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Catalysts or Initiators? Beckmann Rearrangement Revisited

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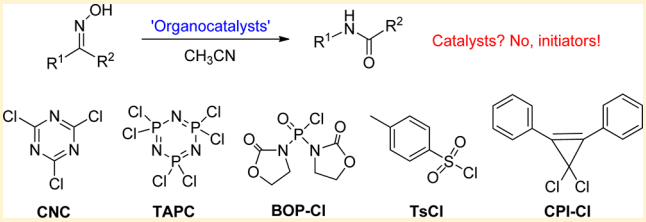
Supporting Information

ABSTRACT: The catalytic mechanism of the organo-mediated Beckmann rearrangement has been modeled using DFT calculations. Five representative promoters were shown to be initiators rather than catalysts. A self-propagating mechanism is shown to be energetically much more favored than the previously proposed mechanisms involving a Meisenheimer complex.



The Beckmann rearrangement (BKR) has been employed successfully in industry, as a powerful tool in organic synthesis for the conversion of cyclohexanone oxime into caprolactam.[1] The conventional BKR, which is catalyzed by strong acids, requires harsh conditions and releases considerable amounts of byproduct.[2] Therefore, mild and efficient organocatalysis of the BKR has been developed to overcome the drawbacks of the conventional BKR.[3−10] Unfortunately, the catalytic mechanisms of these catalysts are poorly understood. Recently, we reported a combined experimental and theoretical study on the mechanism of the BKR catalyzed by *p*-toluenesulfonyl chloride (TsCl),[11] and a novel self-propagating cycle was proposed. In this self-propagating cycle, TsCl does nothing but initializes the BKR by producing the nitrilium cation intermediate, which has shown to be able to catalyze the BKR very efficiently.[11,12] Hence, the role of TsCl was assigned to be an initiator rather than a catalyst.[11,12] In order to test the generality of this self-propagating cycle, we herein report density functional theory (DFT) calculations on the catalytic pathways of five representative organocatalysts of BKR, including TsCl,[3] triphosphazene (TAPC),[4] bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl),[5] cyanuric chloride (CNC),[6] and 3,3-dichloro-1,2-diphenylcyclopropene (CPI-Cl;[7] Scheme 1).

Three different pathways were considered for TsCl, TAPC, BOP-Cl, CNC, and CPI-Cl, using the acetophenone oxime substrate, as illustrated in Schemes 2 and 3. Pathway I is the self-propagating cycle from our previous study;[11] Pathway II, which undergoes a Meisenheimer complex (**TS-4** species), was proposed when the first efficient organocatalyst for the BKR (CNC) was reported;[6] Pathway III is an alternative pathway that undergoes the Meisenheimer complex. Our focus here is whether a Meisenheimer complex is energetically more favored than the self-propagating cycle. The other pathways have been systematically studied and compared in our previous study[11] and thus will not be discussed here.

We first discuss the pathways for TsCl, TAPC, BOP-Cl, and CNC (Scheme 2), because the obtained pathways for CPI-Cl are slightly different from those for the other catalysts (Scheme 3). In the initialization step, the reactant is attached to the catalyst via S_N2-like substitution to give the cationic species **1**. Intermediate **1** may undergo R migration to give **3** + **5** (pathway I and III) or convert to the deprotonated intermediate **2** (pathway II), which further undergoes R migration to give **4**. In pathway I, the nitrilium cation **5** species is able to catalyze the BKR by forming a dimer-like cation species **6**, followed by the R migration of **6** (Scheme 2). Theoretically, once **5** is generated and not quenched by other compounds such as water, the BKR can proceed continuously. In pathway II, the protonated form of **4** (protonated at nitrogen) is attacked by the reactant to give **2** and product. In pathway III, the hydroxyl oxygen of species **3** attacks **5**, followed by deprotonation to give intermediate **4**, which then undergoes reactions similar to pathway II.

Key barriers for different pathways of CNC, TAPC, BOP-Cl, and TsCl are summarized in Table 1, and we here use TsCl as an example to discuss the energy barriers for different pathways (Figure 1). All barrier heights are free energy differences between the turnover frequency-determining intermediates and transition states ($\Delta\Delta G^{\neq 298}_{[\text{TDTS-TDI}]}$), cf. ref 13 for details. For pathway I, after the initialization steps (**R** + **S-0** → **S-TS1**, $\Delta\Delta G^{\neq 298}$ = 28.0 kcal/mol; Figure 1), the reaction enters a self-propagating cycle (**R** + **5** → **7** + **5**), whose barrier height is only 18.1 kcal/mol (Figure 1). For pathway II, both the initialization (**R** + **S-0** → **S-TS2**, $\Delta\Delta G^{\neq 298}$ = 45.5 kcal/mol) and the catalytic cycle (**S-2** → **S-TS2**, $\Delta\Delta G^{\neq 298}$ = 27.0 kcal/mol) are kinetically less favored than for pathway I (Figure 1). For pathway III, although the initialization steps are the same as for pathway I, the catalytic cycle requires higher activation energy (**S-1**→ **S-TS4**, $\Delta\Delta G^{\neq 298}$ = 30.3 kcal/mol). For TAPC, BOP-Cl, and CNC, similar results

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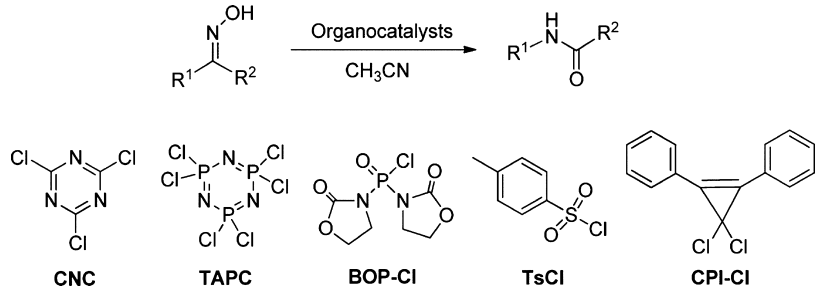
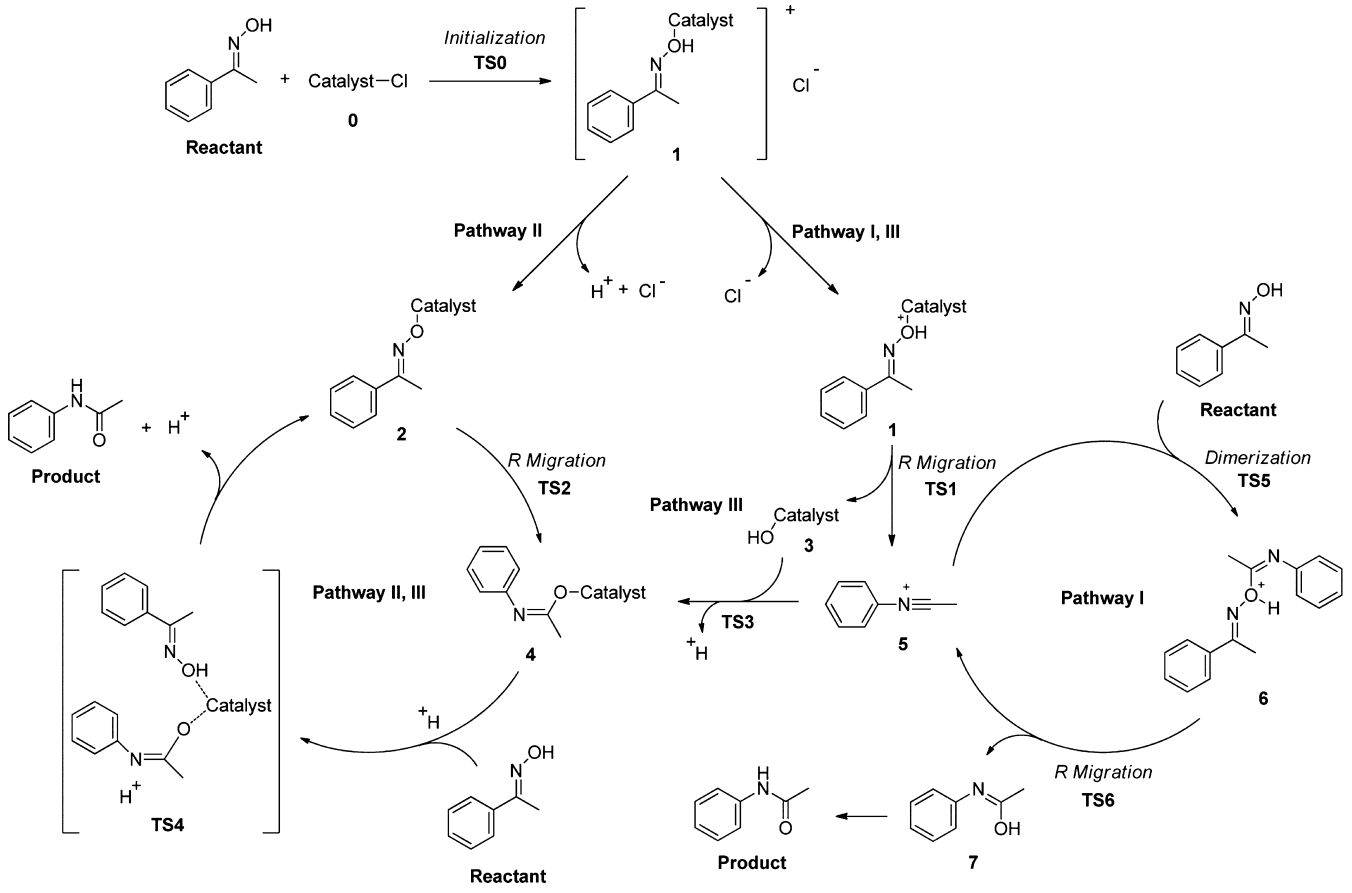
Scheme 1. Organocatalysts of BKR Studied



Scheme 2. Catalytic Pathways for TsCl, TAPC, BOP-Cl, and CNC



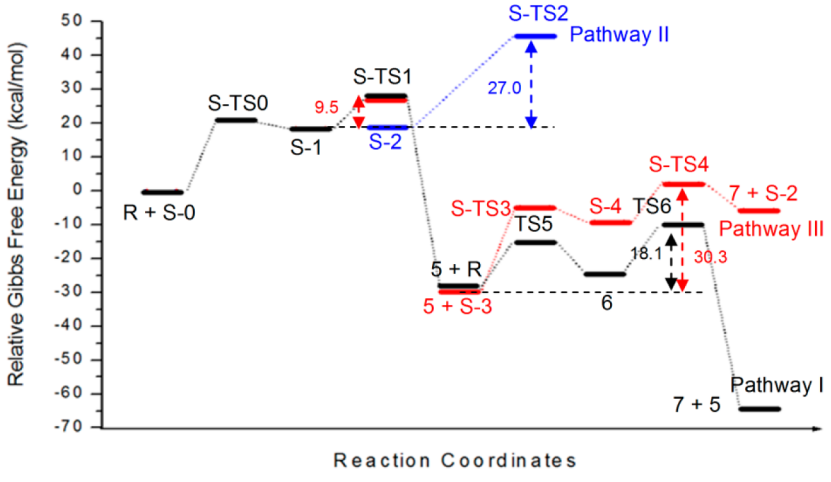


Figure 1. Free energy profiles for the TsCl system. Gibbs free energies are at the M06-2X/6-31+G (d, p) level.

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Scheme 3. Catalytic Pathways for the CPI-Cl System

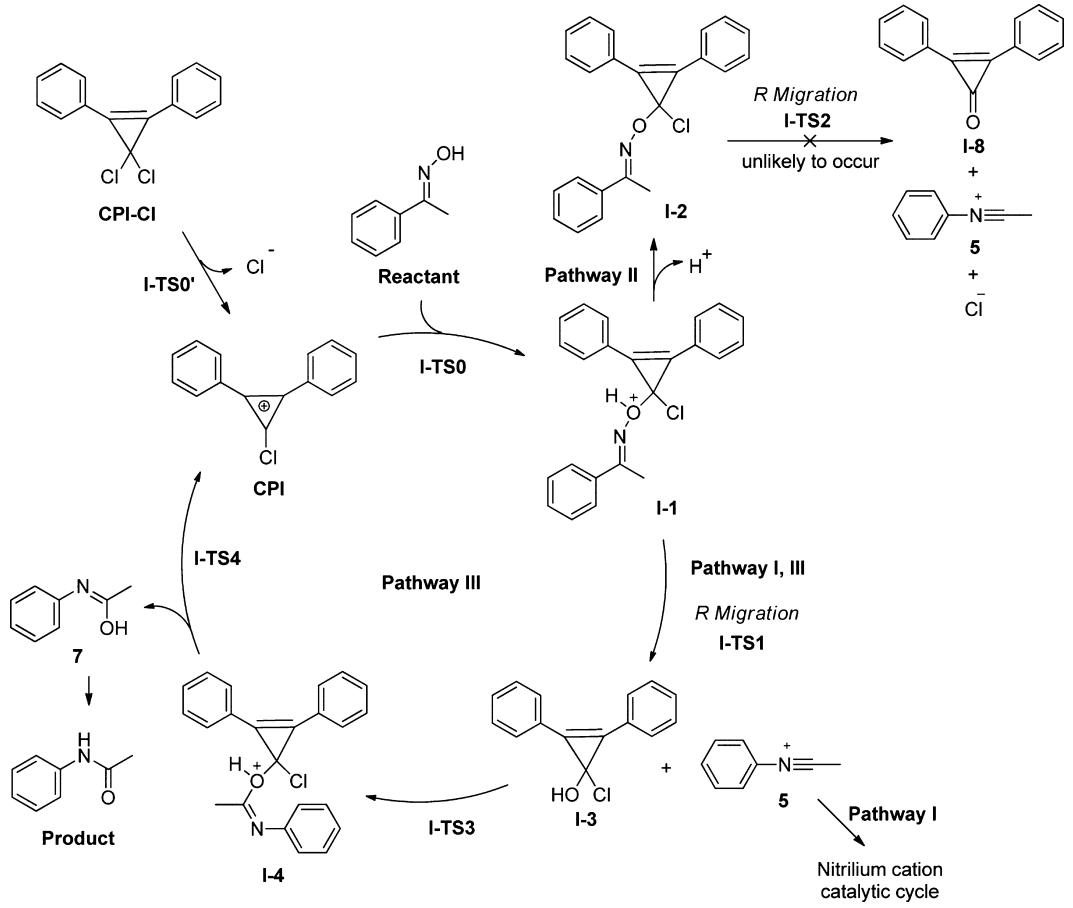

Table 1. Rate-Limiting Barriers of Different Pathways for TsCl, TAPC, BOP-Cl, CNC, and CPI-Cl

	rate-limiting TS[a] (barrier height[b])				
	initialization[c]		catalytic cycle		
catalyst	pathways I, III	pathway II	pathway I	pathway II	pathway III
TsCl	S-TS1 (28.0)	S-TS2 (45.5)	TS6 (18.1)	S-TS2 (27.0)	S-TS4 (30.3)
TAPC	T-TS1 (25.1)	T-TS2 (37.7)	TS6 (18.1)	T-TS2 (25.2)	T-TS4 (27.8)
BOP-Cl	B-TS1 (21.9)	B-TS2 (39.9)	TS6 (18.1)	B-TS2 (27.3)	B-TS3 (22.9)
CNC	C-TS1 (37.2)	C-TS2 (54.9)	TS6 (18.1)	C-TS2 (29.4)	C-TS4 (41.9)
CPI-Cl	I-TS1 (36.5)	I-TS2 (43.1)	TS6 (18.1)	na[d]	I-TS1 (28.7)

[a]Prefix S-, T-, B-, C- and I- were used to distinguish different systems; rate-limiting states were determined by plotting the free energy profiles. For details see Supporting Information S1. [b]Gibbs free energies are at the M06-2X/6-31+G (d, p) level. [c]The steps before entering a cycle, for example, the conversion **R** + **0** → **5** + **3** is the initialization step for pathway I (Scheme 2). [d]Not applicable, cf. Scheme 3.

were obtained (Table 1 and Supporting Information S1). Taken together, our results indicate that pathways II and III are kinetically less favored than pathway I. Hence, we suggest that TsCl, TAPC, BOP-Cl, and CNC are BKR initiators rather than catalysts.

The CPI-Cl system is special, due to the stability of the CPI cation. In the initialization step, CPI-Cl readily loses Cl^- to form CPI, followed by the nucleophilic attack of the reactant hydroxyl, to get **I-1** (Scheme 3). This stepwise process is different from what is observed for the other catalysts, since the corresponding cations are not stable for TsCl, TAPC, BOP-Cl, and CNC. Second, the Meisenheimer complex does not exist in the CPI-Cl system, as R migration of **I-2** forms **5**, **I-8**, and Cl^- (pathway II, Scheme 3), rather than species **4** in Scheme 2. Since **I-8** was not experimentally detected as an intermediate,[7] pathway II is unlikely to occur. In addition, for pathway III, although the rate-limiting barrier for the conversion **5** + **I-3** → **7** + CPI is lower than those for the systems in Scheme 2 ($\Delta\Delta G^{\neq 298}$ = 14.8 kcal/mol versus $\Delta\Delta G^{\neq 298}$ > 20 kcal/mol; Figure 2 and Table 1), the overall rate-limiting barrier for the catalytic cycle of pathway III is still higher than that of pathway I ($\Delta\Delta G^{\neq 298}$ = 28.7 kcal/mol for **R** + CPI → **7** + CPI versus $\Delta\Delta G^{\neq 298}$ = 18.1 kcal/mol for **R** + **5** → **7** + **5**; Figure 2). Therefore, we suggest that the most likely pathway for the CPI-Cl system is pathway I, and CPI-Cl is thus also a BKR initiator rather than a BKR catalyst.

In conclusion, according to our DFT calculations, CNC, TAPC, BOP-Cl, TsCl, and CPI-Cl are likely to catalyze the BKR via the self-propagating pathway I, instead of pathway II or III where a Meisenheimer complex is generated. Hence, we suggest that these "catalysts" are actually BKR initiators.

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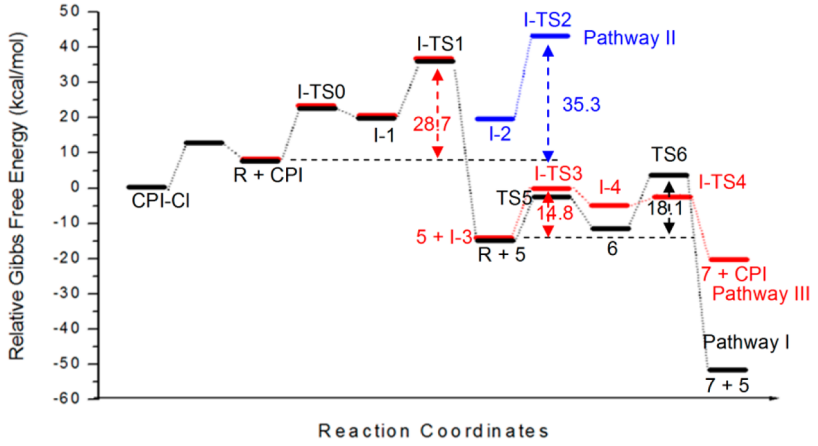

Figure 2. Free energy profiles for the CPI-Cl system. Gibbs free energies are at the M06-2X/6-31+G (d, p) level.

The self-propagating mechanism may in fact be applicable to all organo-mediated BKR, the efficiency of which are thus determined by their initialization steps.

COMPUTATIONAL METHODS

The Gaussian 09 software[14] was used for all the theoretical calculations. Geometry optimizations and frequency calculations were performed at the M06-2X[15]/6-31+G (d,p) level of theory, with inclusion of the IEFPCM[16] implicit solvent model (solvent = CH_3CN). Intrinsic reaction coordinate (IRC) calculations were performed on all transition states to ensure that they connected the correct reactants and products in each step. Explicit solvent molecules (CH_3CN) were included in several systems, so that the reactions involving proton elimination mediated by the solvent molecule can be evaluated. The Cartesian coordinates, energies, and imaginary frequencies can be found in Supporting Information S2.

ASSOCIATED CONTENT

Supporting Information

Free energy profiles for the CNC, BOPCl, and TAPC systems; Cartesian coordinates, energies, and imaginary frequencies for all intermediates and TSs. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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