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CAMPHOR-BASED α-BROMOKETONES FOR THE ASYMMETRIC DARZENS REACTION: INSIGHTS INTO THE MECHANISM USING DENSITY FUNCTIONAL THEORY

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Density functional theory (DFT) calculations at B3LYP/6-31G(d,p) level were carried out to investigate the mechanism of the reaction of benzaldehyde (**BA**) or acetaldehyde (**AD**) with (1R)-2-endo-bromoacetyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (endo-2-bromoacetyliso-borneol) **1** (Scheme 1). The calculations indicate that the reactions are diastereoselective, in good agreement with the experimental results [1]. Moreover, the calculations show that these reactions proceed via two steps: (1) an aldol-like reaction and (2) the formation of an epoxide. Our calculation study of the transition states demonstrate that the terminal hydroxyl group in compound **1** is vital to the stereoselectivity of the reactions.

K e y w o r d s: DFT, Darzens condensation, benzaldehyde, acetaldehyde, endo-2-bromoacety-lisoborneol, mechanism, transition states, diastereoselectivity, aldol, boat-like, chair-like.
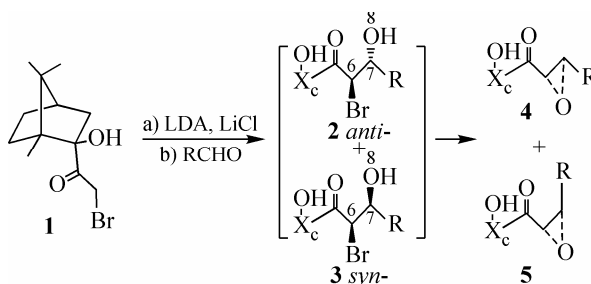
Scheme 1. Darzens Reaction (X_c = camphor substituent; R = Ph or CH_3)

One of the premier topics in modern organic chemistry is asymmetric synthesis [2]. This is a consequence of increasing interest in natural product chemistry and the manufacture of biologically active molecules [3]. Significant progress has been achieved in the development of many aspects of chiral synthesis, but much remains to be done. A major problem is the specificity of synthetic strategies. For example, it is common to find that the degree of asymmetric induction in a particular system is critically dependent on the physical nature of the reagents [4]. Even relatively small changes in their structure have drastic effect on the reaction's products [5]. The development of catalytic carbon-carbon and carbon-oxygen bond-forming reaction is one of the most challenging aspects of organic synthesis [6].

The Darzens condensation reaction represents one of the classical C—C and C—O bond-forming process [1, 7]. It is one of the most potent methodologies for the preparation of epoxy carbonyl com-
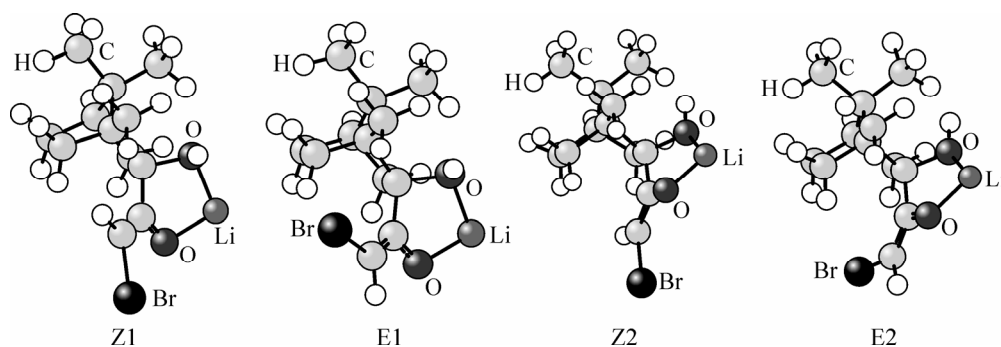
Fig. 1. The complex of Li and compound **1** has four configurations: **Z1**, **Z2**, **E1** and **E2**. The configurations **Z1** and **Z2** are Z enolates. **E1** and **E2** are E enolates. **Z1** and **Z2** as well as **E1** and **E2** differ in the carbonyl orientation in **1**. The energy of **Z2** is 12.2 kJ/mol higher than that of **Z1** and the energy of **E2** is about 18.4 kJ/mol lower than that of **E1**

pounds that have been extensively used in many important syntheses [8]. The first step, the aldol addition reaction, is undoubtedly among the most powerful methods for the formation of carbon-carbon bonds [2, 9] and hydroxy ketones are commonly prepared by an aldol condensation reaction [10] or by reductive cleavage of an epoxy ketone. A number of new methods, including enantioselective and catalytic processes, have been developed as well [9a, b]. In the second step, the epoxide functionality, which affords the chemists an opportunity to manipulate two adjacent functionalized carbons, repeatedly has been demonstrated to be a versatile and useful moiety for organic synthesis [11].

On the basis of Pridgen′s results [12] and those of others [2, 9d, 13—16] to some extent, the following factors govern the energies of the aldol transition states: the steric bulk of the aldehyde [2, 9d, 13], aromaticity [17], Lewis basicity as well as substitution pattern of the aldehyde [18—20], the solvent [9d, 20—23], ligands on the metal countercation [2, 9d, 13, 22, 24—26] and possible secondary molecular orbital interactions [17a, 27]. Although the nucleophilic addition-cyclization process at a carbonyl group has been well documented in the literature [28], a mechanistic route with camphor as a steric component has rarely been studied in calculations. Therefore, in this study, our aim was to investigate the role of the steric bulk of different groups in reactants and to shed light on the mechanistic details of this kind of reaction mechanism. Detailed mechanisms of Darzens Reaction have been discussed [29]. Although many efforts have been performed in recent decades to develop an asymmetric equivalent, there are few examples that proceed catalytically [30]. In this work, we have shown that lithium in LDA plays an important role in the Darzens Reaction.

The stereochemical product of a Darzens reaction is governed by four factors: (1) the E or Z configuration of the enolate; (2) which of the enolate diastereotopic faces reacts; (3) which of the aldehyde enantiotopic faces reacts [31]; (4) the orientation of carbonyl in the compound **1** (Fig. 1). Thus, we chose compound **1**, a camphor ring with three methyl groups and a hydroxyl group, as our chiral auxillary.

COMPUTATIONAL DETAILS

All the calculations of optimizations, frequencies and IRC (intrinsic reaction coordinate) were performed with the DFT method at the B3LYP [32—35] level and 6-31G(*d,p*) basis set implemented in the Gaussian03 suite of programs [36]. Frequency calculations of transition structures were conducted to confirm that there was only unique imaginary frequency. Furthermore, each IRC was traced to verify every transition state connecting the desired reactants and products. Stationary points of reactants and products converged in all cases within the default threshold of force constant and displacement, and their frequencies do not have any imaginary component.

RESULTS AND DISCUSSION

To start the reaction process, a Li atom interacts with the three oxygen atoms of the enolate, carbonyl and hydroxyl yielding an intermediate 1 (**IN1**). Being simultaneously chelated by the three oxy-

gen atoms, the Li atom [31] not only increases the nucleophilicity of C6 and O8, but also strengthens the electrophilicity of C6 and C7 in the two-step reaction process, promoting the formation of the C—C and C—O bonds (for atom numbering see Scheme 1). **IN1** passes transition state 1 (**TS1**) to intermediate 2 (**IN2**). Eventually, the product complex (**PC**) is produced via transition state 2 (**TS2**). We describe eight possible channels for the reaction of **BA** with compound **1** and eight channels for the reaction of **AD** with compound **1**. Each channel corresponds to one of the four enolate configurations **Z1**, **Z2**, **E1** or **E2** (Fig. 1) which produce, as both the *si* and *re* face of the aldehydes can be attacked, eight reacting channels, namely: **Q1**, **Q2**, **Q3**, **Q4**, **Q5**, **Q6**, **Q7** and **Q8** for **BA**+**1** reaction and **T1**, **T2**, **T3**, **T4**, **T5**, **T6**, **T7**, **T8** for **AD**+**1** reaction. To concisely describe the structures of **TSs**, only **Q1**, **Q2**, **Q3**, **Q4** and **T5**, **T6**, **T7**, **T8** reacting channels are presented in Schemes 2 and 3.
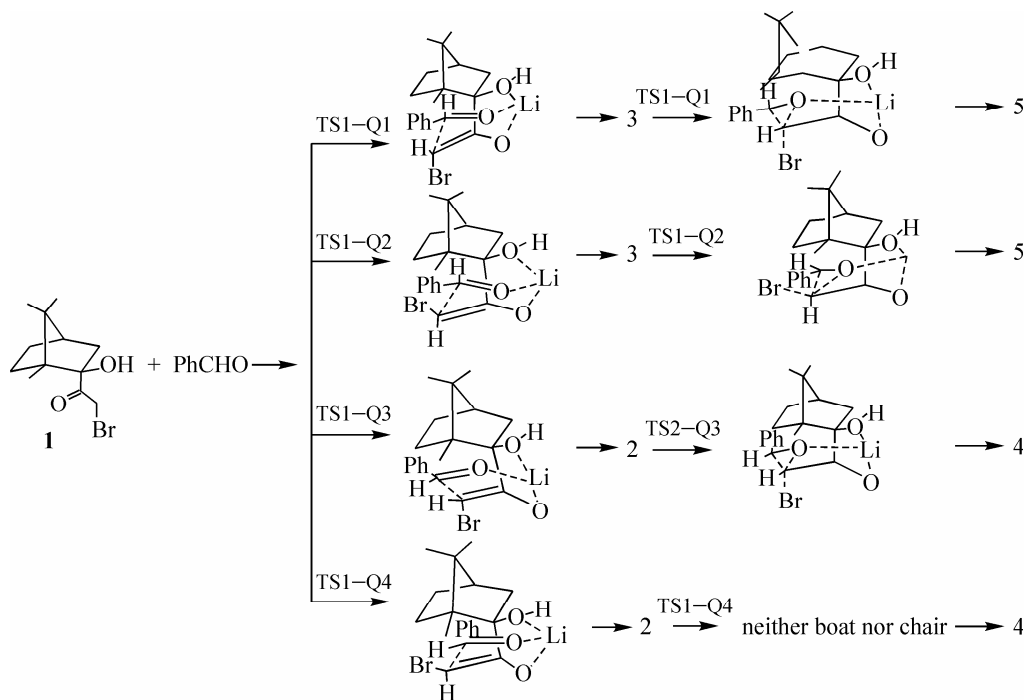
Scheme 2. Four of eight reacting channels for the reaction of **BA** with **1**
(for general formulas of 2—5 see Scheme 1).

The reaction of BA with 1. Over the years, of all the transition states proposed for nucleophilic addition to carbonyls [37—39], the pericyclic Zimmerman-Traxler model has been the most popular and widely applied [39]. This is primarily due to its success as the best available predictive tool for aldol stereoselectivity, particularly when applied to processes where chelated countercations are involved in the addition of enolates (*e.g.* lithium, magnesium, zinc, tin) [9d, 13b, 24] to aldehydes. Lithium enolates are among the most important reagents for carbon-carbon bond formation in organic synthesis, and they have been the subject of numerous theoretical and experimental investigations [40—53].

Table 1 reveals that the activation energy of **TS1—Q3** is 10.3 kJ/mol lower than that of **TS1—Q1**, making **Q3** channel superior to **Q1** channel. This is because **Q3** includes a middle-strength hydrogen bond with bond length of 1.85 Å and bond angle of 131.1°. The activation energy of **TS1—Q4** is 11.5 kJ/mol higher than that of **TS1—Q2** (Table 1). This is because the phenyl group of **TS1—Q4** is located in the axial position, thus 1-methyl and 2-hydroxyl groups repel the phenyl group, giving rise to a stronger steric hindrance than that of **TS1—Q2** in which the phenyl group is located in the equatorial position. Fig. 2 shows the structures of **TS1** and **TS2** for the **Q8** channel. In fact, many aldol reactions are known to proceed through six-center transition states in which the alkyl group of the al-
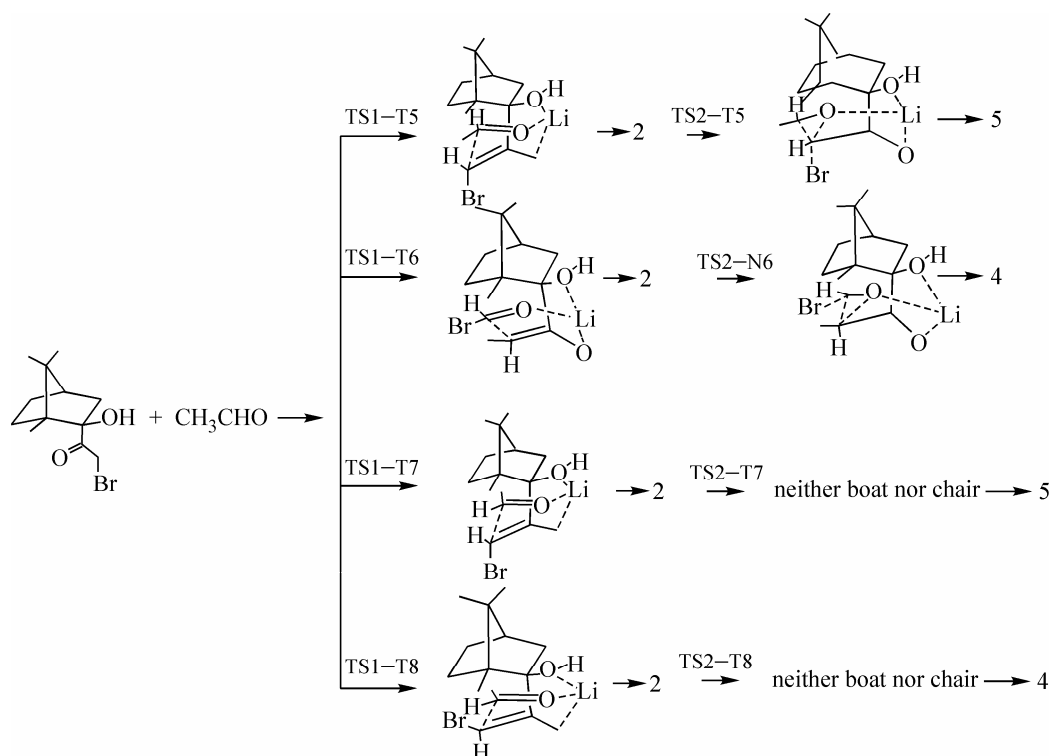
Scheme 3. Four of eight reacting channels for the reaction of **AD** with **1**
(for general formulas of 2—5 see Scheme 1).

T a b l e   1

Activation energies (kJ/mol) *of the sixteen reaction channels studied*

Reaction	TS1	TS2	Reaction	TS1	TS2	Reaction	TS1	TS2	Reaction	TS1	TS2
Q1	72.6	95.0	**Q5**	74.0	35.2	**T1**	71.6	93.6	**T5**	53.6	57.3
Q2	31.4	103.4	**Q6**	30.1	78.1	**T2**	49.6	71.8	**T6**	59.1	51.9
Q3	62.3	71.7	**Q7**	71.5	51.8	**T3**	10.3	105.7	**T7**	11.1	73.3
Q4	42.9	59.9	**Q8**	29.3	52.7	**T4**	28.4	121.4	**T8**	23.4	59.6

hyde preferentially occupies an ″equatorial″ position in the chair-like transition structure [2, 54]. The reaction of a chiral enolate with the aldehyde can produce four diastereomeric aldol products [12]. Activation energies of **TS1—Q5** and **TS1—Q7** are similar (Table 1). Perhaps both transition states are stabilized by hydrogen bonding and the phenyl group is far from 1-methyl and 2-hydroxyl groups in both cases. Finally, **TS1—Q6** and **TS1—Q8** have close activation energies as well.

The second step of the reaction has four diastereomeric products as well. It should be an S_N2 reaction, therefore, the C6 configuration of compound **1** should be inverted, but the second step reaction
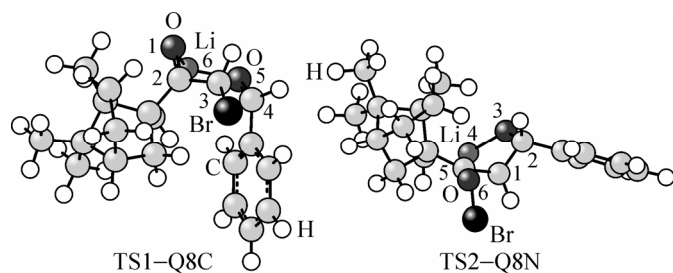

Fig. 2. The two-step transition state structures for **Q8** reacting channel. **C** represents chair; **B** represents boat; **N** represents neither chair nor boat. For example, **TS1—Q8C** represents the first step transition state structure of the **Q8** reacting channel, and it is a chair-like six-membered ring formed by atoms 1, 2, 3, 4, 5 and 6

products of **Q6** and **Q8** actually have the same configurations as the aldol products. Consequently, they may react in a head-on fashion. The activation energy of **TS2—Q1** is 23.4 kJ/mol higher than that of **TS2—Q3**, which indicates that the second step reaction of **Q3** is an easier pathway. It is perhaps because the structure of TS2-Q1 is a six-membered boat-like ring. The phenyl group is located on the axial bond at the front of the boat-like ring. This geometry leads to stronger steric interactions with the oxygen on the other front of the boat, causing the higher activation energy of **TS2—Q1**. The activation energy of **TS2—Q4** is 43.5 kJ/mol lower than that of **TS2—Q2**. This is attributed to **TS2—Q4**, a distorted rather than normal chair, which alleviates steric hindrance. With regard to the transition states of **TS2—Q5** and **TS2—Q7**, the **TS2—Q7** energy is 16.6 kJ/mol higher than that of **TS2—Q5** (Table 1), therefore the second reaction step of **Q5** readily proceeds. The **TS2—Q6** activation energy is about 25.4 kJ/mol higher than that of **TS2—Q8** (Fig. 3). We surmise the twist-boat structure of **TS2—Q6** elevates its energy. According to the calculations, **TS2—Q8** is a ring which has little angle strain or torsion strain.

Based on above analysis, the **Q8** reacting channel is the most energetically favorable and is most likely to be the dominant channel. The energy barrier of **TS1—Q8** (29.3 kJ/mol) is much lower than that of **TS2—Q8** (52.7 kJ/mol), indicating that the second step **TS** is the rate-determining step for the **Q8** reacting channel. In the first step, the attack of **E2** to the *re* face of **BA** yields the complex **IN1— Q8** which is more stable than the reactants. A chair-like six-membered ring transition state, **TS1—Q8**, is then formed with an energy barrier of 29.3 kJ/mol. Afterward, the **IN2—Q8** is formed and it lies 61.50 kJ/mol lower in energy than those of reactants. In the second step, the **IN2—Q8** is transformed to the **PC** via the **TS2—Q8** with an energy barrier of 52.7 kJ/mol. The **PC** is an anti-isomer. These results are in agreement with the experimental results [1]. In fact, by employing lithium as a metal cation chelated by the enolate, predecessors have also yielded predominantly anti isomers with good stereoselectivity in all cases [12].

The reaction of AD with 1. There are eight channels for the reaction of **AD** with **1**. The first step transition states produce four diastereomeric aldol products (see supporting information). High diastereoselectivities have also been attained in aldol reactions using chiral molecules with oxy-function [14c, 31, 55]. The activation energy of **TS1—T2** is 22.1 kJ/mol lower than that of **TS1—T1** (Table 1). This is most likely because **TS1—T2** contains a middle-strength hydrogen bond with bond length of 1.86 Å. **TS1—T4** is a boat-like structure in which **AD'**s methyl group repels 1-methyl group in compound **1**. The activation energy of **TS1—T4** is 18.1 kJ/mol higher than that of **TS1—T3** (Table 1) which has little steric hindrance. The structures of **TS1—T5** (Fig. 4) and **TS1—T6** are chair-like and boat-like frameworks, respectively, and their activation energies are close, the latter only 5.4 kJ/mol higher than that of the former (Fig. 5). We speculate the reason is because the methyl group of the aldehyde is a relatively small group. Furthermore, it is far from the 1-methyl and 2-hydroxyl groups. As for **TS1—T7** and **TS1—T8**, the methyl group in **TS1—T8** lies in an axial position leading to steric constraints with the 2-hydroxyl and camphor groups and this is likely a reason why the acti-
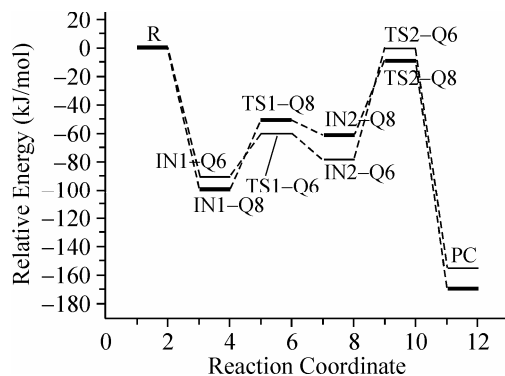

Fig. 3. The potential energy profile for **Q6** and **Q8** reacting channels. The reactants are **E2** and **BA**
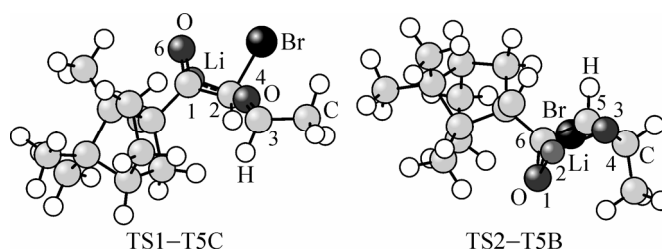

Fig. 4. The two-step transition state structures for **T5** reacting channel
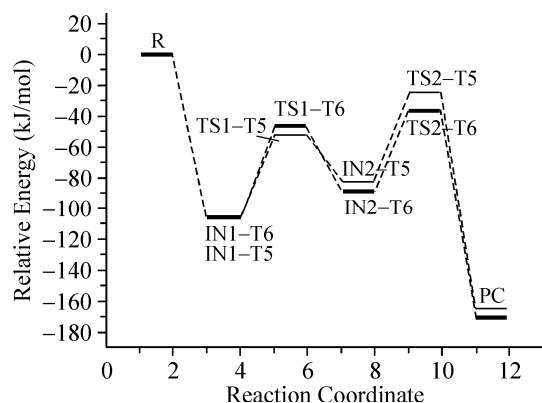
Fig. 5. The potential energy profile for **T5** and **T6** reacting channels. The reactants are **Z2** and **BA**
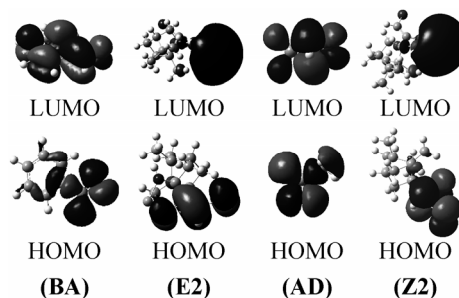

Fig. 6. Frontier molecular orbitals for **BA**, **E2**, **AD** and **Z2**

vation energy of **TS1—T8** is 12.4 kJ/mol higher than that of **TS1—T7** (Table 1). The second step of this reaction gives rise to four diastereomeric products as well. Both **TS2—T5** (Fig. 4) and **TS2—T6** have hydrogen bonds C—H…O on two fronts of the boat. They also have no obvious steric hindrance; therefore, their activation energies are similar, with an activation energy of **TS2—T5** only 5.3 kJ/mol higher than that of **TS2—T6**. Since the methyl group of the aldehyde experiences steric hindrance with the 1-methyl group in compound **1**, the activation energy in **TS2—T7** is 13.7 kJ/mol higher than that in **TS2—T8**.

Based on the above analysis, the **T5** reacting channel is more energetically favorable and is most likely to dominate the reaction. The energy barrier of **T5—TS1** (53.6 kJ/mol) is a little lower than that of **T5—TS2** (57.3 kJ/mol), indicating that **T5—TS2** is the rate-determining step for the **T5** reacting channel. In the first step, the attack of **Z2** to the *re* face of acetaldehyde yields the complex **IN1—T5**. A chair-like six-membered ring **TS1—T5** is then formed with an energy barrier of 53.6 kJ/mol, suggesting that the chair-like **TS** is superior to the boat-like **TS** [1]. Next intermediate produced, **IN2—T5**, is 82.5 kJ/mol lower in energy than that of the reactants. In the second step, the **IN2—T5** intermediate is transformed to the **PC** via **TS2—T5** which has the energy barrier of 57.3 kJ/mol. The **PC** is a *syn*-isomer, in good agreement with the experimental results [1].

Bond lengths, charges in TSs and frontier molecular orbital analysis. Table 2 reveals that the C6—C7 bond lengths for the reaction of **AD** with compound **1** are all longer than those for the reaction of **BA** with **1**. The C6—O8 bond lengths for both reactions range from about 1.62 Å to 2.20 Å in **TS2**. Table 3 shows that C6 is negatively charged, while C7 is positively charged in all **TS1**. This confirms that the two carbons easily react with each other and electrons flow from C6 to C7. Although the charges on C6 for **Q6**, **Q8** and **T7** are negative in **TS2**, the reaction can proceed favorably, because of their O8 possessing a much higher negative charge. Fig. 6 shows that LUMO of the aldehydes and HOMO of **Z2**, **E2** can interact sufficiently. Fig. 7 and Fig. 8 show all orbital energies (HOMO and LUMO) for the reaction. The energies indicate that electrons are donated from HOMO of **Z2**, **E2** to LUMO of the aldehydes. We know from Fig. 6 that these orbitals can overlap significantly; moreover, the lower energy gap (E_{LUMO}—E_{HOMO}) in Fig. 7 and Fig. 8 and Table 3 confirm this conclusion. Re

T a b l e   2

Interatomic distances (Å) C6—C7 *in* **TS1** *and* C6—O8 *in* **TS2** *for each reacting channel*

Reaction	C6—C7	C6—O8	Reaction	C6—C7	C6—O8	Reaction	C6—C7	C6—O8	Reaction	C6—C7	C6—O8
Q1	1.96	1.84	**Q5**	1.89	1.82	**T1**	2.05	1.85	**T5**	1.96	1.82
Q2	1.96	1.81	**Q6**	1.95	2.10	**T2**	2.11	1.85	**T6**	2.01	1.83
Q3	2.05	1.86	**Q7**	1.97	1.83	**T3**	2.07	1.65	**T7**	2.05	2.18
Q4	1.92	1.64	**Q8**	1.96	2.20	**T4**	2.07	1.63	**T8**	2.03	2.20

The Mulliken net charges (e) *on* C6, C7 *in* **TS1** *and* C6, O8 *in* **TS2**

Reaction	C6 (TS1)	C7 (TS1)	C6 (TS2)	O8 (TS2)	Reaction	C6 (TS1)	C7 (TS1)	C6 (TS2)	O8 (TS2)
Q1	−0.24	0.24	0.02	−0.58	**T1**	−0.25	0.27	0.02	−0.59
Q2	−0.24	0.23	0.02	−0.61	**T2**	−0.28	0.28	0.02	−0.60
Q3	−0.26	0.24	0.02	−0.62	**T3**	−0.26	0.28	0.07	−0.58
Q4	−0.24	0.21	0.06	−0.57	**T4**	−0.28	0.28	0.08	−0.58
Q5	−0.23	0.24	0.01	−0.59	**T5**	−0.24	0.27	0.01	−0.59
Q6	−0.24	0.24	−0.08	−0.63	**T6**	−0.28	0.30	0.01	−0.60
Q7	−0.27	0.25	0.01	−0.61	**T7**	−0.26	0.30	−0.07	−0.61
Q8	−0.24	0.20	−0.06	−0.63	**T8**	−0.26	0.27	0.24	−0.60

cently, our group reported the Diels-Alder reactions of *o*-quinone methides and various substituted ethenes and found that the gap between the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) of two reactants is important in predicting the reaction activity [56]. As **Z2**, **E2** with **BA** and **AD** have a lower E_{LUMO}—E_{HOMO} gap, and in conjunction with above activation energy analysis, we determined that **Q8** is the preferred reacting channel for the reaction of **BA** with compound **1**. Meanwhile, **T5** reacting channel is preferred for the reaction of **AD** with compound **1**. In conclusion, we have studied the mechanisms for the two-step reactions of **BA** and **AD** with **1** in detail. Firstly, each reaction have eight possible reacting channels. Each reaction can produce four diastereomeric **PC**. Secondly, all reactions are exothermic [57] which means that lower temperatures favor the reaction. Thirdly, the **Q8** reacting channel is the best for the reaction of **BA** with **1**. Meanwhile, the **T5** reacting channel is the best for the reaction of **AD** with **1**. The second step is the rate-determining step as the activation barriers in the second step for **Q8** and **T5** are higher than those for the first step. Overall, our calculation results are in good agreement with previous experiments and are very useful for the mechanistic study of the asymmetric Darzens reactions.

SUPPORTING INFORMATION

The Cartesian coordinates, energies and imaginary frequencies for all transition states and Cartesian coordiantes, energies for intermediates and product complexes can be obtained from the authors.

Fig. 7. Frontier molecular orbitals for reactions between **BA** and **Z1**, **E1**, **Z2**, **E2**
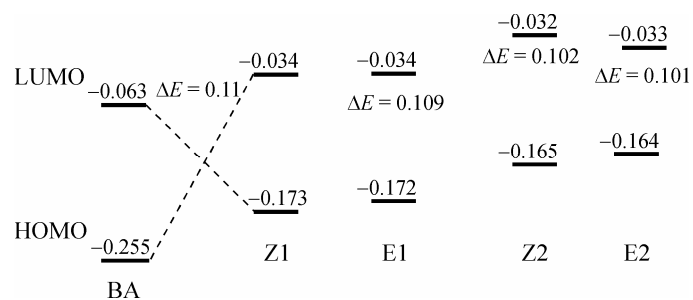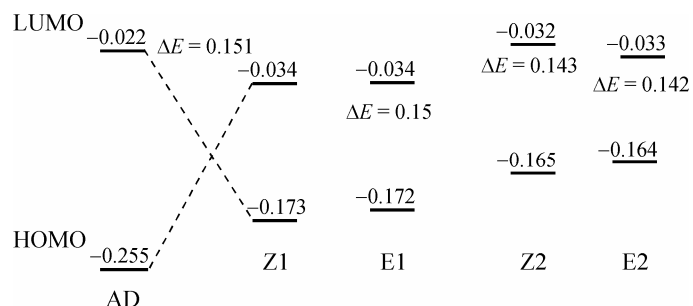

Fig. 8. Frontier molecular orbitals for reactions between **AD** and **Z1**, **E1**, **Z2**, **E2**

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