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ORCID® iDs	Naoki Kise - https://orcid.org/0000-0002-2366-3953

Electroreductive coupling of 2-acylbenzoates with α,β-unsaturated carbonyl compounds: density functional theory study on product selectivity

Naoki Kise* and Toshihiko Sakurai

Address: Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101, Koyama-cho Minami, Tottori 680-8552

Email: Naoki Kise* - kise@tottori-u.ac.jp

* Corresponding author

Abstract

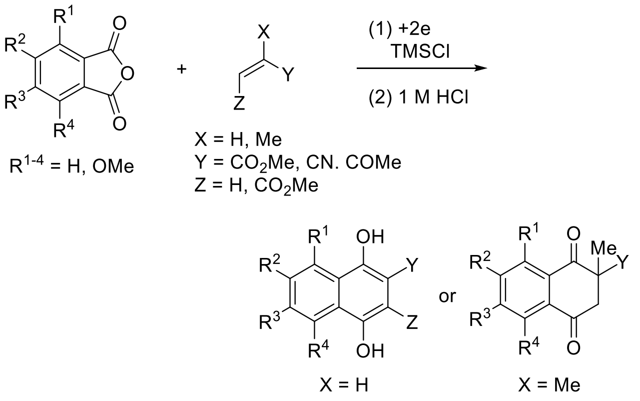
The electroreductive coupling of 2-acylbenzoates with acrylonitrile in the presence of TMSCl and successive treatment with 1 M HCl gave 2-cyanonaphthalen-1-ols or 3-(3-cyanoethyl)phthalides. On the other hand, the reaction of 2-acylbenzoates with methyl vinyl ketone under the same conditions produced 3-(3-oxobutyl)phthalides as the sole products. What determines the product selectivity was studied using the DFT calculations.

Keywords

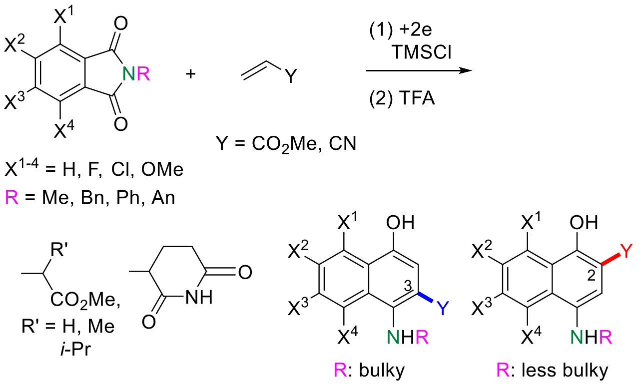
2-acylbenzoates; chlorotrimethylsilane; 3-(3-cyanoethyl)phthalides, 2-cyanonaphthalen-1-ols; electroductive coupling

Introduction

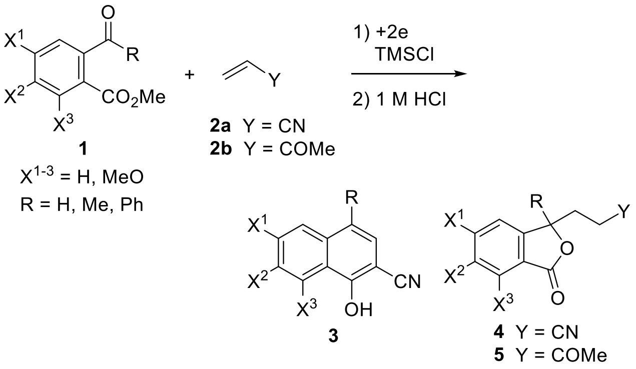
Electroreductive coupling between carbon-hetero atom and carbon-carbon double bonds is one of the promising methods for carbon-carbon formation [1-4]. Recently, we reported the electroreductive coupling of phthalic anhydrides with α,β-unsaturated carbonyl compounds in the presence of chlorotrimethylsilane (TMSCl) and subsequent treatment with 1 M HCl gave 1,4-dihydroxynaphthalenes and 2-methyl-2,3-dihydronaphthalene-1,4-diones (Scheme 1) [5]. In addition, we disclosed that the electroreduction of phthalimides with α,β-unsaturated carbonyl compounds under the same conditions and subsequent treatment with trifluoroacetic acid (TFA) produced 3- and 2-substituted 4-aminonaphthalen-1-ols (Scheme 2) [6]. In this context, we report here that the electroreduction of *o*-acylbenzoates **1** with acrylonitrile (**2a**) in the presence of TMSCl and subsequent treatment with 1 M HCl gave 2-cyanonaphthalen-1-ols **3** or 3-(3-cyanoethyl)phthalides **4** (Scheme 3). The product selectivity depended on the position of the methoxy substituents on the aromatic ring in **1**. On the other hand, 3-(3-oxobutyl)phthalides **5** were obtained by the reaction of **1** with methyl vinyl ketone (**2b**)c as the sole products (Scheme 3). The synthesis of naththalene-1-ols [7-9] and 3-substituted phthalides [11-16] is attracting much attention, since bioactive compounds possessing these structures are known. This method has the potential to be applied to synthesize bioactive 2-cyanonaphthalen-1-ols [8,9] and 3-substituted phthalides [12-16]. Reaction mechanisms of the electroreductive coupling of **1** with **2** and subsequent rearrangement to **3** were also discussed. In particular, the latter mechanism was studied using density functional theory (DFT) calculations and it was suggested that the ΔG for the cyclization step of intermediate enolate anion determines the product selectivity.



Scheme 1: Electroreductive coupling of phthalic anhydrides with α,β-unsaturated carbonyl compounds and subsequent treatment with 1 M HCl (Previous work).



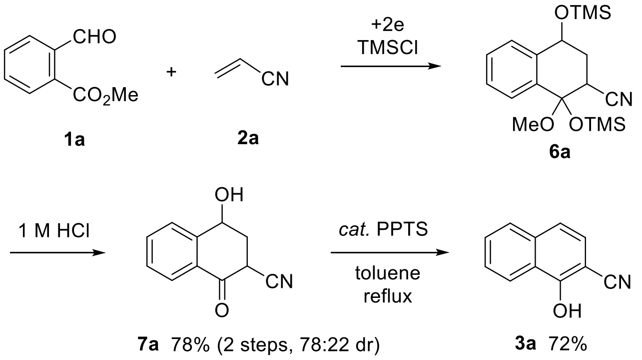
Scheme 2: Electroreductive coupling of phthalimides with α,β-unsaturated compounds and subsequent treatment with TFA (Previous work).



Scheme 3: Electroreductive coupling of 2-acylbenzoates with α,β-unsaturated carbonyl compounds and subsequent treatment with 1 M HCl (This work).

Results and Discussion

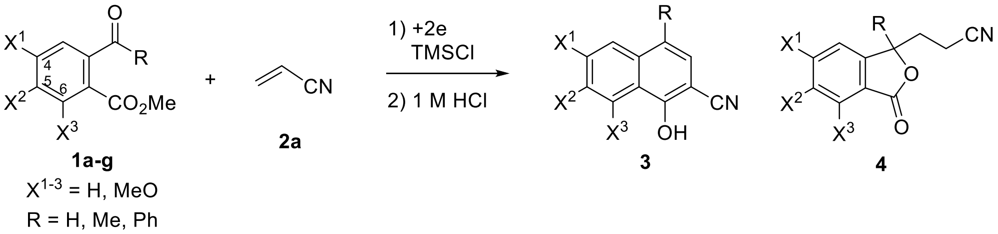
The electroreduction of methyl 2-formylbenzoate (**1a**) with **2a** was carried out in 0.3 M Bu_4NClO_4/THF in the presence of TMSCl at 0.1 A (2.5 *F*/mol). From the crude product, cyclized product **6a** was obtained by column chromatography as a complex mixture of stereoisomers. Since **6a** could not be purified, it was treated with 1 M HCl/dioxane (1:1) at 25 °C for 1 h to give desilylated **7a** in 78% yield (2 steps) as a mixture of two diastereomers (78:22 dr). Dehydration of **7a** in refluxing toluene in the presence of *cat.* PPTS produced 2-cyanonaphthalene-1-ol (**3a**) in 72 % yield (Scheme 4).



Scheme 4: Electroreductive coupling of **1a** with **2a** and subsequent transformation to **3a**.

Next, the crude products of the electroreduction of methyl 2-acylbenzoates **1a-h** with **2a** were successively treated with 1 M HCl/dioxane (1:1) at 25 °C for 1 h and the results are summarized in Table 1. Dehydrated 2-cyanonathlalene-1-ols **3b-d,g** were obtained only by treatment with 1 M HCl without dehydration in refluxing *cat.* PPTS/toluene (entries 2-4 and 7). From 5,6-dimethxy substrate **1d**, phthalide **4d** was also formed together with **3d** (entry 4). In contrast, phthalides **4e,f** were sole products in the reactions of 6-methoxy and 4,5,6-trimethoxy substrates **1e,f** (entries 5 and 6). In the reaction of methyl 2-benzoylbenzoate (**1h**), simply reduced product, 3-phenylphthalide, was formed mainly in 46% yield with phthalide **4h** (24% yield) (entry 8).

Table 1: Electroreductive coupling of **1a-g** with **2a** and subsequent treatment with 1 M HCl.

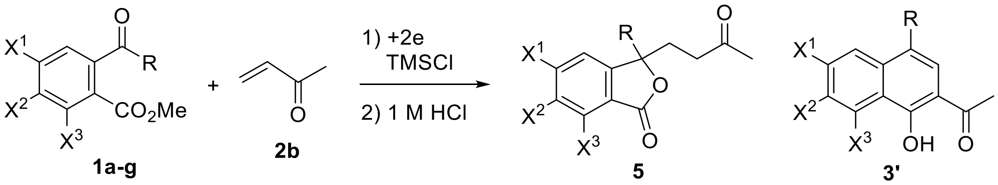


Entry	**1**	R	X^1	X^2	X^3	% Yield[a]
1	**1a**	H	H	H	H	**3a** 56[b]
2	**1b**	H	H	MeO	H	**3b** 71
3	**1c**	H	MeO	MeO	H	**3c** 62
4	**1d**	H	H	MeO	MeO	**3d** 36 **4d** 26
5	**1e**	H	H	H	MeO	**4e** 48
6	**1f**	H	MeO	MeO	MeO	**4f** 41
7	**1g**	Me	H	H	H	**3g** 73[c]
8	**1h**	Ph	H	H	H	**4h** 24[d]

[a]Isolated yields. [b]After dehydration of **7a** by refluxing in *cat.* PPTS/toluene for 1h. [c]The reaction time for treatment with 1 M HCl was extended to 10 h. [d]3-Phenylphthalide (**i**) was obtained mainly (42% yield).

On the other hand, the electroreduction of **1a-h** with **2b** and subsequent treatment with 1 M HCl afforded phthalides **5a-h** in moderate to good yields and naphthalene-1-ols **3’** corresponding to cyclized products **3** were not formed at all in all cases (Table 2).

Table 2: Electroreductive coupling of **1a-g** with **2b** and subsequent treatment with 1 M HCl.



Entry	1	R	X^1	X^2	X^3	% Yield[a]
1	**1a**	H	H	H	H	**5a** 85
2	**1b**	H	H	MeO	H	**5b** 77
3	**1c**	H	MeO	MeO	H	**5c** 88
4	**1d**	H	H	MeO	MeO	**5d** 67
5	**1e**	H	H	H	MeO	**5e** 66
6	**1f**	H	MeO	MeO	MeO	**5f** 73
7	**1g**	Me	H	H	H	**5g** 74
8	**1h**	Ph	H	H	H	**5h** 74

[a]Isolated yields.

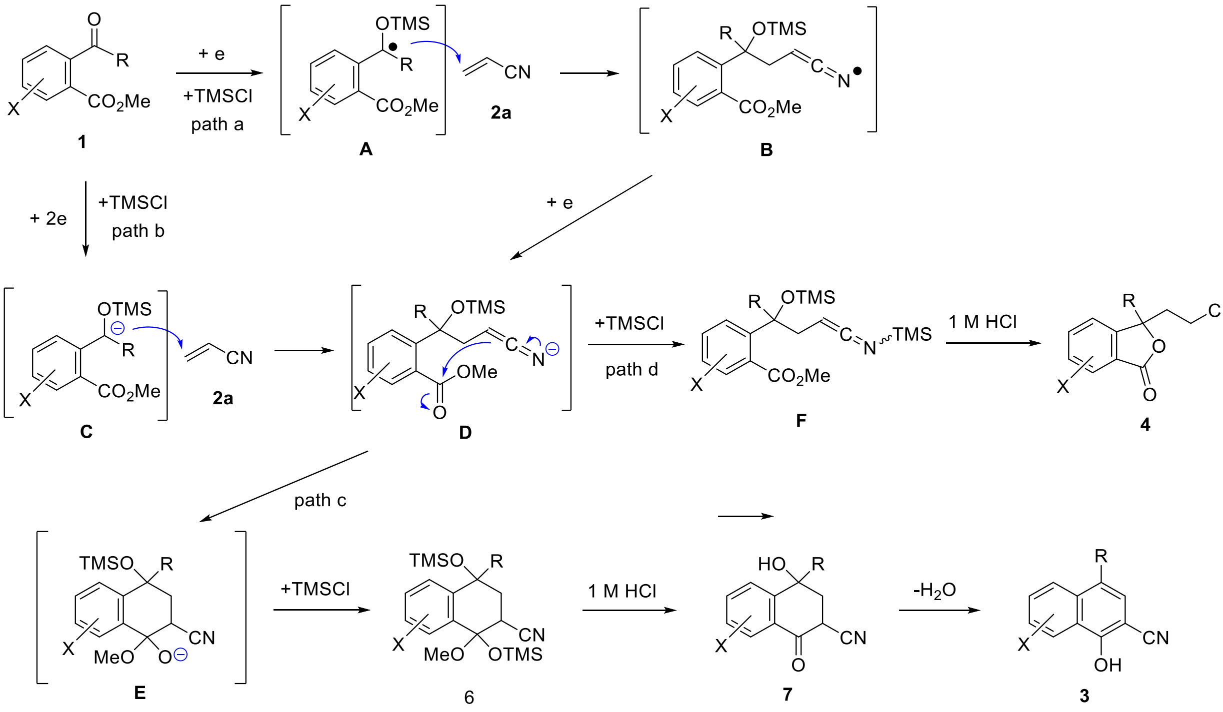
The Ep values of **1a-h** were observed to be in the range from −1.74 to −1.96 V versus SCE by cyclic voltammetry (Table 3) and accepters **2** revealed no reduction peaks from 0 to −2.00 V vs SCE [5,6]. Therefore, this electroreductive coupling is initiated by the reduction of **1**. There are two possible reaction mechanisms for the reductive coupling of **1** with **2a**, that is, radical addition of *O*-trimethylsilyl radical **A** followed by one-electron reduction of **B** (path a) and anionic addition of *O*-trimethylsilyl anion **C** (path b) as illustrated in Scheme 5. Unlike the two reactions we previously reported that are presumed to proceed with the addition of anion species (Schemes 1 and 2) [5,6], methyl acrylate (**2c**) was much less reactive as an accepter in this reaction as shown in Scheme 6. The main product in this case was the same dimeric phthalide **9** as the product without the acceptor. These results suggest that this reaction proceeds with the radical addition of **A** to form anion **D** (path a). Next, intramolecular addition of anion **D** and subsequent *O*-trimethylsilylation of resultant **E** produce **6** (path c). Desilylation of **6** with 1 M HCl and following dehydration of **7** give **3**. On the other hand, *O*-trimethylsilylation of anion **D** forms *N*-trimethylsilyletheneimine **F** and subsequent treatment with 1 M HCl produces phthalide **4** through desilylation and following lactonization of **F** (path d).

Table 3: Ep values of **1a-h** Derived from CV.

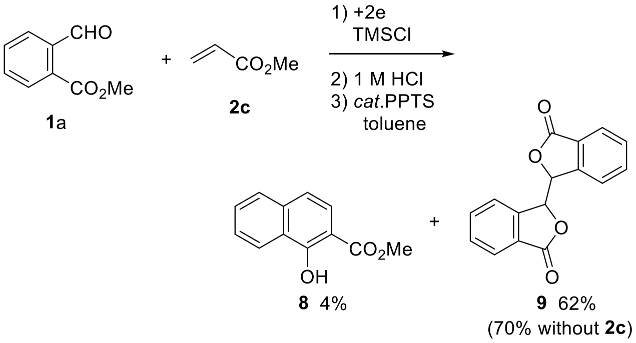
1	E_p[a]	**1**	E_p[a]
1a	-1.74	**1e**	-1.90
1b	-1.86	**1f**	-1.86
1c	-1.74	**1g**	-1.96
1d	-1.92	**1h**	-1.92

[a] First reduction peak (volts vs SCE) in CV of a 3 mM solution in 0.03 M TBAP/DMF at a Pt cathode at 0.1 V/s and 25 °C.

As can be seen From Scheme 5, the cyclization of **D** to **E** is the key step for the formation of **6**. Therefore, we calculated the intermediates (**D** and **E**) and transition states (**D-E TS**) for this step using the DFT method at the B3LYP/6-311+(2d,p)/IEFPCM(THF) level of theory (Supporting Information). From the calculation results for the reactions of **1a-h** with **2a** summarized in Table 4, it was found that the ratio of **D** : **E** calculated from the free energy difference between **D** and **E** (ΔG) and the product ratio of **4** : **3** from the experimental results (Table 1, entries 1-6) were in good agreement. Therefore, it is presumed that whether the cyclization from **D** to **E** proceeds is thermodynamically controlled. Namely, when ΔG was large and negative, **3** was selectively formed (Table 4, entries 1-3), and conversely, when ΔG was large and positive, **4** was selectively produced (entries 5 and 6). When ΔG was close to zero, both **3** and **4** were generated (entry 4). These results suggest that the substitution of the methoxy group at the 6-position tends to suppress the cyclization of **D** to **E** (entries 4-6). From the calculation results for the reaction of **1a** with **2b** (Table 5), it is understood that the cyclization from **Dab** to **Eab** hardly occurs because it shows a relatively large positive ΔG.

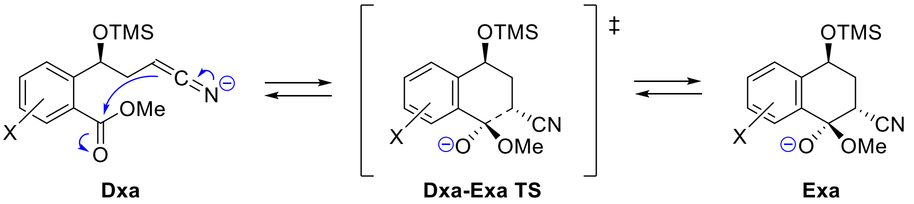


Scheme 5: Presumed reaction mechanism of electroreductive coupling of **1a** with **2a** and subsequent transformation to **3** and **4**.



Scheme 6. Electroreductive coupling of **1a** with **2c** and subsequent treatment with 1 M HCl.

Table 4: Calculations of activation energies ($\Delta G^\ddagger$) and energy differences (ΔG) from **Dxa** to **Exa**.



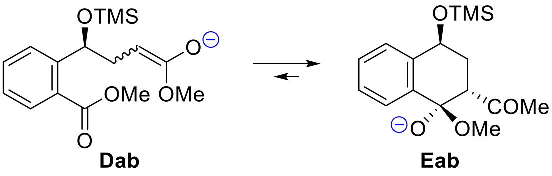
		$\Delta G^\ddagger$	ΔG	**D:E**	**4:3**
Entry	**Dxa**	(kcal/mol)[a]		(calcd)[b]	(exptl)[c]
1	**Daa**	6.73	-1.22	11:89	<1:99
2	**Dba**	5.86	-2.38	2:98	<1:99
3	**Dca**	4.94	-2.17	3:97	<1:99
4	**Dda**	7.82	0.33	36:64	42:58
5	**Dea**	9.16	1.37	91:9	>99:1
6	**Dfa**	9.13	2.55	99:1	>99:1

[a] Calculated at the B3LYP/6-311+G(2d,p)/ICFPCM(THF) level of theory at 25 °C.

[b] Calculated from ΔG on the basis of the Maxwell-Boltzmann distribution law at 25 °C.

[c] Data from entries 1-6 in Table 1.

Table 5: Calculations of ΔG from **Dab** to **Eab**.



	ΔG	D:E	5:3’
Dab	(kcal/mol)[a]	(calcd)[b]	(exptl)[c]
E-form	6.90	100:0	>99:1
Z-form	8.13	100:0	>99:1

[a] Calculated at the B3LYP/6-311+G(2d,p)/ICFPCM(THF) level of theory at 25 °C. [b] Calculated from ΔG on the basis of the Maxwell-Boltzmann distribution law at 25 °C. [c] Data from entry 1 in Table 2.

Conclusion

Electroreduction of *o*-acylbenzoates **1** with acrylonitrile (**2a**) in the presence of TMSCl and subsequent treatment with 1 M HCl gave 2-cyanonaphthalen-1-ols **3** and 3-(3-cyanoethyl)phthalides **4**. Which product was preferentially produced was determined by the position of the methoxy group on the aromatic ring of the substrate **1**. Using the same method, 3-(3-oxobutyl)phthalides **5** were produced as the sole products by the reaction of **1** with methyl vinyl ketone (**2b**). It was found by the DFT calculations for the cyclization step of the intermediate enolate anions that the product selectivity was in good agreement with the free energy differences (ΔG) in the cyclization step.

Experimental

General Information. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured on a JEOL GMX-500 spectrometer with tetramethylsilane (TMS) or the residual signals of protonated solvents as an internal standard: $CDCl_3$ (δ = 77.0 in ^{13}C NMR). IR spectra were recorded on a Shimadzu IRAffinity-1 infrared spectrometer. HRMS were measured on a Thermo Scientific Exactive FTMS spectrometer. Melting points were uncorrected. Column chromatography was performed on silica gel 60. THF was distilled from sodium benzophenone ketyl radical. TMSCl, TEA, and DMF were distilled from CaH_2.

Starting Materials. Methyl 2-fromylbenzoate (**1a**) and methyl 2-benzoylbenzoate (**1h**) were purchased from Tokyo Chemical Industry Corporation. Methyl 2-acetylbenzoate

(**1g**)[7] was prepared from commercially available 2-acetylbenzoic acids (Tokyo Chemical Industry Corporation) by usual esterification using MeI-K_2CO_3/acetone at 25 °C for 12 h. Methoxy substituted 2-formyl benzoates **1b** [18], **1c** [19], **1d** [20], **1e** [21], and **1f** [22] were prepared according to the reported methods.

Typical Procedures for Electroreduction in the Presence of TMSCl (Table 1, Run 1). A 0.3 M solution of Bu_4NClO_4 in THF (15 mL) was placed in the cathodic chamber of a divided cell (40 mL beaker, 3 cm diameter, 6 cm height) equipped with a platinum cathode (5 × 5 cm^2), a platinum anode (2 × 1 cm^2), and a ceramic cylindrical diaphragm (1.5 cm diameter). A 0.3 M solution of Bu_4NClO_4 in DMF (4 mL) was placed in the anodic chamber (inside the diaphragm). Methyl 2-formylbenzoate (**1a**) (161 mg, 1.0 mmol), acrylonitrile (**2a**) (258 mg, 2.5 mmol), TMSCl (0.64 mL, 5 mmol), and TEA (0.14 mL, 1 mmol) were added to the cathodic chamber. After 250 C of electricity (2.5 *F*/mol) was passed at a constant current of 100 mA at room temperature under nitrogen atmosphere (42 min), the catholyte was evaporated in vacuo. The residue was dissolved in diethyl ether (20 mL) and insoluble solid was filtered off. After removal of the solvent in vacuo, the residue was dissolved in 1 M HCl (5 mL)/1,4-dioxane (5 mL) and the solution was stirred at 30 °C for 1 h. The mixture was diluted with sat. NaCl aq (20 mL) and water (20 mL), and then extracted with ethyl acetate (20 mL × 3). The organic layer was washed with sat. NaCl aq, dried over $MgSO_4$, and filtered. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (hexanes-EtOAc) to give 146 mg of **7a** [23] (78% yield) as a mixture of two diastereomers (78:22 dr). A solution of **7a** (146 mg) and PPTS (10 mg) in toluene (10 mL) was refluxed using the Dean-Stark apparatus under nitrogen atmosphere for 1 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (hexanes-EtOAc) to give 95 mg of **3a** [8,23] (56% yield in two steps).

Supporting Information

Supporting Information File 1:

File Name: S1

File Format: pdf

Title: Characterization Data for Compounds, ^{1}H and ^{13}C NMR Spectra of Compounds, X-ray Crystallographic Data (ORTEP) of **3b**, CV Data of **1a-h**, and DFT Calculation data for Cyclization of Enolate Anions

Supporting Information File 2:

File Name: S2

File Format: cif

Title: Cif for **3b**

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ORCID® iDs

Naoki Kise - https://orcid.org/0000-0003-4258-8239

Toshihiko Sakurai - https://orcid.org/0000-0001-7181-9791

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