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TBD-Catalyzed Direct 5- and 6-*enolexo* Aldolization of Ketoaldehydes

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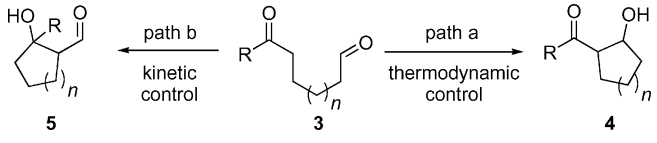
Treatment of unfunctionalized acyclic ketoaldehydes with a catalytic amount of 1,5,7-triazabicyclo[4.4.0]dec-5-ene induces a direct intramolecular 5- and 6-*enolexo* aldolization, furnishing 2-ketocyclopentanols and 2-ketocyclohexanols in good-to-excellent yields.

Introduction

The aldol reaction is one of the most powerful carbon–carbon bond-forming reactions. The versatility as well as the synthetic significance of this transformation has been extensively studied, and many good books and reviews can be found in the literature.[1,2] The direct intramolecular aldol reaction of unmodified dialdehydes, ketoaldehydes and diketones is one of the most efficient means of synthesizing five-, six- and seven-membered rings.[1a] Moreover, for practical reasons, this transformation avoids the formation and/or the isolation of an enolate equivalent.[2a] When unsymmetrical ketoaldehydes such as **3** are submitted to intramolecular aldol reactions, the ketone usually acts as the CH-acidic component, whereas the aldehyde plays the role of the carbonyl-active counterpart to afford regioisomer **4** (Scheme 1, path a). This regiochemical outcome is also favoured when thermodynamic conditions are used.



Scheme 1. Possible regioisomers **4** and **5** from **3**.

The direct 6-*enolexo* aldolization of dialdehydes and ketoaldehydes, allowing the formation of regioisomer **5** (Scheme 1, path b, $n = 2$), has only been reported recently by List et al.[3] The use of enamine catalysis, under kinetic control, allows the more electrophilic aldehyde to react with the (*S*)-proline catalyst, furnishing tertiary alcohol **5** in high enantiomeric purity and yield. Few examples of direct intramolecular aldolization of acyclic unmodified ketoaldehyde compounds leading to ketol **4** (Scheme 1, path a) have been reported.[4,5]

It is well known that nonasymmetric amine-catalyzed aldolizations of such substrates often give aldol condensation byproducts.[2a] This condensation reaction has been widely used for the construction of the D ring in steroids and natural products synthesis.[5] For the selective preparation of ketol **4**, many groups attempted to promote the aldol reaction in an indirect manner by using modified ketoaldehydes.[6] As an example, Krische developed a tandem reduction–aldolization transformation of α,β-unsaturated ketoaldehydes, which gives ketol **4** as the formal addition product of a nucleophilic ketone on an electrophilic aldehyde.[6a,6b] Similarly, Tsuji reported an elegant indirect intramolecular aldolization of palladium enolates generated by the palladium catalyzed decarboxylation of allyl β-keto carboxylates bearing an aldehyde side chain to give cyclic *β-ketols* such as **4**.[6c] It is worthwhile mentioning that these indirect methods leading to product **4** need the multistep synthesis of elaborate functionalized substrates. Interestingly, quite recently, Iwabuchi et al. reported a direct *enolexo* aldolization starting from σ-symmetric ketoaldehydes as an entry to *endo*-8-hydroxybicyclo[3.*n*.1]nonan-2-one.[7] Unfortunately, this direct intramolecular aldolization, using a chiral prolinate, has been found to be substrate dependent and inapplicable to simple ketoaldehydes like **3**.[8] Despite the tremendous and extensive studies devoted to aldol reactions, a general direct intramolecular aldolization method that leads to aldol product **4**, without dehydration (Scheme 1, path a) and starting from unfunctionalized acyclic ketoaldehydes is still lacking.[9] The development of such useful methodology would allow the straightforward construction of 2-ketocyclopentanols and 2-ketocyclohexanols from **3** ($n = 1$ and 2, respectively), avoiding multistep

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Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

sequences and the use of highly reactive reagents for the preparation of these important building blocks.[10]

In this study, we report that triazabicyclo[4.4.0]dec-5-ene (TBD), a cheap and commercially available guanidine reagent, is an efficient organocatalyst for direct intramolecular aldol reactions leading to 2-ketocyclopentanols and 2-ketocyclohexanols in good-to-excellent yields. To the best of our knowledge, this is the first guanidine-catalyzed 5- and 6-*enolexo* aldolizations of ketoaldehydes.

Results and Discussion

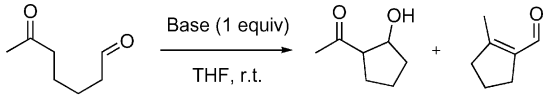
Ketoaldehyde substrates **3** needed for this study were synthesized by initial reduction of oxocarboxylic acid derivatives **1** to their corresponding diols **2**, followed by PCC oxidation with a good overall yield[11] (see Supporting Information).

To investigate the inherent reactivity towards aldolization, 6-oxoheptanal (n = 1, R = Me; **3a**) was first subjected to typical amine bases with low nucleophilicity. We considered the use of dimethylaminopyridine (DMAP), imidazole, triethylamine (TEA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for the intramolecular aldol reaction in THF (0.05 M) at room temperature. DMAP, imidazole and TEA were totally ineffective, and the starting material was recovered unchanged (Table 1, Entries 1–3). The use of a stronger base such as DBU under the same conditions was also unsatisfactory, although **4a** was formed in 11% yield (Table 1, Entry 4). Similarly, the use of an inorganic base such as K_2CO_3 was inefficient in promoting the aldol reaction (Table 1, Entry 5), even in more polar solvents, such as CH_3CN and DMF.

We then considered the use of more nucleophilic bases such as (*S*)-proline and Iwabuchi's catalyst (Figure 1).[8] The use of 30 mol-% of (*S*)-proline in DMSO for 3 h at room temperature led directly to aldol condensation product **6a** as the major compound via tertiary alcohol **5a** (n = 1). The formation of ketol **4a** was not observed, similarly to 6-*enolexo* cyclization of ketoaldehydes (n = 2) promoted by (*S*)-proline under kinetic control, which gave tertiary alcohol **5**.[3] Interestingly, the same reaction performed in CH_2Cl_2, with the same loading of (*S*)-proline, led to the formation of a 1:1 mixture of ketol **4a** (33%) and enal **6a** (38%), along with recovered starting material **3a** (29%; Table 1, Entry 6). This interesting solvent effect showed that in the case of 5-*enolexo* aldolization, performed in CH_2Cl_2, the reaction is not completely regioselective and under kinetic control.

We next tried Iwabuchi's catalyst for the direct intramolecular aldolization of σ-symmetric ketoaldehyde (Figure 1).[8] An extension to acyclic simple ketoaldehydes appeared attractive to us. Unfortunately, the reaction performed under the reported conditions by using **3a** as a substrate did not afford **4a** (Table 1, Entry 7). However, a mixture of dehydrated compound **6a** (14% yield) and an unidentified byproduct (40% yield) were obtained. The starting material was recovered as the major compound (45% yield), even after prolonged reaction (15 h) and an increase in the catalyst loading up to 25 mol-%. This lack of reactivity with Iwabuchi's catalyst might be due to the steric hindrance of the catalyst and/or to the absence of its acidic functionality.

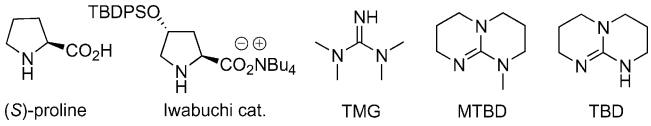
Table 1. Base screening for the formation of **4a**.[a]



3a **4a** **6a**

Entry	Base	Time [h]	*anti*/*syn*	Yield [%][b] **4a**/**6a**
1	DMAP	18	–	0
2	Imidazole	18	–	0
3	TEA	18	–	0
4	DBU	18	52:48	11:0
5	K_2CO_3	18	–	0
6	(*S*)-Proline[c]	140	71:29	33:38[d]
7	Iwabuchi cat.[e]	15	–	0:14
8	TMG	72	55:45	17:0
9	MTBD	72	44:56	39:0
10	TBD	0.5	71:29	94:0
11	TBD[f]	3	71:29	92:0

[a] Conditions: **3a** (1 equiv.), THF (0.05 M), base (1 equiv.; except for Entries 6, 7 and 11), r.t. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. Compound **5a** was not detected and gave **6a** directly. [c] Reaction carried out in CH_2Cl_2 (0.1 M) in the presence of (*S*)-proline (30 mol-%). [d] The formation of five-membered ring product **4a** by using proline catalyst was not described. The %*ee* of **4a** was not determined. [e] Reaction carried out in CH_3CN in the presence of Iwabuchi's catalyst (25 mol-%). [f] TBD (8 mol-%) was used.



(*S*)-proline Iwabuchi cat. TMG MTBD TBD

Figure 1. Organocatalysts used in this study.

On the basis of these results, we turned our attention to guanidine-based compounds, known as highly basic[12] and bifunctional organocatalysts,[13] in order to evaluate their potency in the direct intramolecular aldol reaction of **3a**. Disappointingly, the reactions promoted by 1 equiv. of the acyclic guanidine 1,1,3,3-tetramethylguanidine (TMG, pK_a = 23.7)[15] or the bicyclic guanidine *N*-methyl-TBD (MTBD, pK_a = 25.5)[15] were very slow and did not afford expected aldol product **4a** in an acceptable yield even after 72 h of reaction (Table 1, Entries 8 and 9). In both cases, **5a** and **6a** were not detected. Finally, we found that TBD (Figure 1) led, with total conversion of starting material **3a**, to the clean formation of aldol addition product **4a** as a mixture of two diastereoisomers in an *anti*/*syn* ratio of 71:29 after only 30 min and in 94% yield (Table 1, Entry 10). ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed that **4a** was the major product along with 4% of its dehydrated byproduct.[14] These results were very interesting, as the basicity of TBD alone seems insufficient to

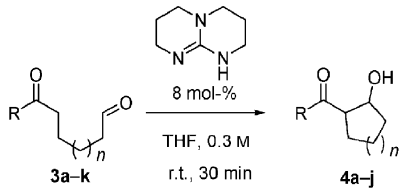
account for its unique reactivity and chemoselectivity (TBD, pK_a = 26.1).[15]

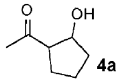
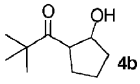
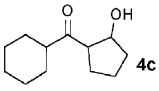
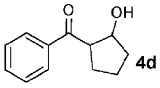
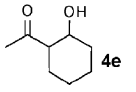
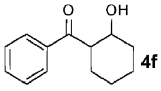
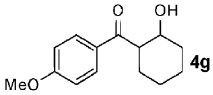
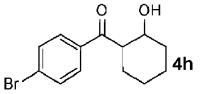
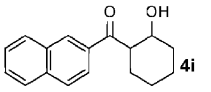
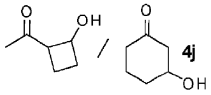
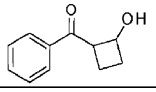
With these results in hand, we decided to test the efficiency of the reaction by using TBD in a catalytic amount. We tested the aldolization by using 8 mol-% of TBD in THF (0.05 M). To our delight, the 5-*enolexo* aldolization was finished after only 3 h and ketol **4a** was obtained in 92% yield along with 8% of its dehydrated product (Table 1, Entry 11). The reaction was complete after only 30 min by concentrating the medium to 0.3 M, affording a yield of 93% of **4a** and 7% of the corresponding aldol condensation byproduct. Finally, the effect of the solvent on the diastereoselectivity of the reaction was studied at the optimized concentration (0.3 M). Aldolizations carried out in toluene, ethyl ether, dioxane, acetonitrile, dimethyl sulfoxide, dimethylformamide and dichloromethane were all successful and led to the exclusive formation of desired regioisomer **4a** (yields >90%) without, however, any improvement in *anti*/*syn* diastereoselectivity, which was always between 66:34 and 77:23. Having identified optimized conditions, the scope and limitations of our facile transformation were then explored by using a panel of different acyclic ketoaldehydes **3**. The direct intramolecular aldolizations proceeded smoothly and chemoselectively to afford 2-ketocyclopentanols (**4a**–**d**) and 2-ketocyclohexanols (**4e**–**j**) in good-to-excellent yields. The TBD-catalyzed intramolecular aldolizations were total (100% conversion of starting material **3a**–**k**) and applicable to a wide variety of substrates with different structural features including aromatic (Table 2, Entries 4, 6–9) and aliphatic (Table 2, Entries 1–3, 5, 10) systems, allowing formation of five-to six-membered rings.

It was found that a moderate electronic effect is observed in the case of aromatic ketoaldehydes having electron-donating (Table 2, Entry 7) and electron-withdrawing (Table 2, Entry 8) groups, which did not afford cyclization products in comparable yields (85 and 66%, respectively). The use of more hindered ketoaldehydes, such as **3b** and **3c**, gave the corresponding aldol products **4b** and **4c** in moderate isolated yields (Table 2, Entries 2 and 3). Interestingly, **3b** exhibited reverse diastereoselectivity in comparison with the other ketoaldehydes probably due to the steric hindrance of the *tert*-butyl group. In the case of substrate **3e**, the reaction was not as selective as for the other ketoaldehydes; regioisomer **5e** was also formed as a mixture of two diastereoisomers in 24% yield (Table 2, Entry 5). This is the sole example for which the chemoselectivity is not total. We were also interested in testing the possibility of a four-membered ring formation by using ketoaldehydes 5-oxohexanal (**3j**) and 5-oxo-5-phenylpentanal (**3k**) as substrates (Table 2, Entries 10 and 11). We did not detect the formation of the desired product in either case, but instead the formation of the thermodynamic *enolendo* product **4j** was exclusive for ketoaldehyde **3j** (Table 2, Entry 10).

From a mechanistic point of view, the strong basicity of TBD and its wide use as a general base catalyst for a variety of transformations[12] suggested that TBD might function by deprotonating the methylene group α to the ketone moi-

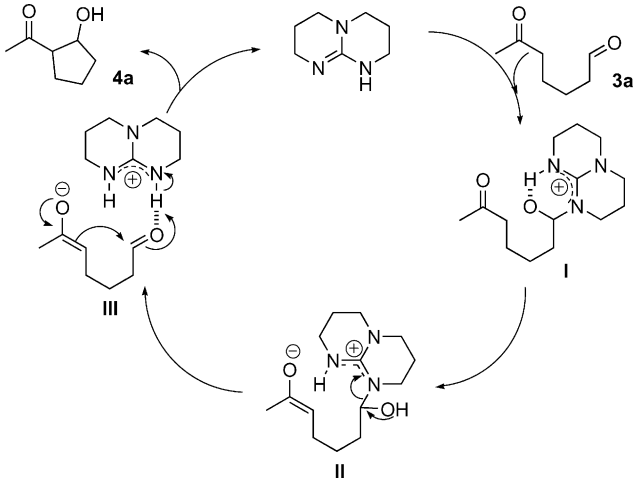
Table 2. TBD-catalyzed intramolecular aldolization of ketoaldehydes.[a]



Entry	Substrates	Products	*anti*/*syn*	Yield [%][b]
1	**3a** $n = 1$ R = Me	 **4a**	69:31	93
2	**3b** $n = 1$ R = *t*Bu	 **4b**	23:77	60
3	**3c** $n = 1$ R = *c*Hex	 **4c**	77:23	59
4	**3d** $n = 1$ R = Ph	 **4d**	83:17	90
5	**3e** $n = 2$ R = Me	 **4e**	83:17	76[c]
6	**3f** $n = 2$ R = Ph	 **4f**	83:17	91
7	**3g** $n = 2$ R = 4-$MeOC_6H_4$	 **4g**	55:45	85
8	**3h** $n = 2$ R = 4-BrC_6H_4	 **4h**	83:17	66
9	**3i** $n = 2$ R = naphthyl	 **4i**	77:23	87
10	**3j**	 **4j**	–	0:82
11	**3k**		–	0[d]

[a] Conditions: **3** (1 equiv.), THF (0.3 M), TBD (8 mol-%), r.t., 30 min. Purification of **4** (where R = alkyl) by flash chromatography resulted in a decrease in the isolated yield, even though ^{1}H NMR spectroscopic analysis of the crude mixture showed the formation of **4** exclusively (except for Entry 5, where regioisomer **5e** was also formed). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [d] Total conversion of **3k** and major formation of an unidentified product.

ety, leading to the more thermodynamically stable enolate. This intermediate would then condense onto the aldehyde affording addition product **4a**. However, MTBD and TMG were found to be less reactive than TBD under the same conditions, despite their similar basicities (pK_a values of conjugate acids are 25.5, 23.7 and 26.1, respectively),[15] suggesting another mechanistic pathway. This possible mechanism is based on the bifunctional reactivity of TBD, nucleophilic and basic (Scheme 2), by analogy with the reports of Waymouth and Mioskowski, who studied the TBD-catalyzed polymerization of cyclic esters[13a] and the aminolysis of esters,[13c] respectively.



Scheme 2. Possible dual activation mechanism proposed for the TBD-catalyzed 5-*enolexo* aldolization.

Inspired by these studies, the first step of the possible mechanism would be a selective nucleophilic addition of TBD on the more electrophilic aldehyde of **3a**, generating tetrahedral intermediate **I**. After proton transfer on the alcohol functionality, the sp^2 nitrogen of TBD would then allow the intramolecular enolization of the ketone, leading to intermediate **II**. This labile species would then release the guanidinium cation, which will activate the aldehyde of intermediate **III**. The subsequent intramolecular addition of the ketone enolate to this intermediate affords aldol addition product **4a** and regenerates the TBD catalyst.

The rationalization of the diastereoselectivity of addition product **4a** is still unclear on the basis of this proposed mechanism.

Conclusions

We described efficient guanidine-catalyzed 5-*enolexo* and 6-*enolexo* aldolizations of acyclic ketoaldehydes that lead to 2-ketocyclopentanols and 2-ketocyclohexanols in high yields. This transformation is organocatalyzed by TBD, an inexpensive and commercially available guanidine reagent. This practical reaction enables the straightforward preparation of important building blocks for further elaboration. In conjunction with these achievements, studies are currently underway in our laboratory to rationalize the stereochemical outcome of the reaction. The development of a catalytic asymmetric version of this aldol condensation is also underway.

Experimental Section

Representative Procedure for the TBD-Catalyzed Intramolecular Aldolization: To a solution of ketoaldehyde **3** (250 mg, 1.95 mmol) in anhydrous THF (0.3 M, 6.5 mL) was added TBD (8 mol-%) at room temperature. The reaction mixture was stirred for 30 min and then quenched with saturated ammonium chloride solution (10 mL). The organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL). The organic layer was dried with magnesium sulfate, filtered and concentrated in vacuo to afford a crude product that was purified by flash chromatography to give desired aldol products **4** as a mixture of two diastereoisomers. The relative stereochemistry of the diastereoisomers was assigned by analogy to our results and to reported data (see Supporting Information).

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and spectroscopic data for new compounds.

Acknowledgments

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[8] We synthesized the (4*R*,2*S*)-tetrabutylammonium 4-TBDPSoxy-prolinate catalyst according to ref.[7] This catalyst was ineffective in promoting the direct intramolecular aldolization of ketoaldehyde **3a**, and no trace amounts of **4a** were formed. However, **6a** (14% yield) and an unidentified product (40% yield) were formed (see results in Table 1, Entry 7). Compound **3a** was recovered as the major product (45% yield).
[9] B. List in *Modern Aldol Reactions* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**, vol. 1, p. 161.
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