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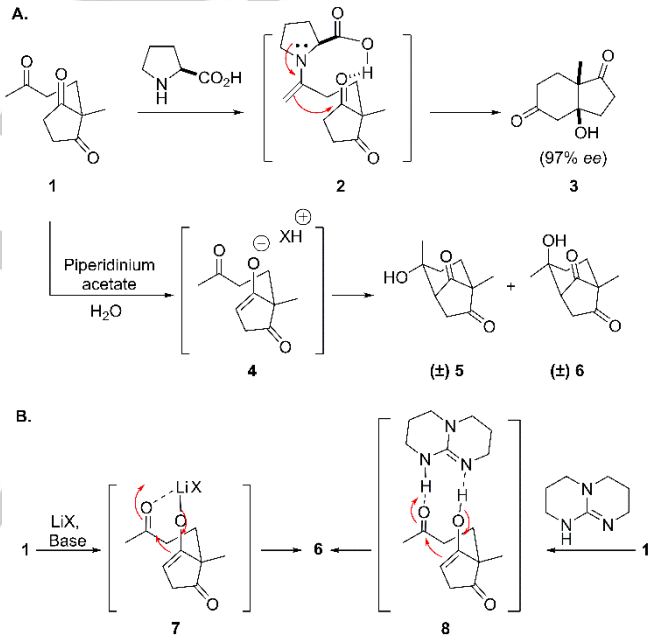
Metal Coordination-controlled and Bifunctional H-bonded Catalysis in Stereoselective Intramolecular Aldol Cyclizations toward Carbocyclic Tertiary β-Ketols

Bin Chen,[a] Gilles Berger[a,b] and Stephen Hanessian*[a]

Abstract: The principle of bifunctional catalysis is shown in the highly regio- and stereoselective intramolecular aldolization of 2-methyl-1,3-cyclopentanedione harboring a C-2 methyl ethyl ketone appendage, to provide [3.2.1]-bicyclooctanol diones in the presence of catalytic amounts of either LiBr and DBU, or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). Mechanistic investigations corroborated by DFT calculations show that LiBr engages in a bifunctional coordination of the two carbonyl moieties and leads to the pre-organization of the reactive enolate intermediate for a base-mediated intramolecular aldol cyclization. On the other hand, TBD-catalysis of the same triketone substrate proceeds through a bifunctional H-bonded mechanism to give the same aldol product as the major diastereomer. The LiBr and TBD-catalyzed highly stereocontrolled intramolecular aldol cyclizations can be extended to other di- and tri-ketones to give carbocyclic and carbobicyclic products as single diastereomers.

While the intramolecular version of the aldol cyclization reaction of carbonyl compounds has been known for many years,[1] a paradigm shift in the field was realized by seminal independent contributions from scientists at Hoffmann-LaRoche and Schering AG over 40 years ago. In particular, Hajos and Parrish[2] demonstrated the feasibility of a proline-catalyzed asymmetric intramolecular aldol reaction of a prochiral triketone leading to the corresponding enantiomerically enriched perhydroindanedione core structure harboring a β-ketol functionality (Scheme 1). This remarkable asymmetric metal-free bond-forming reaction[3,4] was a prelude for what is now known as organocatalysis.[5,6] The translation of this technology to intermolecular aldol condensations was another timely development in the field.[7] Extensive mechanistic and theoretical studies have validated the proposed enamine mechanism for the Hajos-Parrish-Sauer-Eder-Wiechert reaction, wherein triketone **1** is converted to a perhydroindanedione β-ketol **3** in 97% *ee*.[2,8,9] New mechanistic insights have also been advanced based on the formation of discreet intermediates.[10,11] Racemic **3** is obtained in the presence of piperidinium acetate in ether, also proceeding by an enamine mechanism.[2] Importantly, two diastereomeric [3.2.1]-bicyclooctanedione β-ketols **5** and **6** where formed via an alternative intramolecular aldol pathway when the same reaction was conducted in water (Scheme 1).[2] The prerequisite parallel alignment of two of the three carbonyl groups *en-route* to the formation of β-ketols **5** and/or **6** via enolate **4**, prompted us to consider new modes of carbonyl activation leading to intramolecular aldol cyclization under catalytic conditions. In the first of these, we hypothesized that pre-coordination of the triketone **1** with a neutral salt such as a lithium halide[12] would orient one of the carbonyl groups of the 1,3-cyclopentanedione ring and the carbonyl group in the extended chain of triketone **1** in a parallel mode, which in the presence of a non-nucleophilic base, would proceed to the enolate **7,** then undergo intramolecular aldolization to give **6** as the major product (Scheme 1A). In the second case, we envisaged that in the presence of a bicyclic guanidine such as TBD[13] triketone **1** would be transformed to the enol **8** via a bifunctional H-bonded intermediate which would also preferentially lead to **6** (Scheme 1B).



Scheme 1. A. Proline-catalyzed β-ketol formation from triketone **1**; B. Proposed bifunctional pathways to β-ketol **6** from triketone **1**.

In this communication, we provide comprehensive experimental and theoretical evidence that such bifunctional metal-coordinated and H-bonded cooperative catalysis in intramolecular aldol reactions are indeed operative.

Treatment of **1** with diazabicycloundecene (DBU, 1 equiv.) [14,15] at room temperature for 24 h led to a mixture of β-ketol compounds **3**, **5**, and **6** in quasi-equal amounts. However, using catalytic amounts (5 mol % each in THF) of DBU and LiBr at -40 °C afforded **6** with high selectivity and 88% isolated yield. Catalytic DBU and LiCl also generated **6** in good yield. However, switching to $MgBr_2$ or $MgBr_2{\cdot}Et_2O$, led to trace amounts of **6** with recovery of starting triketone **1**.[16] These experiments validated the critical role of lithium bromide in the selective formation of the axial β-ketol **6** (see SI for details).

We also studied a series of bases with different *p*Ka values as catalysts with and without LiBr at -40 °C (see SI for details). Only traces of **6** were formed with relatively weaker bases such as Et_3N and LiBr. Excellent yields of **6** were obtained with

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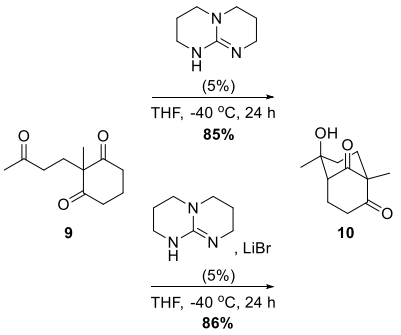
piperidine (*p*Ka = 14.3 in THF) and other bases, but *only* in the presence of LiBr. With the bicyclic Eschenmoser amidine,[17] formation of **6** was significantly enhanced in the presence of 5 mol% LiBr. In the presence of *N*-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (*N*-MeTBD, *p*Ka = 18.6),[14] an excellent yield of **6** was obtained, but only when 5 mol% LiBr was added. On the other hand, using 5 mol% of the more basic 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, *p*Ka = 21.0) gave **6** in 89% yield in the absence of added LiBr. Intrigued by the distinct preference and high yield in the formation of the axial β-ketol product **6** using catalytic amounts of bases, with and without LiBr, we carried out the cyclization reaction of the triketone **1** in the presence of 5 mol% of sparteine,[18] at -40 °C with and without LiBr as catalysts, but no reaction was observed. Upon adding 5 mol% of DBU to the mixture, **6** was obtained in 88% isolated yield, regardless of the order of addition. Unfortunately, the product was racemic.

The guanidine-based bifunctional catalysis[19] was extended to the intramolecular aldolization of the cyclohexanedione analog **9** with and without LiBr to give the corresponding β-ketol **10** in high yields (Scheme 2). In the case of the benzyl triketone **11** and catalytic TBD, the yield of the

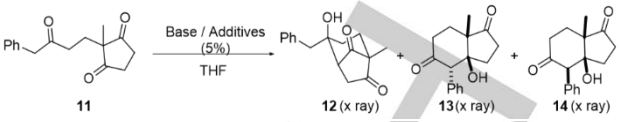


Scheme 2. Intramolecular aldol reactions with triketone **9.**

bicyclic product **12** was modest, even with addition of LiBr. (Table 1, entries 1 and 2). On the other hand, treatment of **11** with 5 mol% DBU at -40 °C led to the diastereomeric β-ketol product **13** in excellent yield (Table 1, entry 3). Under the same conditions, the catalytic DBU/LiBr combination gave **12** and **14** in 16% and 81% yields respectively. Curiously, catalytic DBU by itself also gave **14**, albeit at -78 °C (Table 1, entries 4 and 5).

The formation of the [3.2.1]bicyclooctane β-ketols **5** and **6** has been scarcely studied since the initial report by Hajos and Parrish in 1974. Dauben and Bunce[20] reported formation of **6** under 15 bar in the presence of Et_3N and acetonitrile at 20 °C. In an effort to obtain enantioselective intramolecular aldolization, Shibasaki and coworkers[21] reported the formation of **6** in 52% *ee* and 60% yield (THF, -52 °C, 6 days) in the presence of catalytic amounts of an ytterbium dialkoxide originally prepared from (*R*,*R*)-tartaric acid. Davies and coworkers[22] investigated the asymmetric synthesis of **6** from **1** in the presence of (1'*R*,2'*S*)-5-(2'-aminocyclopentan-1'-yl) tetrazole as a catalyst, however, the product obtained in 67% yield was racemic. Mahrwald and coworkers tested a tetranuclear BINOL-titanium complex catalyst,[23] to give racemic **6** in 44% yield.

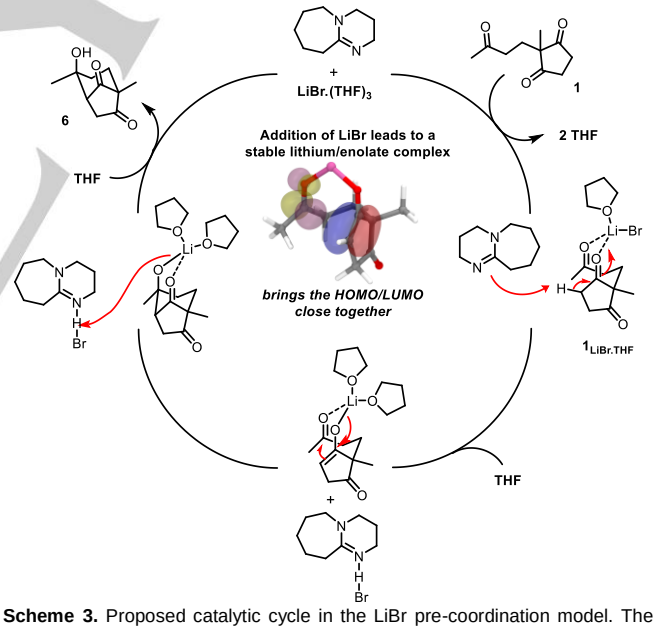
Table 1. Aldol reactions with benzyl triketone **11**.



Entry	Additive	T, °C	Yield, % 12	13	14
1	TBD	-40	33[b]	-	-
2	TBD, LiBr	-40	40[b]	-	-
3	DBU	-40	-	83	-
4	DBU, LiBr	-40	16	-	81
5	DBU	-78	-	-	82

All reactions were run with 0.14 mmol triketone in 1 mL THF for 72 h. [a] Isolated yield. [b] Reaction did not complete and significant amounts of starting material were recovered.

The formation of **6** in high yield in the presence of catalytic DBU and LiBr is attributed to a conformational pre-organization whereby the carbonyl groups of the side-chain and the cyclopentanedione are favorably aligned due to a bidentate coordination with the oxophilic LiBr (Scheme 3).



Scheme 3. Proposed catalytic cycle in the LiBr pre-coordination model. The Li-coordinated endocyclic enolate as calculated from DFT is depicted in the center; showing the pre-organization by Li, which brings the HOMO (red/blue) located on the enolate and the carbonyl LUMO (yellow/purple) close together.

Abstraction of a proton by DBU leads to the corresponding endocyclic lithium enolate, which undergoes cyclization to **6**. Indirect evidence for this proposal is provided by ^{13}C NMR spectra of **1** in the presence of increasing quantities of LiBr in THF-d_8 and observing appropriate shifts (see SI). The failure of the reaction to occur with catalytic DBU alone at -40 °C, attests to the existence of a prior cooperative effect involving LiBr which

also activates the adjacent carbon atom towards enolization with DBU. A similar mechanism could be operative in the presence of the Eschenmoser amidine acting as a base, although the conversion was more efficient with added LiBr. (see SI for details). It is noteworthy that the use of THF as solvent is another important factor most likely due to the coordination of the carbonyl groups of the triketone **1** with a LiBr-THF complex. When MeOH was used as solvent, the major product was the *equatorial* β-ketol **5**, presumably due to the solvation of triketone **1** in MeOH, thus preventing coordination with LiBr.

DFT calculations conducted at the *ω*B97x-D/def2-TZVP level of theory for the LiBr-catalyzed reactions support these findings and highlight the formation of a complex between **1** and LiBr ($\mathbf{1}_{LiBr}$). This results in a stabilization energy of about 2 kcal.mol^{-1} while forming a pre-organized reactive intermediate, which is followed by proton abstraction and enolization with a strong preference (5 kcal.mol^{-1}) for the formation of the endocyclic enolate (Figure 1). Activation barriers to the transition states (TS) leading to **6** and **3** are found around 10 kcal.mol^{-1}, with a $\Delta\Delta G^{\ddagger}$ of 1.2 kcal.mol^{-1} favoring the formation of β-ketol **6** (Figure 1).

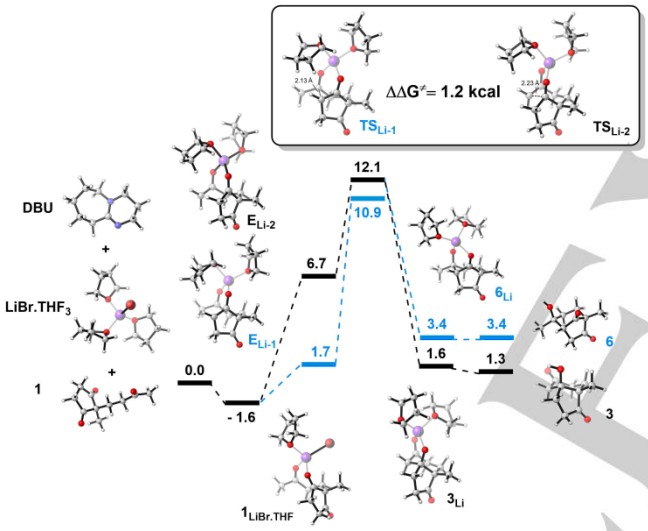


Figure 1. Free energy profile for the LiBr-catalyzed reaction using DBU as base, in THF at 233 K. Reaction pathway undergoing enolization on the 5-membered ring is represented in blue, while the enolization occurring in the side-chain is drawn in black.

The newly forming C-C bond length is significantly shorter for the most stable transition structure (2.13 Å versus 2.23 Å). The overall free energy of the reaction for both pathways remains positive, which is experimentally observed as products kept in THF tend to revert to **1**, and is in accordance with previous DFT studies.[8e,13a] Therefore, when Li is used to conformationally lock the exo- and endocyclic carbonyl groups to be aligned parallel to each other, β-ketol **6** is produced kinetically as the endocyclic enolate and the subsequent transition structures are favored, even though β-ketol **3** resulting from exocyclic enolization is thermodynamically preferred. Without the addition of LiBr, the endocyclic enolate is still favored but the absence of any pre-organization and parallel alignment of the C-O bonds leads to the equatorial β-ketol **5**, with a 3 kcal.mol^{-1} preference with respect to the axial β-ketol **6** (Figure 2).

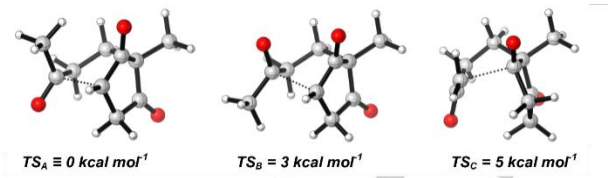


Figure 2. Transition states and free energies for the non-catalyzed reaction, in THF at 298 K, resulting from both conformations of endocyclic enolization ($\mathbf{TS_A}$ and $\mathbf{TS_B}$) and exocyclic enolization ($\mathbf{TS_C}$). Side-chain enolization is disfavored and the preferred reaction pathway involves the equatorial conformation of the exocyclic ketone leading to the β-ketol **5**.

Since the equatorial β-ketol **5** is the kinetic product for the non-catalyzed reaction, it could transform to the thermodynamically-preferred axial product **6** by a retro-aldol reaction. However, β-ketol **5** was stable under the same reaction conditions (5 mol% DBU and LiBr at -40 °C for 24 h), and was converted to **6** only upon warming to room temperature. Thus, the thermodynamically stable ketol **6** is produced directly from starting triketone **1.** With strong bases, such as *N*-methyl TBD, a significant lithium effect is observed when comparing the product distribution in the presence of 5 mol% of *N*-methyl TBD when β-ketol **6** was obtained in 5% yield at -40 °C for 24 h. In contrast, inclusion of 5 mol% LiBr led to the formation of **6** in 88% yield (see SI for details).

A different mechanism can be suggested for the catalytic action of a cyclic guanidine like TBD (Scheme 1). Enolization could also lead to a favorable alignment of the enol and the side-chain carbonyl bridged by TBD. We propose that catalysis is occurring through a bifunctional H-bonded mechanism, since there was no yield difference in the presence or absence of LiBr. A dual role of TBD, acting as a proton donor and acceptor is most likely taking place in the intramolecular aldol reaction of triketone **1** leading to β-ketol **6**.

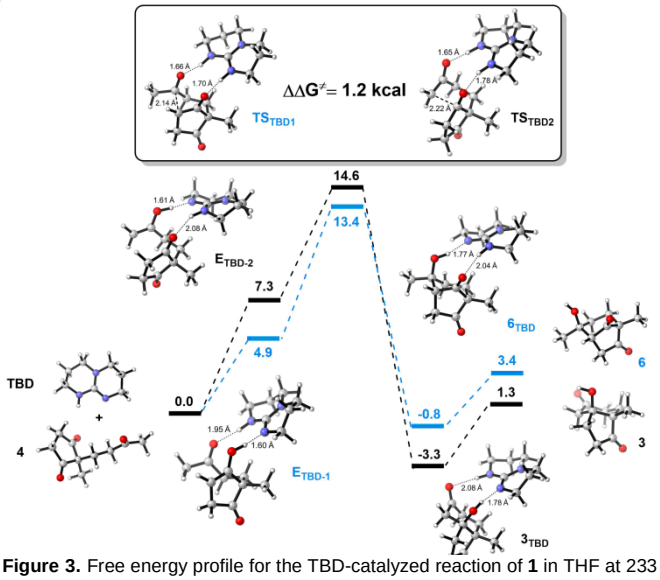


Figure 3. Free energy profile for the TBD-catalyzed reaction of **1** in THF at 233 K leading to β-ketol 6. Reaction pathway undergoing enolization on the 5-membered ring is represented in blue, while the enolization occuring in the side-chain is drawn in black.

DFT optimization led to the formation of stable adducts involving bifunctional H-bonding (H-bond lengths between 1.7 and 2.1 Å) with an activation energy for the C-C bond formation in the same range as for the LiBr-catalyzed reaction (Figure 3). In this case, however, the activation energy was slightly higher, 13.4 and 14.6 kcal/mol^{-1} respectively for the endocyclic enolate and the side-chain enolate pathways. The C-C distance at the stationary saddle point is also shorter for the preferred TS, which leads to product **6** (**TS_{TBD1}**). The axial β-ketol **6** is therefore produced due to a favored enolization and transition state. In a related isolated example, Baati, Himo and coworkers[13] have studied the intramolecular aldol reaction of an acyclic keto aldehyde catalyzed by TBD through DFT calculations and proposed a proton shuttling general base mechanism. We have recently used the presently described TBD-catalyzed intramolecular aldol cyclization reaction in a critical key step toward the total synthesis of isodaphlongamine H.[24] To the best of our knowledge, the intramolecular TBD-catalyzed aldol reaction of a triketone such as **1** has not been previously reported[25] and offers distinct advantages.

The proposed LiBr pre-coordination and bifunctional H-bonding mechanisms can also explain the diastereoselectivities in the reactions of benzyl triketone **11**. When LiBr is added, pre-organization leads to a favored chair conformation with the phenyl group occupying the equatorial position to give β-ketol **14** (Figure 4).

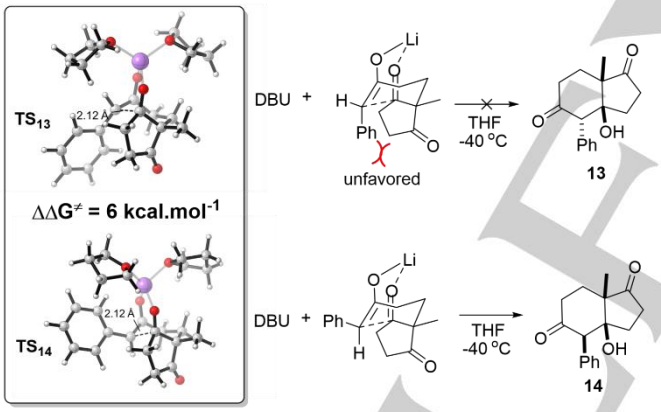
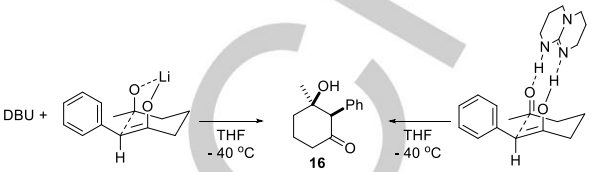


Figure 4. Proposed coordination transition states for the reaction of benzyl triketone **11** in THF.

This is further predicted by the optimization of both TSs (**TS_{13}** and **TS_{14}**) leading to **13** and **14** in which $\Delta\Delta G^{\ddagger}$ is found around 7 kcal.mol^{-1} in favor of the equatorial conformation of the phenyl ring. Catalysis in the presence of DBU alone appears to be temperature dependent, leading to **14** at -78 °C, possibly through an H-bonded enol intermediate similar to a Li-coordination (Figure 4). At higher temperatures (Table 1, entry 3) the diastereomeric **13** was favored, with minimal retro-aldol formation. Unfortunately, these results could not be rationalized based on DFT calculations.

Finally, based on these experimental observations and mechanistic studies, we were curious to see if the LiBr/DBU dual catalyst combination could also be operative via bidentate coordination in the case of the *acyclic* benzyl diketone **15** (Table 2). Although no reaction occurred in the presence of 5 mol% DBU, addition of 5 mol% LiBr, led to a 74% yield of a single diastereomer **16** (Table 2, entries 1 and 2) The same product was also formed in the presence of 5 mol% TBD (Table 2, entry 3). These results provide good support for our proposed lithium pre-organization and bifunctional H-bonded mechanisms in these stereoselective intramolecular aldol cyclizations to β-ketols.

Table 2. Intramolecular aldol reaction of diketone **15**.



Entry	Additive (5mol%)	T, °C	Yield, %[a]
1	DBU	-40	No reaction
2	DBU, LiBr	-40	74
3	TBD	-40	85

The reactions were run with 0.14 mmol triketone in 1 mL THF for 12 h.
[a] Isolated yield.

In conclusion, we have shown that the combination of 5 mol% DBU/LiBr forms an excellent catalyst duo, combining oxophilicity and basicity to effect highly stereoselective intramolecular aldol cyclizations of 1,5-diketones in monocyclic and acyclic substrates, affording diastereomeric carbocyclic, and bicyclic β-hydroxy ketones. Remarkably, these reactions take place at temperatures as low as -78 °C. DFT calculations confirms the formation of spatially pre-organized and Li-coordinated 1,5-enolate/carbonyl intermediates which then undergo cyclization. The same intramolecular aldol cyclizations can be achieved in the presence of 5 mole% TBD as a catalyst, proceeding via a donor-acceptor bifunctional H-bonded cooperative mechanism that engages an enol and a carbonyl group simultaneously. High-level DFT calculations support this pathway and account for the formation of the axial β-ketols resulting from the conformation lock and the kinetically-favored endocyclic enolization. Extensions to other 1,5-diketones and the prospects of asymmetric induction using chiral non-racemic amidines and guanidines are in progress.

Experimental Section

Copies of ^{1}H and ^{13}C NMR spectra of new compounds, computational details and chemistry procedures can be found in the provided supporting information. CCDC 1468933, 1468934, 1468935, 1468936 and 1468937 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Acknowledgements

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Keywords: Organocatalysis • Intramolecular aldol • Bifunctional catalysis • DFT • β-Ketol

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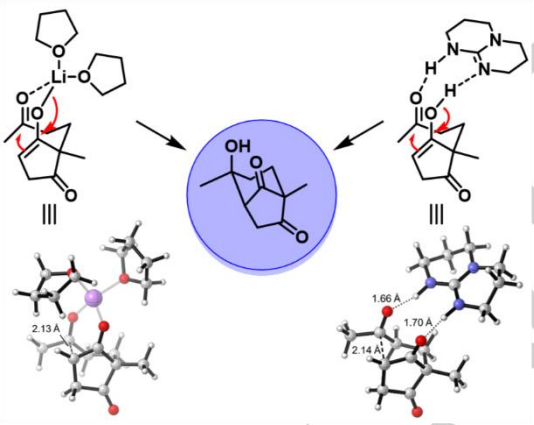
Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Ménage à trois (ou quatre). The oxophilic LiBr/DBU combination or a bicyclic guanidine such as TBD are excellent catalysts for the activation of carbonyl groups in acyclic and carbocyclic 1,5-diketo compounds, generating energetically favored metal (Li) and H-bonded (TBD) intermediates in which a carbonyl group and an enol(ate) are exquisitely aligned to undergo intramolecular aldolization leading to conformationally and stereochemically distinct beta-ketols.



*Bin Chen, Gilles Berger and Stephen Hanessian**

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Metal Coordination-controlled and Bifunctional H-bonded Cooperative Catalysis in Stereoselective Intramolecular Aldol Cyclizations toward Carbocyclic Tertiary β-Ketols