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Catalytic Diastereoselective Tandem Conjugate Addition–Elimination Reaction of Morita–Baylis–Hillman C Adducts by C–C Bond Cleavage

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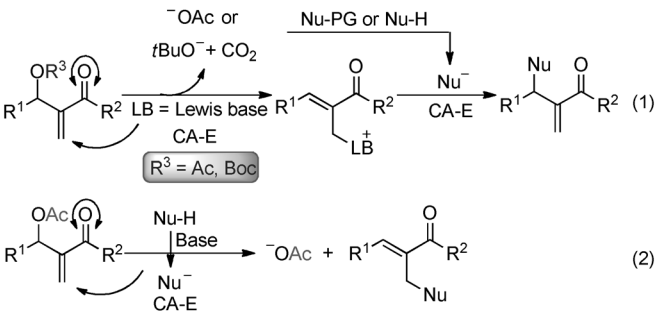
Abstract: Through the cleavage of the C–C bond, the first catalytic tandem conjugate addition–elimination reaction of Morita–Baylis–Hillman C adducts has been presented. Various S_N2'-like C-, S-, and P-allylic compounds could be obtained with exclusive *E* configuration in good to excellent yields. The Michael product could also be easily prepared by tuning the β-C-substituent group of the α-methylene ester under the same reaction conditions. Calculated relative energies of various transition states by DFT methods strongly support the observed chemoselectivity and diastereoselectivity.

Keywords: catalysis · C–C bond cleavage · diastereoselectivity · density functional calculations · Morita–Baylis–Hillman adducts

Introduction

Morita–Baylis–Hillman[1] (MBH) adducts, such as acetates and carbonates are attractive and synthetically interesting compounds owing to their convenient synthesis and modification. For example, the allylic alkylation (AA) reaction of MBH adducts by the catalysis of Lewis bases has been demonstrated to achieve various O-,[2] N-,[3] P-,[4] and C-allylic[5] compounds. As postulated by established mechanisms, the AA reaction could be considered as a double tandem conjugate addition–elimination (CA–E) reaction[6] [Scheme 1, Eq. (1)]. On the other hand, in the presence of Brønsted bases, the CA–E reactions of MBH acetates often afford S_N2'-like allylic alkylation adducts, which contain internal alkenes instead [Scheme 1, Eq. (2)].[7] This class of compound has great commercial potential, especially in the synthesis of N-heterocyclic compounds. To remove acetic acid generated in situ from MBH acetates, the use of stoichiometric or excess base is unavoidable. To the best of our knowledge, the CA–E reaction of MBH carbonates is rare.[8] The main driving force for the CA–E reaction as mentioned in these reports is facile cleavage of the C–O bond. Herein, we wish to report the first catalytic CA–E reaction of MBH C adducts through an intriguing cleavage of the C–C bond to afford various CA–E adducts with excellent yields and diastereoselectivies.



Scheme 1. Proposed mechanism of allylic alkylation (double CA–E) and CA–E of MBH acetates and carbonates. PG = protecting group.

Recently, our research group have developed an enantioselective allylic alkylation of MBH carbonates with bis(phenylsulfonyl)methane (BSM) and fluoro-bis(phenylsulfonyl)-methane (FBSM).[5p] With the removal of sulfonyl groups of AA adducts from the breakage of the C–S bond,[9] various enantiopure β-methyl-γ-monofluoromethyl-substituted alcohols were attained. As the allylic alkylation adducts could also serve as Michael acceptors, we attempted to synthesize chiral γ-amino acids bearing the BSM group. However, when the AA adduct **1a** was treated with 10 mol% 1,1,3,3-tetramethylguanidine[10] (TMG) with CH_3NO_2 as solvent at

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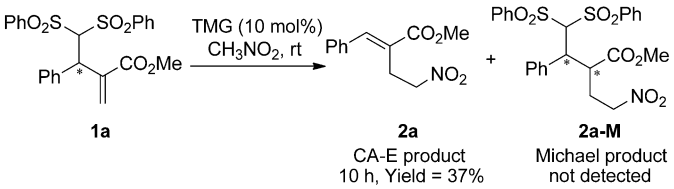
room temperature, the CA–E product **2a** was obtained rather than the desired Michael adduct **2a-M**. This indicates that the BSM group is cleaved in the elimination step through the cleavage of the C–C bond (Scheme 2). Notably,



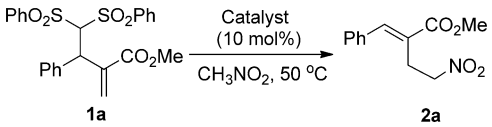
Scheme 2. Initial result of the reaction between **1a** with CH_3NO_2.

in 2010, Mayr and co-workers presented the first example of the C–C bond cleavage of MBH C adducts in a tandem CA–E reaction of allylammonium halides and potassium malonates.[11] On the basis of these results, we were interested in the possibility of developing a catalytic tandem CA–E reaction between the MBH C adducts with different nucleophiles.

Results and Discussion

Preliminary studies with the model substrate **1a** were carried out in neat CH_3NO_2. Initially, we found that the reaction proceeded slowly at room temperature in the presence of 10 mol% TMG. We then examined the catalytic ability of organic Brønsted bases at 50°C (Table 1, entries 1–5), and all reactions were completed in 24 hours with moderate yields except when Et_3N was used (Table 1, entry 4). The best yield was achieved when inorganic base Cs_2CO_3 was used (Table 1, entry 6). Furthermore, the CA–E reaction of

Table 1. Screening studies of the CA–E of **1a** with CH_3NO_2.[a]



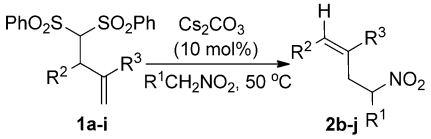
Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]
1	TMG	Neat	24	70
2	DBU	Neat	24	54
3	Et_3N	Neat	24	N.R.[c]
4	Imidazole	Neat	14	72
5	DABCO	Neat	16	65
6	Cs_2CO_3	Neat	24	96
7	Cs_2CO_3	DCE	12	trace
8	Cs_2CO_3	1,4-dioxane	12	82
9	Cs_2CO_3	THF	12	trace
10	Cs_2CO_3	DMF	14	40%

[a] Unless otherwise noted, the reaction was carried out with 0.1 mmol of **1a** in 1.0 mL CH_3NO_2 (neat) or 1.0 mmol of **1a** and 10 mmol CH_3NO_2 in 1.0 mL solvent. [b] Yield of isolated product. [c] N.R. = No reaction. DBU = 1,8-diazabicyclo[5,4,0]undec-7-ene, DABCO = 1,4-diazabicyclo-[2,2,2]octane, DCE = dichloroethane, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide.

1a also formed **2a** when CH_3NO_2 was utilized as a reagent in different solvents (Table 1, entries 7–10). Under these conditions, no Michael adduct **2a-M** was detected. The best-performing solvent with regard to reactivity and yield was 1,4-dioxane (Table 1, entry 8). Under all of the above-mentioned conditions, only the *E* isomer of **2a** was observed.

A wide range of MBH adducts (**1a–i**) and nitroalkanes as C nucleophiles were explored under the optimized neat reaction conditions (Table 2). All reactions completed in

Table 2. Reactions between MBH adducts (**1a–i**) and nitroalkanes.[a]



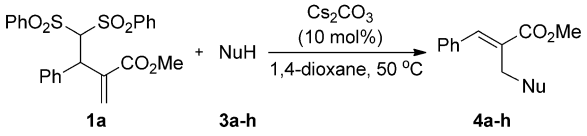
Entry	R^1	R^2	R^3	**1**	**2**	*t* [h]	Yield [%][b]
1	H	4-$CF_3C_6H_4$	$COOCH_3$	**1b**	**2b**	9	96
2	H	2-FC_6H_4	$COOCH_3$	**1c**	**2c**	12	85
3	H	2-ClC_6H_4	$COOCH_3$	**1d**	**2d**	9	89
4	H	4-MeC_6H_4	$COOCH_3$	**1e**	**2e**	12	81
5	H	4-$MeOC_6H_4$	$COOCH_3$	**1f**	**2f**	9	89
6	H	2-naphthyl	$COOCH_3$	**1g**	**2g**	9	89
7	H	C_6H_5	COO*t*Bu	**1h**	**2h**	12	92
8	H	C_6H_5	CN	**1i**	**2i**	12	91
9	CH_3	C_6H_5	$COOCH_3$	**1a**	**2j**	12	89

[a] Unless otherwise noted, the reaction was carried out with 0.1 mmol of **1** in 1.0 mL R^1NO_2. [b] Yield of isolated product.

12 hours and the CA–E products (**2b–j**) with *E* configurations were efficiently synthesized in good to excellent yields (81–96%). The trend in the electronic and steric effects of the substituents on the aromatic ring of the allylic alkylation adducts was not obvious.

To further expand the scope of this protocol, various C-, S-, and P-nucleophiles were investigated (Table 3). The reactions with these nucleophiles were conducted in 1,4-dioxane. Dimethyl malonate (**3a**) as the C nucleophile gave product **3a** in 99% yield after 12 hours (Table 3, entry 1). S nucleo-

Table 3. Reactions between S- and P-nucleophiles (**3a–h**) with **1a**.[a]

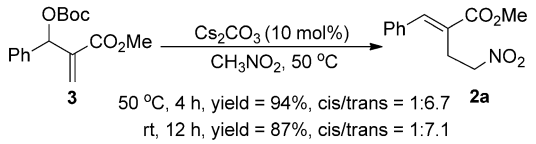


Entry	NuH	**3**	**4**	*t* [h]	Yield [%][b]
1	$CH_2(COOMe)_2$	**3a**	**4a**	12	99[c]
2	PhSH	**3b**	**4b**	13	92
3	BnSH	**3c**	**4c**	13	97
4	EtSH	**3d**	**4d**	13	97
5	*n*PrSH	**3e**	**4e**	12	91
6	*t*BuSH	**3f**	**4f**	13	90
7	$(PhO)_2POH$	**3g**	**4g**	75	81
8	Ph_2POH	**3h**	**4h**	48	N.R.[d]

[a] Reactions were carried out with 1.0 mmol of **1a** and 10 mmol **3a–h** in 1.0 mL 1,4-dioxane. [b] Yield of isolated product. [c] d.r. = 20:1. [d] N.R. = No reaction.

philes, such as aromatic (**3b**), benzyl (**3c**), and aliphatic thiols (**3d–f**), showed relatively higher reactivities and afforded CA–E products (**4b–f**) in excellent yields (90–97%; Table 3, entries 2–6). P nucleophiles, on the other hand, were less reactive. For diphenylphosphite (**3g**), the reaction required 75 hours to afford **4g** in 81% yield (Table 3, entry 7). No reaction occurred for diphenylphosphine oxide (**3h**) (Table 3, entry 8). In all reactions, only the *E*-isomeric products were detected by ^{1}H NMR spectroscopy. It is noteworthy that this is the first integrated report of the CA–E reaction of MBH adducts with various C-, S-, and P-nucleophiles.[7]

As the MBH adducts (**1a–i**) were prepared from the allylic alkylation of MBH carbonates and BSM, it is necessary to investigate the reaction between MBH carbonates and CH_3NO_2. As shown in Scheme 3, the reaction between

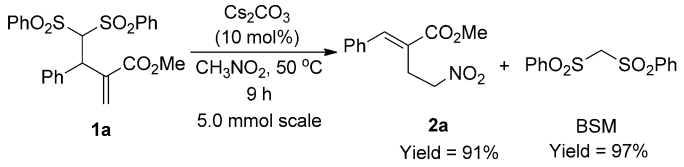


Scheme 3. The CA–E reaction between MBH carbonate **3** with CH_3NO_2.

MBH carbonate **3** and CH_3NO_2 could afford CA–E product **2a** in 4 hours with 94% yield, however, the diastereoselectivty was unsatisfactory even at ambient temperature.

In addition, gram-scale synthesis of **2a** was carried out smoothly under the established reaction conditions in 91% yield (Scheme 4). In this case, BSM was isolated as the only by-product in 97% yield, which could then be recycled to prepare **1a**. Thus, this process is atom-economic.

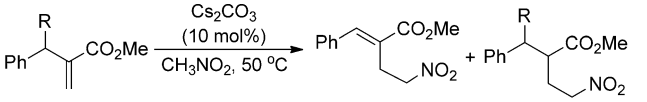
A summary of the results from the examination of various



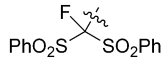
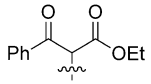
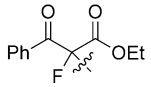
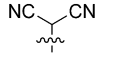
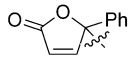
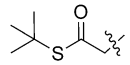
Scheme 4. Gram-scale synthesis of **2a**.

C-allylic alkylation compounds with CH_3NO_2 under the optimized neat reaction conditions is described in Table 4. When the R groups were FBSM (**5a**), ethyl benzylacetate (**5b**), 2-fluoroethyl benzylacetate (**5c**), malonitrile (**5d**), and α,β-butenolide (**5e**)[5g] good to excellent yields of **2a** could be achieved (Table 4, entries 1–5), with no detection of the corresponding Michael adducts (**6a–e**). Interestingly, Chen and co-workers previously reported that the reaction of **5e** and nitromethane catalyzed with TMG in refluxing tetrahydofuran (THF) led to the bis-Michael adduct.[5g] In our reaction system, the Michael adducts **6f/g** could be obtained from **5f/g**, in which the R group substituents were thioalkyl acetate and nitromethane (Table 4, entries 6 and 7). From

Table 4. The reaction between allylic alkylation adducts (**5a–g**) and nitromethane.[a]



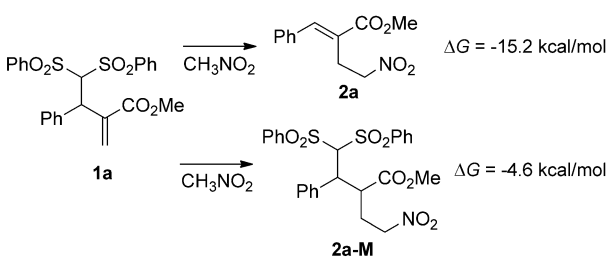
5a-g **2a** Tandem CA-E adduct **6a-g** Michael adduct

Entry	R	5	*t* [h]	Product	Yield [%][b]
1		**5a**	17	**2a**	92
2		**5b**	39	**2a**	84
3		**5c**	39	**2a**	99
4		**5d**	24	**2a**	93
5		**5e**	24	**2a**	89
6		**5f**	24	**6f**	83[c]
7	CH_2NO_2	**5g**	6	**6g**	79[d]

[a] Unless otherwise noted, the reaction was carried out with 0.1 mmol of **2** in 1.0 mL nitromethane **1**. [b] Yield of isolated product. [c] d.r. > 99:1. [d] d.r. = 1:1.

these results, we rationalized that the formation of different product was determined by the anionic stability of the leaving group. This allows for greater tunability and control over the type of product formation by simple alteration of the R group substituent.

Density functional theory (DFT)[12] calculations were performed to provide an explanation for the formation of the observed products. Preliminary calculations in the gas phase revealed that the product **2a** was more stable than the product **2a-M** by a significant energy difference of 10.6 kcal mol^{-1} (Scheme 5). In addition, by comparison of the energies of the *cis* and *trans* conformers of **2a**, it was found that the *trans* isomer was 2.6 kcal mol^{-1} more stable than the *cis* isomer. Cs_2CO_3 and substrate **2a** were then selected for the modeling of the reaction profile using nitromethane as the solvent (neat conditions) as Cs_2CO_3 gave the best yield among all catalysts screened (Figure 1). It is conceivable



Scheme 5. DFT calculation of the free energies of the CA–E reaction and Michael addition between **1a** and nitromethane.

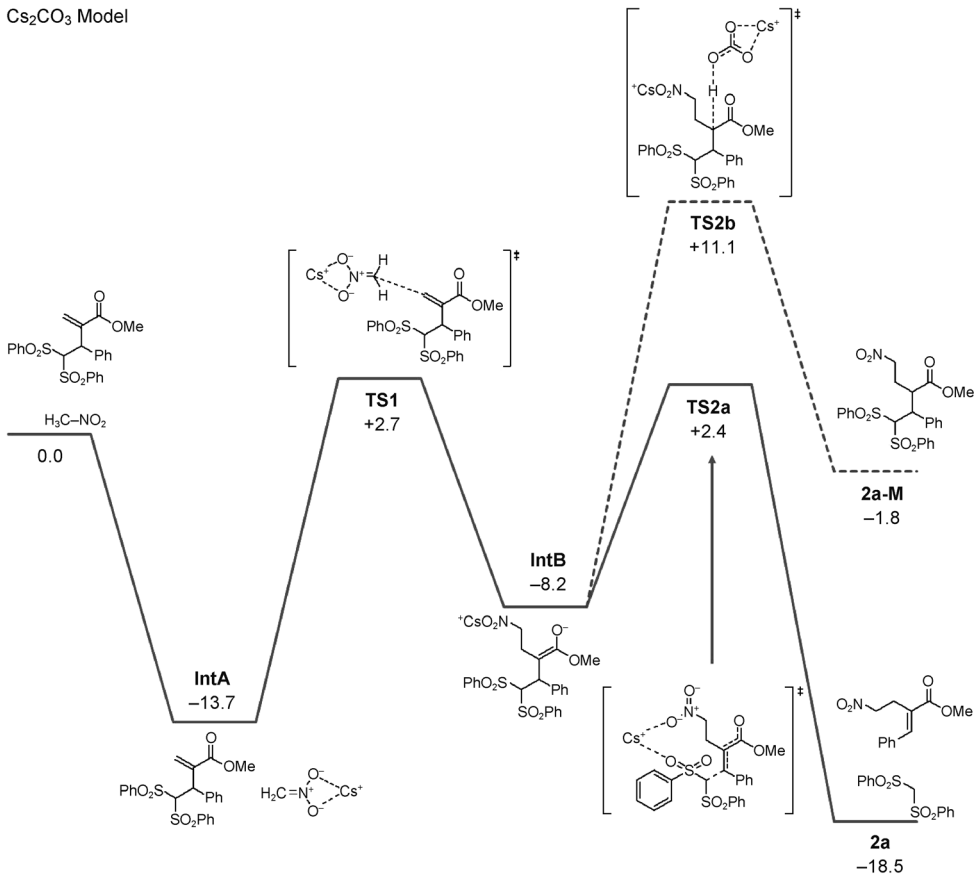


Figure 1. Reaction profile for the CA–E reaction catalyzed by Cs_2CO_3. Relative free energies of possible intermediates and transition states are shown.

that Cs_2CO_3 initially abstracted a proton from nitromethane to form a Cs^+-stabilized nitronate anion **IntA**. Subsequent nucleophilic Michael addition of the nitronate to the α,β-unsaturated ketone substrate generated intermediate **IntB** via transition state **TS1**, thereby overcoming an activation barrier of 15.4 kcal mol^{-1}. The reaction might proceed through two pathways: 1) protonation and tautomerization to form the ketone product **2a-M** through **TS2b**, and 2) elimination of a BSM molecule to form **2a** through **TS2a**. Based on the calculated result, the former pathway will need to overcome a higher overall activation barrier of 19.3 kcal mol^{-1} while the latter one requires a lower barrier of 10.6 kcal mol^{-1}. The second pathway will be both the kinetically and thermodynamically preferred course owing to the lower activation barrier and the formation of the more stable product.[13]

In addition, modeling was also performed using CO_3^{2-} (Figure 2). The CO_3^{2-} modeling profile showed an even more pronounced energy difference and preference for the formation of **2a** over **2a-M**. The activation barrier for the **TS2a** was only 7.1 kcal mol^{-1}, compared to that of **TS2b**, which was a staggering 25.0 kcal mol^{-1}.[13]

In summary, we have reported an unusual catalytic diastereoselective CA–E reaction of MBH C adducts through the cleavage of a C–C bond. A series of C-, S-, and P-allylic compounds with inner alkenes have been synthesized in high yields and diastereoselectivities. From a green chemistry standpoint, this is an atom-economic methodology. Based on our established protocol, we can synthesize S_N2'-like allylic alkylation or Michael products by simply tuning the β-C-substituent groups of α-methylene esters under the same reaction conditions. Quantum modeling revealed that the CA–E reaction from the cleavage of the C–C bond with BSM as a leaving group is both the thermodynamically and kinetically favored pathway. Further development on this system is currently ongoing in our laboratories.

Experimental Section

*Typical Experimental Procedure for the Reaction between MBH Adduct **1a** in CH_3NO_2 Catalyzed by Cs_2CO_3*

1a (47 mg, 0.1 mmol, 1.0 equiv) and Cs_2CO_3 (3.3 mg, 0.01 mmol, 0.1 equiv) were dissolved in nitromethane (1.0 mL). The reaction mixtures were stirred at 50 °C and monitored by TLC. Upon complete consumption of **1a**, the reaction mixtures were directly loaded onto a short silica-gel column, followed by gradient elution with a PE/EtOAc mixture (15:1–10:1). Removing the solvent in vacuo afforded products **2a** (22.6 mg, 96 % yield).

*Typical Experimental Procedure for the Reaction between MBH Carbonate **1a** and CH_3NO_2 in 1,4-Dioxane Catalyzed by Cs_2CO_3*

1a (47 mg, 0.1 mmol, 1.0 equiv), nitromethane (61 mg, 1.0 mmol, 10.0 equiv), and Cs_2CO_3 (3.3 mg, 0.01 mmol, 0.1 equiv) were dissolved in 1,4-dioxane (1.0 mL). The reaction mixtures were stirred at 50 °C and monitored by TLC. Upon complete consumption of **1a**, the reaction mixtures were directly loaded onto a short silica-gel column, followed by gradient elution with a PE/EtOAc mixture (15:1–10:1). Removing the solvent in vacuo afforded products **2a** (19.2 mg, 82 % yield).

*Compound **2a**[7o]*

Colorless oil, 96 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1H), 7.45–7.36 (m, 3H), 7.32 (d, J = 7.2 Hz, 2H), 4.58 (t, J = 7.7 Hz, 2H), 3.85 (s, 3H), 3.26 ppm (t, J = 7.7 Hz, 2H).

*Compound **2b***

Colorless oil, 96 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 4.60 (t, J = 7.3 Hz, 2H), 3.87 (s, 3H), 3.19 ppm (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 141.8, 138.1, 131.0, 130.7, 128.9, 128.8, 125.8 (three peaks), 125.7, 125.1, 122.4, 73.5, 52.5, 25.8 ppm; LRMS (ESI): m/z: 326.3 [M+Na$^+$]; HRMS (ESI): m/z: 326.0611 [M+Na$^+$], calcd for $C_{13}H_{12}F_3O_4NNa$ 326.0622.

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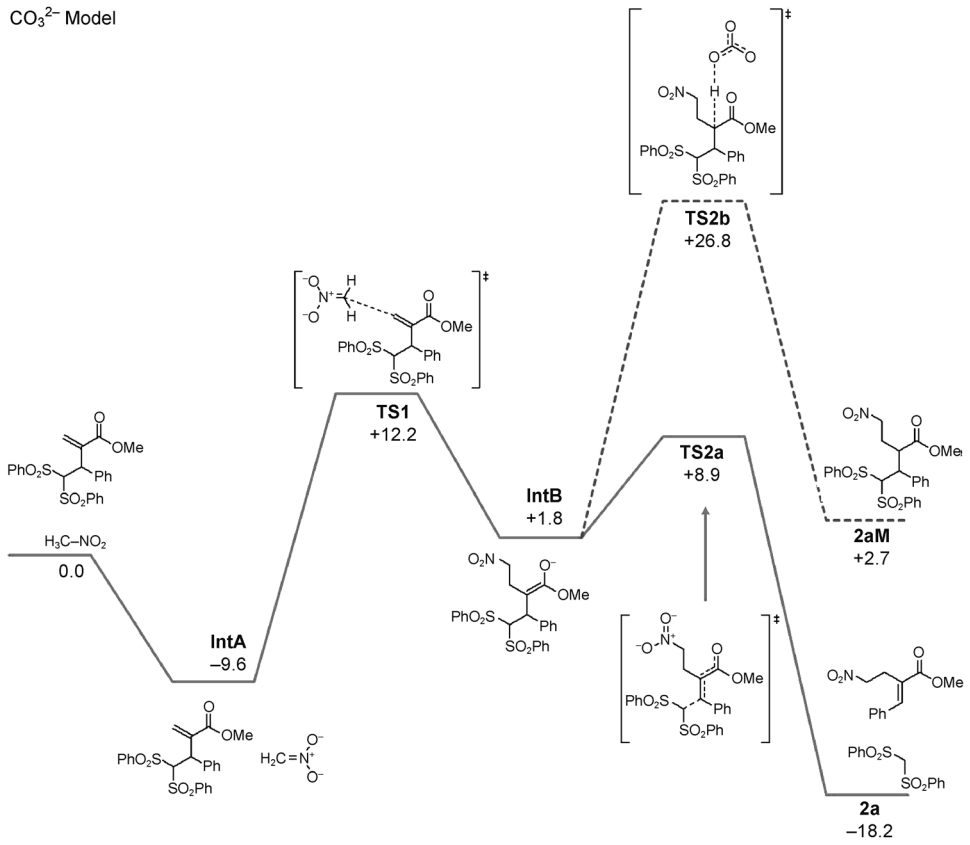

Figure 2. Reaction profile for the CA–E reaction catalyzed by CO_3^{2-}. Relative free energies of possible intermediates and transition states are shown.

Compound ***2 c***[7o]

Colorless oil, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 8.2 Hz, 2H), 4.58 (t, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.23 ppm (t, J = 7.5 Hz, 2H).

Compound ***2 d***[7o]

Colorless oil, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 1H), 7.46–7.44 (m, 1H), 7.34–7.31 (m, 2H), 7.20–7.18 (m, 1H), 4.55 (t, J = 7.4 Hz, 2H), 3.87 (s, 3H), 3.08 ppm (t, J = 7.4 Hz, 2H).

Compound ***2 e***[7o]

Colorless oil, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 1H), 7.24 (s, 4H), 4.58 (t, J = 7.8 Hz, 2H), 3.84 (s, 3H), 3.27 (t, J = 7.8 Hz, 2H), 2.38 ppm (s, 3H).

Compound ***2 f***[7o]

Colorless oil, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1H), 7.33 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.59 (t, J = 7.8 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.20 ppm (t, J = 7.8 Hz, 2H).

Compound ***2 g***

White solid, M.p. 79.4–81.2 °C; 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.90–7.83 (m, 4H), 7.56–7.51 (m, 2H), 7.43 (dd, J = 1.6, 10.1 Hz, 1H), 4.64 (t, J = 7.7 Hz, 2H), 3.88 (s, 3H), 3.35 ppm (t, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 143.4, 133.3, 133.1, 131.8, 128.9, 128.6, 128.4, 127.7, 127.2, 126.8, 126.6, 125.9, 73.7, 52.4, 26.0 ppm; LRMS (ESI): m/z: 308.0 [M+Na^+]; HRMS (ESI): m/z: 308.0893 [M+Na^+], calcd for $C_{16}H_{15}O_4NNa$ 308.0904.

Compound ***2 h***[7o]

Colorless oil, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1H), 7.44–7.29 (m, 5H), 4.57 (t, J = 7.6 Hz, 2H), 3.20 (t, J = 7.6 Hz, 2H), 1.56 ppm (s, 9H).

Compound ***2 i***

Colorless oil, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.72 (m, 2H), 7.44–7.43 (m, 3H), 7.09 (s, 1H), 4.69 (t, J = 6.7 Hz, 2H), 3.11 ppm (t, J = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 132.7, 130.9, 129.0, 128.9, 117.4, 104.6, 72.8, 33.6 ppm; LRMS (EI): m/z: 202.1 [M^+]; HRMS (EI): m/z: 202.0742 [M^+], calcd for $C_{11}H_{10}O_2N_2$ 202.0748.

Compound ***2 j***[7i]

Colorless oil, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1H), 7.43 –7.34 (m, 3H), 7.29 (d, J = 7.0 Hz, 2H), 4.93–4.88 (m, 1H), 3.85 (s, 3H), 3.26 (dd, J = 8.0, 14.2 Hz, 1H), 2.96 (dd, J = 6.4, 14.2 Hz, 1H), 1.47 ppm (d, J = 6.4 Hz, 3H).

Compound ***4 a***

Colorless oil, 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 1H), 7.41–7.30 (m, 5H), 3.82 (s, 3H), 3.76 (t, J = 7.9, 1H), 3.60 (s, 6H), 3.21 ppm (d, J = 7.8, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 167.9, 142.2, 134.9, 129.0, 128.7, 128.6, 128.5, 52.4, 52.2, 50.3, 26.2 ppm; LRMS (EI): m/z: 306.1 [M^+]; HRMS (EI): m/z: 306.1101 [M^+], calcd for $C_{16}H_{18}O_6$ 306.1103.

Compound ***4 b***[7p]

Colorless oil, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (s, 1H), 7.42–7.33 (m, 7H), 7.25–7.20 (m, 2H), 4.05 (s, 2H), 3.82 ppm (s, 3H).

Compound ***4 c***

Colorless oil, 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (s, 1H), 7.46–7.44 (m, 2H), 7.37–7.26 (m, 8H), 3.87 (s, 3H), 3.79 (s, 2H), 3.62 ppm (s, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 140.6, 138.1, 134.7, 129.6, 129.0, 128.8, 128.5, 128.3, 126.8, 52.1, 37.2, 28.4 ppm; LRMS (EI): m/z: 298.1 [M^+]; HRMS (EI): m/z: 298.1025 [M^+], calcd for $C_{18}H_{18}O_2S$ 298.1028.

Compound ***4 d***

Colorless oil, 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (s, 1H), 7.50 (d, J = 7.4 Hz, 2H), 7.41 (t, J = 7.0 Hz, 2H), 7.35 (d, J = 7.2 Hz, 1H), 3.85 (s, 3H), 3.66 (s, 2H), 2.56 (q, J = 11.1 Hz, 2H), 1.19 ppm (t, J = 7.4 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 140.3, 129.6, 129.5, 128.8, 128.5, 52.2, 28.2, 26.8, 14.6 ppm; LRMS (ESI): m/z: 236.8; HRMS (ESI): m/z: 237.0944 [M+H]$^+$, calcd for $C_{13}H_{17}O_2S$ 237.0942.

Compound ***4 e***

Colorless oil, 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (s, 1H), 7.50 (d, J = 7.3 Hz, 2H), 7.41 (t, J = 7.0 Hz, 2H), 7.36 (d, J = 7.1, 1H), 3.85 (s, 3H), 3.64 (s, 2H), 2.51 (t, J = 7.2 Hz, 2H), 1.58–1.49 (m, 2H), 0.92 ppm (t, J = 7.3 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 140.3, 135.0, 129.7, 129.5, 128.8, 128.6, 52.2, 34.9, 28.5, 22.8, 13.4; LRMS

(ESI) m/z 250.9 ppm; LRMS (ESI): m/z: 250.1 [M^+]; HRMS (EI): m/z: 250.1030 [M^+], calcd for $C_{14}H_{18}O_2S$ 250.1028.

*Compound **4f***

Colorless oil, 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1H), 7.61 (d, J = 7.3 Hz, 2H), 7.43–7.35 (m, 3H), 3.84 (s, 3H), 3.66 (s, 2H), 1.37 ppm (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 141.0, 135.0, 129.6, 128.9, 128.5, 128.1, 52.2, 43.2, 30.6, 25.9 ppm; LRMS (EI): m/z: 264.1 [M^+]; HRMS (EI): m/z: 264.1188 [M^+], calcd for $C_{15}H_{20}O_2S$ 264.1184.

*Compound **4g***

Colorless oil, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 5.7 Hz, 1H), 7.59 (d, J = 6.8 Hz, 2H), 7.41–7.35 (m, 3H), 7.30–7.26 (m, 4H), 7.16–7.11 (m, 6H), 3.79 (s, 3H), 3.59 ppm (d, J = 22.6 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 150.4, 150.3, 142.8, 142.7, 134.5 (two peaks), 129.6, 129.3 (two peaks), 129.1, 128.7, 125.0, 122.8, 122.7, 120.4, 120.3, 52.4, 27.5, 26.0 ppm, ^{15}P NMR (162 MHz, $CDCl_3$): δ = 18.7 ppm; LRMS (EI): m/z: 408.1 [M^+]; HRMS (ESI): m/z: 408.1133 [M^+], calcd for $C_{23}H_{21}O_5P$ 408.1127.

*Compound **6f***

Colorless oil, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (t, J = 7.0 Hz, 2H), 7.25–7.23 (m, 1H), 7.13 (d, J = 7.1 Hz, 2H), 4.32–4.18 (m, 2H), 3.75 (s, 3H), 3.50–3.44 (m, 1H), 2.81–2.75 (m, 3H), 2.05–1.96 (m, 2H), 1.30 ppm (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6, 173.6, 139.2, 128.8, 128.0, 127.5, 73.1, 52.2, 48.5, 48.2, 47.6, 44.4, 29.6, 27.3 ppm; LRMS (EI): m/z: 367.1; HRMS (EI): m/z: 367.1458, calcd for $C_{18}H_{25}NO_5S$ 367.1453.

*Compound **6g***

Colorless oil, 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.31 (m, 3H), 7.20–7.09 (m, 2H), 4.94–4.80 (m, 1H), 4.67 (dd, J = 7.3, 2.8 Hz, 1H), 4.47–4.25 (m, 2H), 3.84–3.78 (m, 1H), 3.69 (d, J = 57.7, 3H), 2.94–2.84 (m, 1H), 2.27 −2.21 (m, 1H), 2.11–2.03 ppm (m, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 171.7, 135.9, 135.4, 129.4, 129.1, 128.7, 128.6, 127.9, 127.8, 78.3, 77.2, 73.0, 72.6, 52.5, 52.2, 45.7 (two peaks), 45.4, 45.2, 27.4, 27.1 ppm; LRMS (EI): m/z: 296.6; HRMS (EI): m/z: 296.1012, calcd for $C_{13}H_{16}N_2O_6$ 296.1008.

Density Functional Theory Calculation Perimeters

All intermediates and transition state geometries were optimized at the B3LYP level of theory[14] using 6–31G(d) and 6–31+G(d) Pople basis sets[15] for the Cs_2CO_3 and CO_3^{2-} models, respectively, with Polarizable Continuum Model (PCM) utilizing the integral equation formalism variant (IEF) as the Self-Consistent Reaction Field (SCRF)[16] with nitromethane as the solvent. This was achieved by employing the Gaussian 09 program. In addition, the LANL2DZ effective core potential (ECP) of Hay and Wadt was applied for Cs.[17]

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