ORGANIC LETTERS

2012
Vol. 14, No. 11
2810–2813

Origin of Stereoselectivity in a Chiral N-Heterocyclic Carbene-Catalyzed Desymmetrization of Substituted Cyclohexyl 1,3-Diketones

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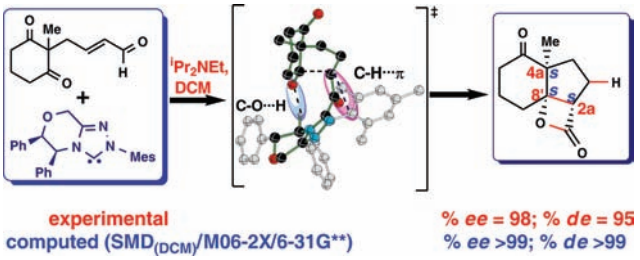
Received April 19, 2012

ABSTRACT



The mechanism and stereoselectivity in a chiral N-heterocyclic carbene-catalyzed desymmetrization of a 1,3-diketone is established by using density functional theory computations. The Breslow intermediate formation is identified to involve Hunig's base-assisted proton transfer. The relative energies of stereoselectivity-determining intramolecular aldol cyclization transition states reveal that in the most preferred mode the *re*-face of enolate adds to the *si*-face of carbonyl leading to a tricyclic lactone with a configuration (2a*S*,4a*S*,8′*S*) in excellent agreement with previous experimental reports.

Impressive developments in organocatalytic protocols have offered interesting avenues to chiral synthetic targets.[1] A number of nucleophilic N-heterocyclic carbenes (NHC) came into recent prominence owing to their potential as organocatalysts.[2] Some of the quintessential applications of NHC in carbon−carbon and carbon−heteroatom bond formation reactions include Stetter, crossed-benzoin, Mannich, Michael, Mukaiyama−aldol, and cycloaddition reactions.[3] Very recently, more advanced applications encompassing multicomponent reactions[4] and cooperative catalysis (in conjunction with Lewis acids)[5] have also been reported. Most of the nucleophilic carbenes employed in asymmetric reactions belong to the imidazoline or triazoline family. One such chiral triazoline catalyst motif and a plethora of successful applications toward realizing congested stereocenters are succinctly illustrated in Scheme 1.[6]

Among the strategies for inducing chirality, desymmetrization could help create stereogenic quaternary carbons. Chiral NHCs have been successful in desymmetrization of 1,3-dicarbonyls.[7] Scheidt and co-workers demonstrated

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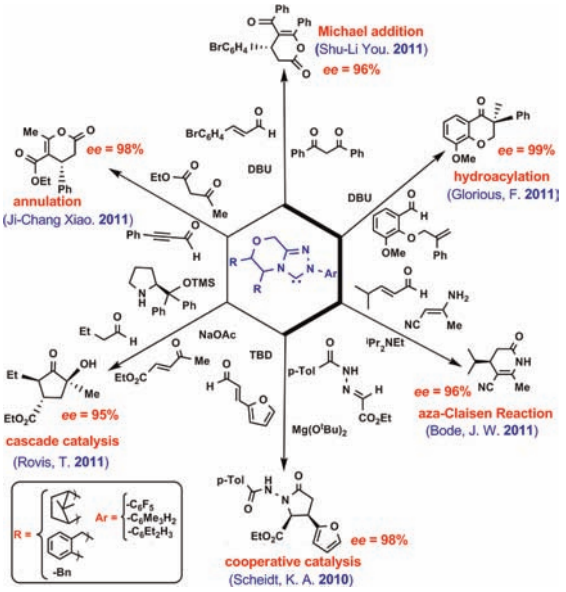
10.1021/ol301036u
Published on Web 05/08/2012

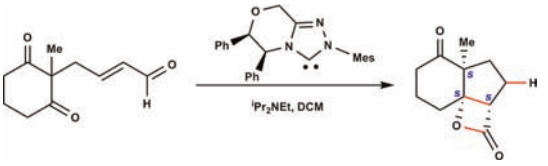
the synthesis of an interesting tricyclic ring system consisting of quaternary stereogenic carbons using such an approach (Scheme 2).[8]

Scheme 1. Select Applications of Chiral Triazole NHC

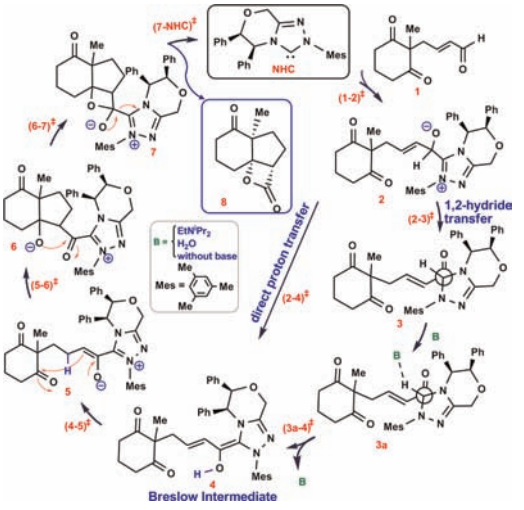


As the experimental developments in triazole-based NHCs continue to flourish, the demand for improved mechanistic insights naturally grows steadily. While there have been some recent efforts in this direction,[9] no studies to date have focused on the mechanism and stereoselectivity issues of bicyclic triazolium NHC catalyzed reactions. As part of our endeavors toward obtaining molecular-level understanding of stereoselective organocatalytic reactions,[10] we decided to examine the origin of stereoselectivity of the title reaction by using three widely used density functional theory methods, namely B3LYP, mPW1K, and M06-2X in conjunction with the 6-31G** basis set, both in the gas phase and in the condensed phase in dichloromethane solvent.[11] The discussions are presented on the basis of Gibbs free energies obtained at the SMD$_{(DCM)}$/M06-2X/6-31G**//M06-2X/6-31G** level of theory.

Scheme 2. Desymmetrization of (*E*)-4-(1-Methyl-2,6-dioxocyclohexyl)but-2-enal



Scheme 3. Key Mechanistic Steps Involved in Desymmetrization



We envisaged the mechanism of desymmetrization as consisting of the key steps as shown in Scheme 3. The nucleophilic NHC first acts on the most electrophilic carbon of butenal to give a zwitterionic intermediate **2**. Multiple ways of converting **2** to Breslow intermediate **4** are examined next. Subsequent intramolecular aldol cyclization in intermediate **5** leads to intermediate **6**. Lactonization of **6** gives a tetrahedral intermediate **7**, which ultimately furnishes the tricyclic product through catalyst release.

In the initial C−C bond formation step between the catalyst and the substrate, the nucleophilic carbene can approach either the *re* or *si* face of the aldehyde. The *N*-mesityl group of the chiral catalyst can remain nearer or farther to the cyclohexyl group of the substrate besides presenting additional possibilities arising due to the orientation of the cyclohexyl methyl group with respect to the incoming NHC. After careful examination of several such

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(11) Full details of computational methods are provided in the Supporting Information.

possibilities, differing in the dihedral angles along the incipient C−C bond, we could identify the lowest energy transition state **TS(1−2)**.[12] The most preferred C−C bond formation is found to involve the *re* face of aldehyde with a barrier of about 16 kcal/mol.

The zwitterionic species (**2**) thus generated can convert to Breslow intermediate in multiple ways such as (i) direct 1,2-proton transfer or (ii) a sequential 1,2-hydride transfer and keto−enol tautomerization. The energetic comparison between these possibilities, as given in Table 1, reveals interestingly vital mechanistic details. The direct 1,2-proton transfer transition state **TS(2−4)** is of higher energy as compared to the alternative possibilities. The 1,2-hydride transfer transition state **TS(2−3)** leading to another neutral intermediate, **3**, is found to be of lower energy. However, the transition state for the subsequent conversion of **3a** to the Breslow intermediate **4** is of prohibitively higher energy than the direct 1,2-proton transfer. This situation conspicuously implies that the tautomerization could involve an assisted proton transfer from triazolyl carbon to the carbonyl oxygen.

Two scenarios of assisted-proton transfers, such as a base-assisted and a water-assisted pathway are examined.[13] The analysis of the transition-state geometries and the IRC trajectories for both assisted proton transfers revealed a concerted transfer from carbon to oxygen (Figure 1).[14] Most importantly, the Gibbs free energies of these TSs are much lower than the unassisted proton transfer TS. For instance, the base-assisted TS is about 13.9 kcal/mol lower than the direct proton transfer TS. The activation barriers, computed with respect to the preceding intermediates, for base- and water-assisted pathways are, respectively, 22.7 and 38.3 kcal/mol.[15] It is therefore evident that Hunig's base is the most effective way of assisting the proton transfer involved in the formation of Breslow intermediate, **4**. The formation of **4** is found to be exoergic by about 12 kcal/mol.

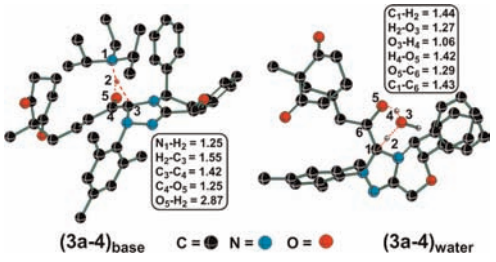

Figure 1. Key transition states involved in the formation of Breslow intermediate obtained at the M06-2X/6-31G** level. Bond lengths are given in angstroms.

In another vital step, a lower barrier intramolecular 1,4-proton transfer converts Breslow intermediate **4** to a reactive enolate **5**. The subsequent intramolecular aldol cyclization holds the key to the stereochemical outcome of the reaction. The C−C bond formation between the enolate (donor) and carbonyl (acceptor) offers distinct stereochemical modes. First, either of the two carbonyl carbons (C2 and C6) can act as the acceptor. Second, prochiral donor and acceptor can lead to different product configurations depending on the stereochemical mode of addition.[16]

Table 1. Relative Energies (in kcal/mol) of Transition States

	mPW1K		B3LYP		M06-2X	
TS	G_{gas}	G_{DCM}	G_{gas}	G_{DCM}	G_{gas}	G_{DCM}
1−2	8.7	15.4	12.3	18.0	9.0	16.6
2−3	21.5	29.1	27.8	35.1	22.8	32.0
3a-4	56.7	65.9	58.0	66.5	56.4	67.1
(3a-4)$_{base}$	44.0	55.0	50.6	60.8	26.5	38.8
(3a-4)$_{water}$	35.8	48.9	40.0	52.9	33.4	48.6
2−4	44.4	51.1	47.5	54.0	45.1	52.7
4−5	20.5	28.0	24.1	31.4	21.2	29.9
5−6	0.1	7.7	8.7	15.9	−0.3	8.4
6−7	3.2	9.3	15.5	21.2	5.7	11.9
7-NHC	−11.4	−3.4	2.8	10.7	−9.5	−1.1

The success of the chiral catalyst would depend on the relative energies of the diastereomeric transition states in this step wherein new chiral centers are created. A total of eight crucial stereoisomeric additions, involving the *re* or *si* face of enolate to the *re* or *si* face of either C2 or C6 carbonyl carbons, are examined. These modes, as shown in Scheme 4, would lead to different product configurations. The important questions at this juncture are to identify which one of these possibilities are energetically preferred and what is the origin of the relative energy order.

The computed relative energies of the transition states for the stereocontrolling C−C bond formation are provided in Table 2. The attack of the *re* face of enolate on the *si* face of carbonyl carbon at C2 is identified as stereochemically the most preferred addition. The optimized geometry of the corresponding transition state **TS(*re*-*si*)$_{C2}$** is provided in Figure 2. The bicyclic intermediate **6** thus produced presents either a *syn* or *anti* relative disposition of the alkoxide oxygen and the carbonyl group with respect to the methyl group at the ring junction.[17] The resulting product exhibits (2a*S*,4a*S*,8′*S*) configuration, in concert with the previous experimental report.[8] Different configurations of the

(12) The structure and energies of 24 such transition states are provided in Figure S2 and Table S1 in the Supporting Information.

(13) (a) We have previously reported assisted proton transfers in other reactions. Roy, D.; Sunoj, R. B. *Chem. −Eur. J.* **2008**, *14*, 10530. Patil, M. P.; Sunoj, R. B. *J. Org. Chem.* **2007**, *72*, 8202. Reference 9e. (b) Since complete extrusion of moisture/water under the experimental conditions is not described, it is sensible to consider a water-assisted proton transfer. Similar examples include: Jaramillo, P.; Coutinho, K.; Canuto, S. *J. Phys. Chem. A.* **2009**, *113*, 12485. Chen, P.-T.; Wang, C.-C.; Jiang, J.-C.; Wang, H.-K.; Hayashi, M. *J. Phys. Chem. B.* **2011**, *115*, 1485.

(14) IRC trajectories along with the corresponding geometries are provided in Figure S5 in the Supporting Information.

(15) See Table S4 in the Supporting Information for additional details.

(16) Total stereochemical possibilities considered are eight. These are 2 × 2 (due to prochiral faces of enolate and carbonyl) multiplied by 2 (due to mesityl group nearer/farther).

(17) Among eight stereochemical possibilities, only four diastereomeric TSs are considered for the formation of C−C bond as the ensuing bicyclic structure cannot undergo lactonization owing to the inherent lack of proximity between the alkoxide oxygen and the carbonyl carbon. See Scheme S2 in the Supporting Information.

tricyclic lactone framework can be generated through other modes of aldol cyclizations as depicted in Scheme 4.

Scheme 4. Stereochemical Possibilities for Intramolecular Aldol Cyclization

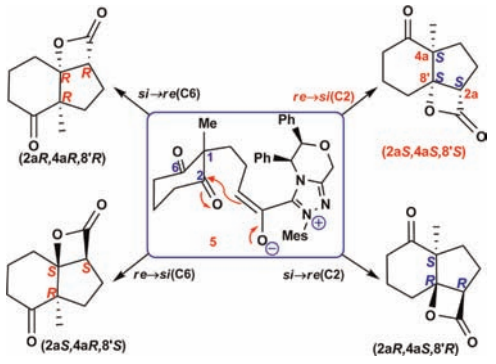

Table 2. Relative Energies (in kcal/mol) of Transition States for the Stereoselective C−C Bond Formation[a]

		mPW1K		B3LYP		M06-2X	
TS **5**−**6**	product config	G_{gas}	G_{sol}	G_{gas}	G_{sol}	G_{gas}	G_{sol}
		attack at C2					
re-si	2a*S*,4a*S*,8′*S*	0.0	0.0	0.0	0.0	0.0	0.0
si-re	2a*R*,4a*S*,8′*R*	13.6	10.6	16.5	14.2	11.8	9.0
		attack at C6					
re-si	2a*S*,4a*R*,8′*R*	17.9	9.8	6.9	6.0	16.3	7.5
si-re	2a*R*,4a*R*,8′*R*	6.6	5.8	8.1	7.2	5.1	3.7

[a] Computed with respect to the lowest energy TS.

A direct comparison between different stereochemical modes of addition can be performed on the basis of the relative energies of the vital transition states (Table 2). It is evident that the addition of *si* face of enolate on the *re* face of C2 or C6 positions are much higher in energy than the corresponding *re*−*si* addition. More specifically, the Gibbs free energy difference between the diastereomeric **TS(*re-si*)$_{C2}$** and **TS-(*si-re*)$_{C6}$** responsible for the formation of enantiomeric products suggest more than 99% *ee* in favor of (2a*S*,4a*S*,8′*S*) configuration. High diastereomeric excess is similarly predicted on the basis of the relative energies of **TS(*re-si*)$_{C2}$** and **TS(*si-re*)$_{C2}$**.

The key geometric features of the stereochemically significant TSs are carefully analyzed so as to decipher the origin of stereoinduction. A few important stereoelectronic features are identified as contributing to the differential stabilization of these TSs. These include (i) the role of the phenyl substituents on the morpholine ring positioned nearer to the reaction site, (ii) a pivotal O4···H6 interaction between the developing alkoxide and morpholine, and (iii) C−H···π interaction between the enolate C5−H and the aryl group of the mesitylene moiety. In the most preferred **TS(*re-si*)$_{C2}$**, the mesityl as well as the phenyl groups of the catalyst are found to remain away from the region of the incipient C−C bond formation (Figure 2). A short O4···H6 hydrogen bonding (1.94 Å) as well as a C5−H···π interaction (2.71 Å) renders improved stability to this TS. The higher energy **TS(*si-re*)$_{C6}$** on the other hand, exhibits increased crowding of substituents around the C−C bond, weaker hydrogen bonding (O4···H6, 2.2 Å), and C5−H···π interactions (2.97 Å).

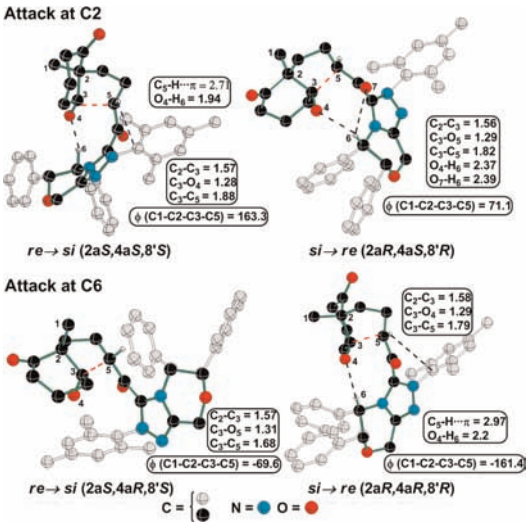

Figure 2. M06-2X/6-31G** geometries of diastereomeric transition states for the C−C bond formation. Bond lengths are given in angstroms and angles in degrees.

As described above, the most preferred aldol cyclization provides a bicyclic alkoxide **6** with a definite configuration of the new chiral centers. Now, a facile intramolecular lactonization via **TS(6−7)** yields another tetrahedral intermediate **7**, which upon the expulsion of the catalyst through **TS(7-NHC)** furnishes the final tricyclic lactone, **8**. The product stereochemistry (2a*S*,4a*S*,8′*S*) is found to be in excellent agreement with the experimental report. The overall formation of the tricyclic lactone is also found to be exergonic by about 21 kcal/mol.

In conclusion, mechanism and stereocontrolling step in a chiral NHC-catalyzed asymmetric desymmetrization of substituted cyclohexyl-1,3-diketone leading to a tricyclic lactone is established using transition-state modeling.

Acknowledgment. Generous computing time from the IIT Bombay computer center is gratefully acknowledged. Y.R. is thankful to Garima Jindal (IIT Bombay) and R. Rajeev (IIT Bombay) for valuable discussions.

Note Added after ASAP Publication. Due to an error the toc/abstract graphic was replaced and reposted May 10, 2012.

Supporting Information Available. Optimized geometries for all stationary points obtained at different levels of theory, total electronic energies etc. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.