-ketol product was observed as a sole product in the presence of L-proline at rt, although with low conversion (Table 1, entry 1). To our delight, the employment of higher reaction temperatures (70–110 °C) allowed a significant increase in yield in neat acetone (Table 1, entries 2-4) without the formation of either self-aldol products. Curiously, no aldol-condensation product 3 was detected despite the harsh conditions. Above 110 °C, the conversion started to decrease due to the decomposition of the catalyst (Table 1, entries 5-6). Although the L-proline proved to be an efficient catalyst, the applied high temperature would limit the general applicability of this reaction. Thus, further screens for an improved catalyst were pursued.<sup>10</sup> Finally, we found that 20 mol % of pyrrolidine was an efficient promoter of the cross-ketol formation at rt (Table 1, entry 7) while it maintained the previously found exclusive selectivity in the crossketol reaction. Lowering the catalyst load to 10 mol % resulted in



 Table 1. Catalyst Screening for Cross-Ketol Reaction of

 Azetidinone 1a with Acetone

	Ph Ph 1a	Ph 2	<b>X→</b> PI		<sup>₽</sup> °
entry	catalyst	cat. load (mol %)	temp (°C)	time	$_{(\%)^a}^{\operatorname{conv}}$
1	L-proline	20	25	10 d	30
2	L-proline	20	$70^{b}$	16 h	>99
3	L-proline	20	100 <sup>c</sup>	1 h	66
4	L-proline	20	110 <sup>c</sup>	1 h	>99
5	L-proline	20	120 <sup>c</sup>	1 h	85
6	4-OH-L-proline	20	$120^{b}$	1 h	27
7	pyrrolidine	20	25	16 h	85
8	pyrrolidine	10	25	16 h	29
9	pyrrolidine	10	40	16 h	30
10	pyrrolidine	40	25	16 h	90
11	pyrrolidine	20	25	2 d	>99
12	pyrrolidine	20	25	16 h	$78^d$

<sup>*a*</sup>Conversion was determined by <sup>1</sup>H NMR. <sup>*b*</sup>The reaction was carried out in a sealed tube. <sup>*c*</sup>The reaction was carried out in a microwave reactor. <sup>*d*</sup>Reaction conditions: **1a** (0.5 mmol), acetone (1.0 mmol), and pyrrolidine (0.1 mmol) in 0.5 mL of isopropanol.

a significant decrease of the conversion (Table 1, entry 8), which could not be restored by applying a higher reaction temperature (Table 1, entry 9). On the other hand, only a slight increase of conversion was obtained when a 40 mol % catalyst load was employed (Table 1, entry 10). Nevertheless, the reaction proceeded to near full conversion after 2 days without the formation of dehydration product 3 (Table 1, entry 11). A subsequent brief survey of solvents identified isopropanol as a viable alternative of acetone. This modification also allowed reduction of excess acetone (1:20 vs 1:2).<sup>10</sup>

Having identified optimal reaction conditions for a cross-ketol reaction, we next examined the scope of the electro- and nucleophilic components (Scheme 1). Thus, the commercially available four-membered heterocyclic ketones 1a-d were reacted with cyclic and acyclic ketones. The acetone, cyclohexanone and cyclopentanone generally reacted well and in the catalytic cross-ketol protocol affording selectively the desired products 2-13 in moderate to excellent yields. Notably, there was a remarkable difference in the reactivity between the two azetidinone substrates 1a,b; the Boc protected derivative 1b has an augmented efficiency in the ketol formation. Using chiral amines, no asymmetric induction was realized in the case of 7-9.10 Moreover, thiethan-3-one (1d) proved to be the least reactive electrophile in this series; only a moderate yield was achieved with acetone (Scheme 1, 6) whereas no product (Scheme 1, 10) was observed with cyclohexanone. The reactions of acetone with 1a-d have been carried out also in isopropanol using only a 2 molar excess of the nucleophilic component (Scheme 1). The isolated yields generally proved to be lower, and no product formation was observed in the reaction with 1d. Next, acyclic ketones were explored to gauge the generality of crossketol reactions. The butan-2-one showed lower catalytic capacity, because pyrrolidine formed a stable enamine adduct with the products. To overcome this limitation, L-proline was employed at 80 °C. As a result, the reactions furnished the inseparable mixture of regioisomers that arose from two possible nucleophilic sites of methyl-ethyl-ketone. The evaluation of the diethyl ketone and an acetophenone derivative, however, afforded no reaction (14 and

Scheme 1. Scope of Cross-Ketol Formation<sup>a</sup>



<sup>*a*</sup>Isolated yields are shown. <sup>*b*</sup>Reaction conditions: **1a**–**d** (2.0 mmol), nucleophile (15 equiv), pyrrolidine (20 mol %), 25 °C, 2 days. <sup>*c*</sup>Reaction conditions: **1a**–**d** (2.0 mmol), nucleophile (2 equiv), pyrrolidine (20 mol %), 25 °C, isopropanol (20 equiv), 2 days. <sup>*d*</sup>Reaction conditions: **1a**–**d** (2.0 mmol), nucleophile (15 equiv), L-proline (20 mol %), 80 °C, 24 h. <sup>*e*</sup>Mixture of the 2 regioisomers; only one of isomers was highlighted.

**18**). These experiments revealed that this cross-ketol reaction works with cyclic or aliphatic methyl-ketones as nucleophiles and even a slight structural modification or an increase of steric demand of the nucleophile could result in a notable change in the outcome. Nevertheless, it is worth mentioning the practical utility of this organocatalytic approach; a previous attempt to construct a *N*-benzyloxy analog of **8** opted for the Mukaiyama aldol reaction with a markedly lower yield.<sup>11</sup>

These results indicate that the strain relief during ketol formation drives not only the thermodynamics but also the selectivity of the reaction. Thus, the strained 1a-d ketones invariably act as an electrophile in these reactions of non-equivalent enolizable ketones. As a second issue, these ketones 1a-d seem to have diminished reactivity as a nucleophile in the aldol reaction compared to acetone, as the self-dimerization ketol-product<sup>12</sup> of 1a-d was not observed.

Intrigued by the tempered reactivity of 1a-d ketones via the enol or enamine mechanism, we sought to explore their capacity to act as a nucleophilic donor in aldol reactions. Of particular relevance to our study were the recent organocatalytic applications of cyclobutanone that suggested that this strained ketone could be converted to a putative enamine species.<sup>13</sup> With this in mind, we embarked on studying the reaction of 1a-c with a nonenolizable aldehyde, benzaldehyde, utilizing different tertiary (DBU) and chiral primary and secondary amines as an organocatalyst.<sup>10</sup> Surprisingly, neither the oxetane-3-one (1c) nor the *N*-Boc-azetidin-3-one (1b) showed any reactivity; only the starting materials could be recovered (Scheme 2). Nonetheless, further test reactions disclosed that the desired aldol union is indeed possible; however, the reaction of ketone 1a with Scheme 2. Investigation of Cross-Aldol Reaction of 1a-e and H-D Exchange



benzaldehyde proceeded without added amines, reinforcing the previous finding of Masuda.<sup>12</sup> Interestingly, no rate acceleration was observed in the presence of more basic amines. We could only isolate the anti aldol adduct 20a because the isolation of the syn product was hampered by its tendency to undergo syn-anti isomerization. Additionally, no aldol condensation product 19 was observed in the reaction suggesting the relative stability of the aldol adduct owing to the ring strain. The observed aldol reactivity could be rationalized by a self-activation mechanism by the tertiary amine of 1a; therefore, hydrogen-deuterium exchange studies (Scheme 2) and preliminary kinetic investigations<sup>10</sup> have been performed. Somewhat astoundingly, there was no detectable hydrogen-deuterium exchange in 1a when CD<sub>3</sub>OD was applied; only the rapid formation of hemiacetal occurred. The unexpected lack of H-D exchange suggested if the H-D exchange via enol intermediate is operating at all that process should be rather slow (compared to the acyclic analog). To minimize the hemiacetal formation, the proton-deuterium exchange experiment was conducted in  $d_8$ -propan-2-ol (Scheme 2, IPA- $d_8$ ). After 24 h, only one out of four  $\alpha$ -hydrogens exchanged at rt and no hemiacetal formation was observed. Subsequent kinetic investigations suggested that the ratedetermining step is the formation of the zwitterionic intermediate I and not the subsequent C-C bond formation.<sup>10</sup>

As revealed in a subsequent solvent screening,<sup>10</sup> this unique aldol coupling can be easily accomplished in a wide range of solvents, among which the polar protic isopropanol proved to be the optimal one. Accordingly, the role of the solvent is to encourage the self-activation pathway14 via stabilizing the zwitterionic intermediate I. Next, the capacity of 1a to participate in cross-aldol and -ketol reactions was probed to investigate the robustness and generality of the method. As highlighted in Scheme 3, a series of aldehyde and ketone acceptors were able to suppress the homodimerization reaction (21) and afforded high yields of the desired products with low to modest diastereoselectivities. Notably, one of the diastereomers could only be isolated in pure form due to the rapid syn-anti isomerization process. It is also important to note that byproducts deriving from the dehydration of the aldol/ketol products were not detected.

As outlined in Scheme 3, efficiencies of the aldol reactions were dependent on the reactivity of the acceptor. More specifically, the reaction with the *p*-nitrobenzaldehyde went to near full conversion to afford **22a**,**b** after 2 days at rt, but with benzaldehyde, more than 1 week was necessary to complete the reaction, unless heated to 40 °C for 2 days. Thus, electron-poor

# Scheme 3. Reaction Scope of Cross-Aldol Reaction of 1a<sup>*a,b*</sup>



<sup>*a*</sup>Isolated yields of diastereomers. <sup>*b*</sup>The diastereomeric ratio in the crude reaction product was determined by <sup>1</sup>H NMR. <sup>*c*</sup>Reactions were run at 40 °C for 2 d. <sup>*d*</sup>Reactions were run at 25 °C for 2 d. <sup>*e*</sup>Reaction was run at 80 °C for 16 h.

pyridine-aldehydes were suitable coupling partners at rt (23a,b-24a,b). Nevertheless, the reaction afforded the desired crossaldol adducts (25a,b-27a,b) if bulky ortho-, meta-substituted or electron-rich benzaldehydes were applied. Interestingly, a selective cross-ketol reaction was realized to furnish 28a,b-30when isatin or 1b,c was employed as an electrophile. At moderately high temperature  $(80 \ ^{\circ}C)$  even double substitution was achieved with the highly reactive *p*-nitro-benzaldehyde (Scheme 3, 31). To our surprise, the highly reactive and enolizable acetaldehyde was found to be amenable for cross-aldol reaction. The formation of such a peculiar product (Scheme 3, 32a,b) was interpreted by the unique intramolecular activation mode of 1a. Finally, this method was also found to be applicable toward sterically more demanding, but still enolizable aliphatic aldehyde (33a,b).

The above results prompted us to examine whether the two reactivity profiles of strained ketone **1a** can be combined together to carry out an iterative aldol sequence (Scheme 4). Thus, upon exposure to the reaction conditions of cross-ketol formation, the isolated diastereomer of **20a** proved to be a competent acceptor, with the corresponding single diastereomer **34** isolated in a 69% yield. As the X-ray structural determination indicates, the acetone was added to the least hindered face of **20a**.<sup>10</sup> Accordingly, the

## Scheme 4. Iterative Cross-Aldol and Cross-Ketol Reactions



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pyrrolidine catalyst did not facilitate the isomerization and/or the retro-aldol reaction of **20a**.

Since isopropanol proved to be a suitable solvent for both the cross-ketol and -aldol reactions, the iterative double-aldol sequence could be further streamlined. In a simple one-pot, two-step procedure, we observed the formation of two diastereomers (Scheme 4) with a moderate isolated yield. Thus, the overall sense of diastereoselective induction was unaltered in the second step and acetone functioned as a capping agent for the first aldol step. The principal issue in this procedure, however, is that no preformed enols were required to generate a double-aldol product **35a,b**.

In summary, we have documented that ring strain combined with a unique  $\alpha$ -heteroatom effect in four-membered heterocyclic ketones can be exploited in the development of direct cross-ketol and -aldol reactions providing several discrete building blocks in an operationally simple manner. Significantly, we have also demonstrated that azetidinone **1a** can serve as a linchpin element in an iterative double aldol sequence without the need for preformed enols. We expect that the strain-directed cross-aldol and -ketol reactions will provide a convenient synthetic strategy to new classes of constrained building blocks. Further investigation of the mechanism, scope, and limitations of these reactions and the exploration of the altered reactivity of four-membered heterocycles are underway.

## ASSOCIATED CONTENT

## Supporting Information

Experimental procedure, NMR spectra, and analytical data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01002.

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## Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) (a) Carreira, E. M.; Fessard, T. C. Chem. Rev. 2014, 114, 8257. (b) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. Chem. Rev. 2014, 114, 8323. (c) Han, M.; Song, C.; Jeong, N.; Hahn, H.-G. ACS Med. Chem. Lett. 2014, 5, 999. (d) Lowe, J. T.; Lee, M. D., IV; Akella, L. B.; Davoine, E.; Donckele, E. J.; Durak, L.; Duvall, J. R.; Gerard, B.; Holson, E. B.; Joliton, A.; Kesavan, S.; Lemercier, B. C.; Liu, H.; Marié, J.-C.; Mulrooney, C. A.; Muncipinto, G.; Welzel-O'Shea, M.; Panko, L. M.; Rowley, A.; Suh, B.-C.; Thomas, M.; Wagner, F. F.; Wei, J.; Foley, M. A.; Marcaurelle, L. A. J. Org. Chem. 2012, 77, 7187. (e) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. J. Med. Chem. 2010, 53, 3227. (f) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. Angew. Chem., Int. Ed. 2010, 49, 9052. (g) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. Angew. Chem., Int. Ed. 2006, 45, 7736. (h) Dejaegher, Y.; De Kimpe, N. Chem. Rev. 2002, 102, 29.

(2) Selected examples: (a) Skoda, E. M.; Sacher, J. R.; Kazancioglu, M. Z.; Saha, J.; Wipf, P. ACS Med. Chem. Lett. **2014**, *5*, 900. (b) McLaughlin, M.; Yazaki, R.; Fessard, T. C.; Carreira, E. M. Org. Lett. **2014**, *16*, 4070.

(c) Burkhard, J. A.; Wuitschik, G.; Plancher, J.-M.; Rogers-Evans, M.; Carreira, E. M. Org. Lett. **2013**, *15*, 4312. (d) Stepan, A. F.; Karki, K.; McDonald, W. S.; Dorff, P. H.; Dutra, J. K.; DiRico, K. J.; Won, A.; Subramanyam, C.; Efremov, I. V.; O'Donnell, C. J.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Sneed, B.; Sun, H.; Lu, Y.; Robshaw, A. E.; Riddell, D.; O'Sullivan, T. J.; Sibley, E.; Capetta, S.; Atchison, K.; Hallgren, A. J.; Miller, E.; Wood, A.; Obach, R. S. J. Med. Chem. **2011**, *54*, 7772.

(3) Recent examples: (a) Hodgson, D. M.; Mortimer, C. L.; McKenna, J. M. Org. Lett. 2015, 17, 330. (b) Kern, N.; Felten, A.-S.; Weibel, J.-M.; Pale, P.; Blanc, A. Org. Lett. 2014, 16, 6104. (c) Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.; Brellier, M.; Guérinot, A.; Cossy, J. Org. Lett. 2014, 16, 6160. (d) Zhang, H.-H.; Luo, Y.-C.; Wang, H.-P.; Chen, W.; Xu, P.-F. Org. Lett. 2014, 16, 4896. (e) Hodgson, D. M.; Pearson, C. I.; Kazmi, M. Org. Lett. 2014, 16, 856. (f) Davis, O. A.; Bull, J. A. Angew. Chem., Int. Ed. 2014, 53, 14230. (g) Boyd, S.; Davies, C. D. Tetrahedron Lett. 2014, 55, 4117. (h) Morgan, K. F.; Hollingsworth, I. A.; Bull, J. A. Chem. Commun. 2014, 50, 5203. (i) Zhang, L. Acc. Chem. Res. 2014, 47, 877. (j) Ravelli, D.; Zoccolillo, M.; Mella, M.; Fagnoni, M. Adv. Synth. Catal. 2014, 356, 2781. (k) Takizawa, S.; Arteaga Arteaga, F.; Yoshida, Y.; Suzuki, M.; Sasai, H. Org. Lett. 2013, 15, 4142. (1) Selig, P.; Turočkin, A.; Raven, W. Chem. Commun. 2013, 49, 2930. (m) Maegawa, T.; Otake, K.; Hirosawa, K.; Goto, A.; Fujioka, H. Org. Lett. 2012, 14, 4798. (n) Ye, L.; He, W.; Zhang, L. Angew. Chem., Int. Ed. 2011, 50, 3236. (o) Denis, J.-B.; Masson, G.; Retailleau, P.; Zhu, J. Angew. Chem., Int. Ed. 2011, 50, 5356.

(4) (a) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. Angew. Chem., Int. Ed. 2010, 49, 3524. (b) Beasley, B. O.; Alli-Balogun, A.; Clarkson, G. J.; Shipman, M. Tetrahedron Lett. 2014, 55, 541. (c) Allwood, D. M.; Blakemore, D. C.; Brown, A. D.; Ley, S. V. J. Org. Chem. 2014, 79, 328. (d) Geden, J. V.; Beasley, B. O.; Clarkson, G. J.; Shipman, M. J. Org. Chem. 2013, 78, 12243. (e) Ruider, S. A.; Müller, S.; Carreira, E. M. Angew. Chem., Int. Ed. 2013, 52, 11908. (f) Burkhard, J. A.; Tchitchanov, B. H.; Carreira, E. M. Angew. Chem., Int. Ed. 2011, 50, 5379. (g) Meyers, M. J.; Muizebelt, I.; van Wiltenburg, J.; Brown, D. L.; Thorarensen, A. Org. Lett. 2009, 11, 3523. (h) Alcaidea, B.; Almendrosb, P.; Lunaa, A. Tetrahedron 2007, 63, 3102.

(5) Selected examples: (a) Albert, B. J.; Yamamoto, H. Angew. Chem., Int. Ed. 2010, 49, 2747. (b) Lenagh-Snow, G. M. J.; Araújo, N.; Jenkinson, S. F.; Martínez, F.; Shimada, Y.; Yu, C.-Y.; Kato, A.; Fleet, G. W. J. Org. Lett. 2012, 14, 2142.

(6) (a) Alcaide, B.; Almendros, P. Angew. Chem., Int. Ed. 2003, 42, 858.
(b) Modern Aldol Reactions; ed. Mahrwald, R., Ed.; WILEY-VCH: Weinheim, 2008.

(7) (a) Brown, H. C.; Ichikawa, K. Tetrahedron 1957, 1, 221.
(b) Modelli, A.; Martin, H.-D. J. Phys. Chem. A 2002, 106, 7271.

(8) Cope, S. M.; Tailor, D.; Nagorski, R. W. J. Org. Chem. 2011, 76, 380.

(9) In conformationally constrained,  $\alpha$ -heteroatom substituted ketones, such as 3-pyrrolidinone, the enolization of ketones prefers to be nonconjugated with the amino group. Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, J. *J. Org. Chem.* **1980**, 45, 2307.

(10) For more details see the Supporting Information.

(11) The only example of analog cross-ketol reaction based on the Mukaiyama aldol reaction Exelixis, Inc. Azetidines as MEK inhibitors for treatment of proliferative diseases. WO2007/44515 A1, 2007; p 239.

(12) Morimoto, A.; Okutani, T.; Masuda, K. *Chem. Pharm. Bull.* **1973**, 21, 228. They mentioned that ketol-dimerization to afford **12** was the major side reaction during the synthesis of **1a**. Additionally, they reported the reaction of **1a** with benzaldehyde.

(13) (a) Aitken, D. J.; Bernard, A. M.; Capitta, F.; Frongia, A.; Guillot, R.; Ollivier, J.; Pira s, P. P.; Secci, F.; Spiga, M. Org. Biomol. Chem. 2012, 10, 5045. (b) Moles, F.; Guillena, G.; Nájera, C. Tetrahedron: Asymmetry 2014, 25, 1323.

(14) Recent examples for spontaneous aldol reaction of tropinone: Lazny, R.; Nodzewska, A.; Tomczuk, I. *Tetrahedron Lett.* **2011**, *52*, 5680. Interestingly, in these reactions, the *syn*-diastereomers were thermodynamically favored.