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CuCN-Mediated Cascade Cyclization of 4-(2-Bromophenyl)-2-butenoates: A High-Yield Synthesis of Substituted Naphthalene Amino Esters

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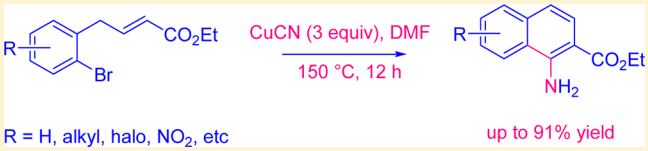
Supporting Information

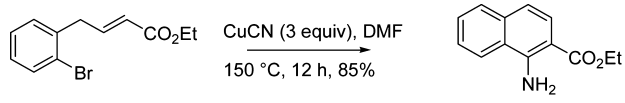
ABSTRACT: A new method of CuCN-mediated one-pot cyclization of 4-(2-bromophenyl)-2-butenoates leading to efficient synthesis of substituted naphthalene amino esters including phenanthrene aromatic structural units is described. Deuterium labeling studies establish that this one-pot cascade cyclization proceeds through isomerization of olefin, intramolecular C−C bond cyclization, and aromatization as the key intermediates, all occurring in a single step.



Substituted naphthalene amino esters are important building blocks for the synthesis of pharmaceuticals[1] and polycyclic aromatic electronic materials.[2] Conceptually, two strategies are reported in the literature for their synthesis: (i) introduction of functional groups onto a naphthalene nucleus and (ii) assembly of naphthalene ring from benzene precursor. Evidently, the annulation strategy is preferable since the availability of functionalized naphthalene precursors is scarce and further complicated by the fact that the reactive sites on a naphthalene core are primarily governed by pre-existing functional group orientations.[3] Fortunately, many cyclization methods are reported, that include annulations *via* Fischer carbenes,[4a] Pd-catalyzed cyclization of alkynes with benzynes,[4b−d] addition of α-lithio derivatives of 2-alkylbenzonitriles onto α,β-unsaturated carboxylic acid derivatives,[4e] intramolecular cyclization of 4-(2-cyanophenyl)-2-butenoic acid,[4f] [3 + 3] benzannulation of benzenoid ring systems,[5a] reaction of 1-methoxybenzocyclobutene with alkynes,[5b] $TiCl_4$-mediated annulations of α-aryl-substituted carbonyl compounds with alkynes,[5c] benzotriazole-assisted aromatic ring annulations,[5d] Au-catalyzed annulations with C−C triple bond,[5e−i] Pd-catalyzed sequential C−C bond formation,[5j−m] and using nonmetallic processes.[5n,o] However, the use of multiple reaction sequences, the expense of lithiated reagents, considerably varying yields, and poor atom economy are the major limitations often associated with these reports. In continuation of our studies on the development of newer synthetic methodologies,[6] herein we report a novel CuCN-mediated "one-pot" cascade cyclization that affords substituted naphthalene amino esters directly from 4-(2-bromophenyl)-2-butenoates.

The classical reaction of bromobenzene derivatives with stoichiometric amount of CuCN in DMF at reflux temperature (Rosenmund−von Braun reaction)[7] invariably affords the corresponding cyanobenzene derivatives.[7] However, when the same reaction was carried out with ethyl 4-(2-bromophenyl)-2-butenoate **1a** in the presence of CuCN (3 equiv) in DMF at 150 °C, the corresponding ethyl 1-aminonaphthalene-2-carboxylate **2a** was isolated in 85% yield (Scheme 1).

Scheme 1. Synthesis of Ethyl 1-Aminonaphthalene-2-carboxylate (2a)



1a **2a**

For determining the optimal conditions (Table 1), substrate **1a** was treated with CuCN (1 equiv) in DMF at 150 °C, which gave the corresponding annulated product **2a** in 28% yield. The

Table 1. CuCN-Mediated One-Pot Synthesis of Ethyl 1-Aminonaphthalene-2-carboxylate 2a: Optimization Studies[a]

entry	CN source (equiv)	temp (°C)	solvent	yield (%)[b]
1	CuCN (1)	150	DMF	28
2	CuCN (2)	150	DMF	53
3	CuCN (3)	150	DMF	85
4	CuCN (3.5)	150	DMF	85
5	CuCN (3)	120	DMF	48
6	CuCN (3)	150	DMSO	trace
7	CuCN (3)	150	DMAc	25
8	NaCN (1.2) + CuI (10 mol %)	110	toluene; DMF	30[c]; −[d]
9	CuCN (1.3) + L-proline	120	DMF	49

[a]Substrate **1a** (1 mmol), CuCN (3 mmol), DMF (10 mL), 12 h. [b]Isolated yield after column chromatographic purification. [c]Substitution of Br with CN coupled with isomerized alkene was observed. [d]No reaction.

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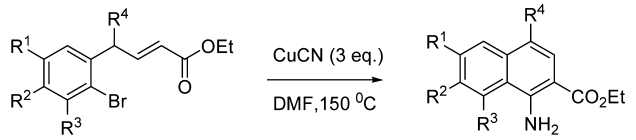
yield of **2a** was significantly improved to 53% when the CuCN quantity was increased to 2 equivalents under the same reaction conditions.

Interestingly, on further increasing the CuCN concentration to 3 equiv, a dramatic improvement in the yield of **2a** (85%) was realized. However, lowering the temperature of the reaction had a deleterious effect on the conversion. A brief evaluation of solvents confirmed that DMF was the most suitable one. In order to provide a catalytic process, we have carried out the Cu-catalyzed reaction[8] [CuI (10 mol %), KI, DMEDA, NaCN] in toluene, which gave unexpectedly cyanated product with isomerized alkene (30%). Further, use of L-proline as an additive[9] to minimize the CuCN quantity gave **2a** in moderate yield. After several experimentations, it was thus found that a combination of *o*-bromo ester **1a** (1 equiv) and CuCN (3 equiv) in DMF at 150 °C for 12 h was the best optimized conditions in achieving excellent product yields **2a**–**k** (Table 2).

Table 2. CuCN-Mediated One-Pot Synthesis of Substituted Naphthalene Amino Esters



1a-k 2a-k

	substrates (**1a**–**k**)				
entry	R^1	R^2	R^3	R^4	products (**2a**–**k**) yield (%)[a]
a	H	H	H	H	85
b	OMe	H	H	H	78
c	OMe	OMe	H	H	74
d	H	OMe	OMe	H	73
e	OBn	OMe	H	H	76
f	H	Me	H	H	81
g	F	H	H	H	88
h	NO_2	H	H	H	91
i	-O-CH_2-O-		H	H	82
j	OMe	OMe	H	Me	86
k	H	benzo fused		H	78

[a]Isolated yield after column chromatographic purification.

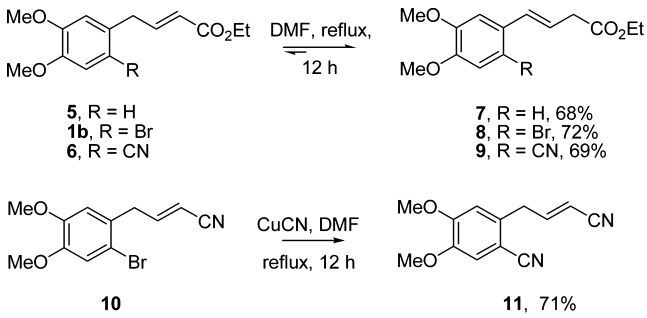
Encouraged by the result, we became interested in determining its scope by subjecting several 4-(2-bromophenyl)-2-butenoates **1a**–**k** to the CuCN-promoted cascade annulation. Several starting materials **1a**–**k** were readily prepared in three steps starting from *o*-bromobenzaldehydes **3a**–**k** following a modified procedures.[10] Thus, Wittig olefination ($MeOCH_2PPh_3Cl$, KO^tBu, THF) of **3a**–**k** gave the corresponding enol ethers **4a**–**k** in 84–92% yield and isomers in 1:1 mixtures of *E*/*Z* (determined from ^1H NMR analysis of their crude samples). However, acid hydrolysis of **4a**–**k** afforded the corresponding phenyl acetaldehydes in good yields, which were then immediately subjected to two-carbon Wittig reaction (PPh_3CHCO_2Et, CH_2Cl_2) to afford 4-(2-bromophenyl)-2-butenoates **1a**–**k** in 84–93% yield (Scheme 2).

When subjected to the CuCN-promoted cascade annulation reaction with 3 equiv of CuCN, several 4-(2-bromophenyl)-2-butenoates **1a**–**k** gave the corresponding annulated substituted naphthalene amino esters **2a**–**k** in 73–91% yields. For instance, substrates bearing halogen, alkyl, alkoxy, nitro, methylenedioxy groups, etc. on the aromatic nucleus were well-tolerated under the reaction conditions. Interestingly, electron-deficient substrates gave higher yields of products as compared to electron-rich substrates due to the mesomeric effect of electron-withdrawing groups, thus increasing the electropositive character of carbon in the CN group (Table 2).

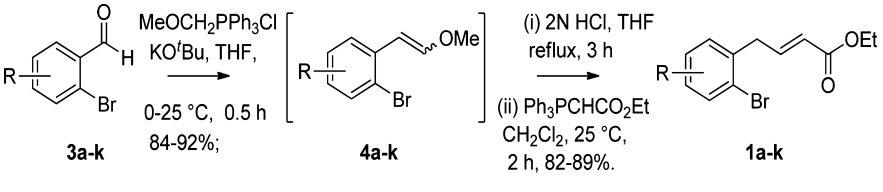
It is found that the annulation is not merely restricted to the synthesis of naphthalene derivatives **2a**–**j**; it allows for the synthesis of phenanthrene derivative (**2k**) as well (78% yield). The formation of products **2a**–**k** was confirmed from NMR, HRMS, and X-ray crystallographic analysis (**2h**) (Supporting Information).

In order to gain insight into the mechanistic details of the reaction, the following experiments were conducted: (a) when *α*,*β*-unsaturated ester **5**, **1b**, or **6** was refluxed in DMF in the absence of CuCN, the corresponding *β*,*γ*-unsaturated ester **7**, **8**, or **9**, respectively, in equilibrium with starting material **5**, **1b**, or **6** (ratio 3:2) was isolated; (b) additionally, when *o*-bromoaromatic derivative **10** was subjected to CuCN-mediated cyanation reaction, mere substitution of Br with CN took place giving **11** without the isomerization of the C=C bond (Scheme 3). This observation suggests that, under thermal conditions, the isomerization of C=C bond might probably be involved.[11]

Scheme 3. Control Experiments



Scheme 2. Synthesis of 4-(2-Bromophenyl)-2-butenoates 1a–k



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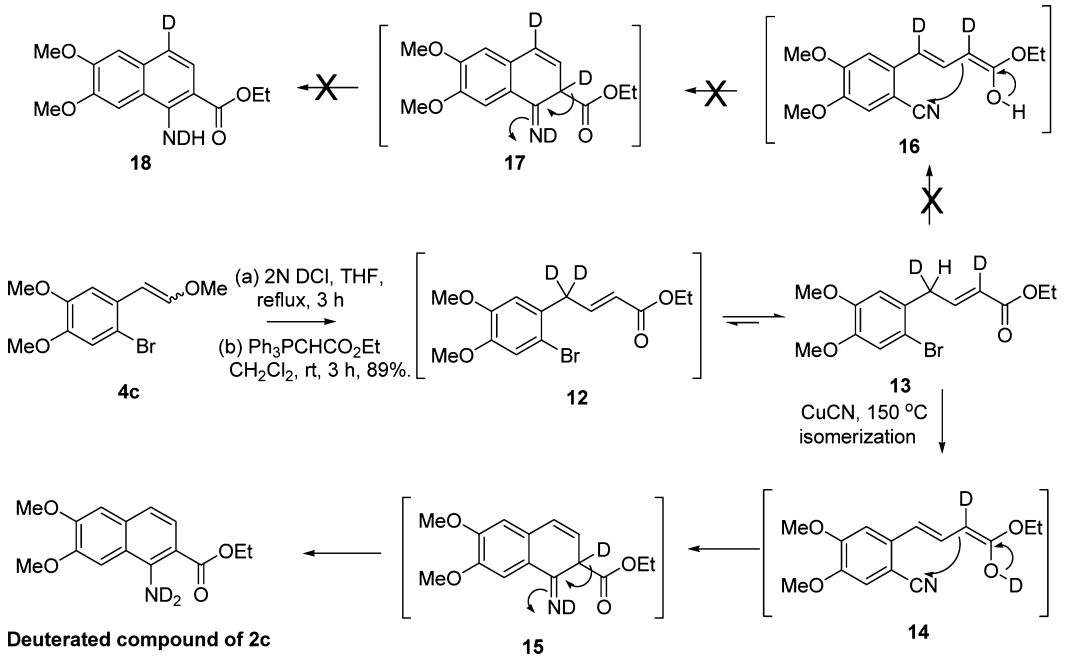
Scheme 4. Proposed Mechanism



To support this hypothesis, deuterium labeling experiments were carried out as follows: when enolether **4c** was hydrolyzed with 2 N DCl and the product immediately subjected to Wittig olefination, a mixture of **12** and **13** (3:2 ratio from ^{1}H NMR study) was obtained. This mixture on treatment with CuCN (3 equiv) in DMF resulted in the deuterated amino ester, i.e., deuterated compound **2c** (73% yield), whose structure has been established from deuterium NMR studies.[12] In ^{1}H NMR spectrum of product **18** benzylic deuterium was not observed, which confirms the isomerization *via* intermediate **14** in our proposed mechanism. Based on this observation, a probable mechanism is proposed in Scheme 4, in which a series of transformations involving a isomerization of olefin (**13** to **14**), intramolecular C−C bond cyclization (**14** to **15**), and aromatization (**15** to deuterium compound of **2c**) are presented as the key intermediates, all occurring sequentially in a single step.

In conclusion, we have disclosed a simple annulation strategy that affords a variety of substituted naphthalene amino esters **2a**−**k** in high yields from the corresponding ethyl 4-(2-bromophenyl)-2-butenoate derivatives **1a**−**k** *via* CuCN-promoted cyclization in a single step. Mechanistically, this annulation involves isomerization of olefin, intramolecular C−C bond cyclization, and aromatization as the key intermediates. We believe that this one-pot cascade cyclization strategy will find tremendous applications in the synthesis of bioactive molecules.

EXPERIMENTAL SECTION

General Description. Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60−80 °C was used. Melting points are uncorrected and recorded on a Buchi B-542 instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer unless mentioned otherwise. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer. Infrared spectra were recorded on Shimadzu FTIR-8400 spectrometer, and absorption is expressed in cm^{-1}. Purification was done using column chromatography (230−400 mesh). Starting materials **3a**, **3f**, and **3g** are commercially available and were purchased from Sigma Aldrich, and **3b**, **3c**, **3d**, **3e**, **3h**, **3i**, **3j**, and **3k** were synthesized by reported methods.[13]

General Experimental Procedure for the Preparation of Ethyl 4-(2-Bromophenyl)-2-butenoate Derivatives (1a−k). To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (6.5 mmol) in THF (25 mL) was added KO^{t}Bu (5.75 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 1 h. A solution of 2-bromo aldehydes **3a**−**k** (5.0 mmol) in THF (5 mL) was added to the reaction mixture, and the resulting mixture was stirred at room temperature. After 30 min, it was quenched with water and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL); the combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product.

To a stirred solution of crude methyl vinyl ether derivatives **4a**−**k** (5.0 mmol) in THF (10 mL) was added an aqueous solution of 1 N aq HCl (10 mL) at room temperature. The resulting solution was refluxed for 3 h. After evaporation of the organic solvent *in vacuo*, water was added to the mixture, and the resulting slurry was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The obtained crude aldehydes were immediately used for the next reaction without purification because of their instability to air and moisture.

To a stirred solution of the above crude aldehydes in CH_2Cl_2 (5 mL) at room temperature was added a Wittig reagent (5.5 mmol), and the resulting mixture was stirred for 2 h at the same temperature. After the completion of reaction, CH_2Cl_2 was distilled out to give the crude product. Chromatographic purification of crude product [silica gel (230−400 mesh) and petroleum ether/ethyl acetate (80:20) as eluent] afforded the unsaturated esters **1a**−**k** in pure form.

Data Analysis for the Synthesis of New Compounds.[14] (*E*)-Ethyl 4-(2-Bromo-4,5-dimethoxyphenyl)but-2-enoate (1c). Yield: 84% (1.38g, 4.192 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 780, 936, 1032, 1071, 1156, 1176, 1239, 1280, 1468, 1712, 2978; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 3.61 (dd, J = 1.6, 6.4 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.18 (q, J = 7.2 Hz, 2H), 5.76 (td, J = 1.5, 15.7 Hz, 1H), 6.81−7.13 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 38.1, 55.8, 60.0, 113.0, 114.2, 115.5, 122.4, 128.9, 146.7, 145.5, 148.4, 148.5, 166.0. Anal. Calcd for $C_{14}H_{17}BrO_4$: C, 51.08; H, 5.21; Br, 24.27. Found: C, 50.95; H, 5.13; Br, 24.34.

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(*E*)-Ethyl 4-(2-Bromo-3,4-dimethoxyphenyl)but-2-enoate (1d). Yield: 82% (1.35g, 4.101 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 895, 978, 1024, 1050, 1142, 1188, 1245, 1276, 1477, 1714, 2965; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 3.61 (dd, J = 1.3, 7.1 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.17 (q, J = 7.2 Hz, 2H), 6.81−7.27 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 38.1, 56.0, 60.1, 111.3, 120.3, 125.2, 130.2, 145.8, 146.7, 152.3, 166.2. Anal. Calcd for $C_{14}H_{17}BrO_4$: C, 51.08; H, 5.21; Br, 24.27. Found: C, 50.98; H, 5.14; Br, 24.32.

(*E*)-Ethyl 4-(5-(Benzyloxy)-2-bromo-4-methoxyphenyl)but-2-enoate (1e). Yield: 84% (1.70g, 4.195 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 780, 882, 1035, 1072, 1151, 1190, 1278, 1292, 1456, 1712, 2974; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 3.27 (dd, J = 1.4, 7.1 Hz, 2H), 3.89 (s, 3H), 4.19 (q, J = 7.2 Hz, 2H), 5.10 (s, 2H), 6.14 (td, J = 7.2, 15.8 Hz, 1H), 7.02 (s, 2H), 7.32−7.44 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 38.1, 55.8, 60.0, 113.0, 114.2,115.5, 122.4, 128.8, 145.5, 148.4, 166.0. Anal. Calcd for $C_{20}H_{21}BrO_4$: C, 59.27; H, 5.22; Br, 19.72. Found: C, 59.34; H, 5.28; Br, 19.65.

(*E*)-Ethyl 4-(2-Bromo-4-nitrophenyl)but-2-enoate (1h). Yield: 84% (1.32g, 4.202 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 768, 878, 1018, 1085, 1178, 1285, 1298, 1455, 1716, 2960; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 3.63 (dd, J = 1.3, 7.1 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 5.74 (td, J = 3.8, 15.7 Hz, 1H), 6.36 (dd, J = 1.8, 2.9 Hz, 2H), 6.97−7.12 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 38.1, 60.2, 98.0, 105.1, 106.8, 122.7, 139.1, 145.3, 156.9, 159.6, 166.2. Anal. Calcd for $C_{12}H_{12}BrNO_4$: C, 45.88; H, 3.85; Br, 25.44; N, 4.46. Found: C, 45.76; H, 3.76; Br, 25.36; N, 4.39.

Ethyl 4-(2-Bromo-4,5-dimethoxyphenyl)pent-2-enoate (1j). Yield: 89% (1.53g, 4.458 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 856, 937, 1030, 1133, 1233, 1268, 1445, 1716,2984; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.37 (d, J = 7.0 Hz, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.06 (qd, J = 5.5, 1.5 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 5.80 (dd, J = 15.79, 1.64 Hz, 1H), 6.63 (s, 1H), 7.01 (s, 1H), 7.09 (dd, J = 15.79, 5.69 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 19.1, 40.1, 55.8, 60.0, 110.6, 113.9, 115.5, 120.4, 134.0, 148.2, 148.7, 150.9, 166.2 Anal. Calcd for $C_{15}H_{19}BrO_4$: C, 52.49; H, 5.58; Br, 23.28. Found: C, 52.33; H, 5.12; Br, 23.18.

Ethyl 4-(1-Bromonaphthalen-2-yl)but-2-enoate (1k). Yield: 89% (1.49g, 4.458 mmol); yellow oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 758, 872, 1058, 1175, 1184, 1245, 1468, 1713, 2962; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 3.89 (dd, J = 6.3, 1.6 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 5.77 (dt, J = 15.6, 1.6 Hz, 1H), 7.06−7.30 (m, 2H), 7.45−7.62 (m, 2H), 7.77 (t, J = 8.5 Hz, 2H), 8.30 (d, J = 8.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 39.8, 60.2, 122.9, 124.4, 126.3, 127.4, 127.5, 127.8, 128.0, 128.3, 132.6, 133.5, 135.2, 145.2, 166.1. Anal. Calcd for $C_{16}H_{15}BrO_2$: C, 60.21; H, 4.74; Br, 25.03. Found: C, 60.11; H, 4.32; Br, 24.90.

General Experimental Procedure for the Preparation of Substituted Naphthalene Derivatives (2a−k). To a stirred solution of alkenes **1a−k** (1 mmol) in dry DMF (10 mL) was added CuCN (3 mmol,) and the entire solution was refluxed under N_2 for 12 h (monitored by TLC). The reaction mixture was then cooled to room temperature and diluted with water (20 mL) and EtOAc (15 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product, which was purified by column chromatography [silica gel (230−400 mesh) and petroleum ether/EtOAc (7:3) as an eluent] to give ethyl 1-amino-2-naphthalene carboxylate derivatives (**2a−k**) in 73−91% yield.

Ethyl 1-Aminonaphthalene-2-carboxylate (2a). Yield: 85% (0.183g, 0.850 mmol); gum; IR ($CHCl_3$, cm^{-1}) υ_{max} 798, 865, 964, 1015, 1135, 1157, 1232, 1264, 1471, 1665, 2965, 3335, 3346; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (t, J = 7.1 Hz, 3H), 4.37 (q, J = 7.1 Hz, 2H), 7.05 (d, J = 8.9 Hz, 1H), 7.44−7.53 (m, 2H), 7.72 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 8.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 60.1, 104.2, 115.7, 121.4, 123.1, 125.0, 126.6, 128.2, 128.4, 136.4, 148.8, 168.8; HRMS (ESI+) m/z calcd for $(C_{13}H_{13}NO_2)^+$ [(M + Na)$^+$] 238.0844, found 238.0836. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.46; H, 6.24; N, 6.62.

Ethyl 1-Amino-6-methoxynaphthalene-2-carboxylate (2b). Yield: 78% (0.191g, 0.778 mmol); gum; IR ($CHCl_3$, cm^{-1}) υ_{max} 870, 1076, 1245, 1340, 1599, 1672, 3346, 3457; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (t, J = 7.1 Hz, 3H), 3.92 (s, 3H), 4.36 (q, J = 7.1 Hz, 2H), 6.97 (d, J = 8.8 Hz, 1H), 7.02−7.11 (m, 2H), 7.82 (t, J = 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 55.2, 60.0, 103.2, 107.0, 115.1, 117.0, 117.9, 123.3, 127.5, 138.3, 148.9, 159.6, 168.8; HRMS (ESI+) m/z calcd for $(C_{14}H_{15}NO_3)^+$ [(M + Na)$^+$] 268.0950, found 268.0944. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.44; H, 5.99; N, 5.49.

Ethyl 1-Amino-6,7-dimethoxynaphthalene-2-carboxylate (2c). Yield: 74% (0.204g, 0.741 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 798, 865, 964, 1015, 1135, 1157, 1232, 1264, 1471, 1665, 2965, 3335, 3346; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (t, J = 7.1 Hz, 3H), 4.00 (s, 3H), 4.01 (s, 3H), 4.36 (q, 2H, J = 7.1 Hz), 6.95 (d, J = 8.9 Hz, 1H), 7.02 (s, 1H), 7.05 (s, 1H), 7.77 (d, 1H, J = 8.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 55.6 60.1, 101.1, 103.8, 107.1, 114.8, 117.6, 125.1, 132.4, 147.6, 148.6, 150.9, 168.8; HRMS (ESI+) m/z calcd for $(C_{15}H_{17}NO_4)^+$ [(M + Na)$^+$] 298.1055, found 298.1062. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.69; H, 6.18; N, 5.11.

Ethyl 1-Amino-7,8-dimethoxynaphthalene-2-carboxylate (2d). Yield: 73% (0.201g, 0.730 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 779, 826, 956, 1018, 1267, 1579, 1672, 3334, 3464; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 3.97 (s, 6H), 4.35 (q, J = 7.2 Hz, 2H), 6.82 (d, J = 10.4 Hz, 1H), 7.24−7.28 (m, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 56.8, 61.5, 102.7, 114.1, 116.8, 118.0, 124.4, 125.3, 133.2, 147.0, 148.7, 151.1, 168.9; HRMS (ESI+) m/z calcd for $(C_{15}H_{17}NO_4)^+$ [(M + Na)$^+$] 298.1055, found 298.1049. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.35; H, 6.31; N, 5.12.

Ethyl 1-Amino-6-(benzyloxy)-7-methoxynaphthalene-2-carboxylate (2e). Yield: 76% (0.267 g, 0.759 mmol); colorless solid; mp 144−145 °C; IR ($CHCl_3$, cm^{-1}) υ_{max} 1247, 1483, 1619, 1676, 3434, 3452; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (t, J = 7.1 Hz, 3H), 4.00 (s, 3H), 4.35 (q, J = 7.1 Hz, 2H), 5.26 (s, 2H), 6.95 (d, J = 8.8 Hz, 1H), 7.04 (s, 1H), 7.18 (s, 1H), 7.30−7.51 (m, 5H), 7.76 (d, J = 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 55.8, 60.1, 71.3, 104.3, 107.6, 115.2, 117.9, 125.5, 127.4, 128.1, 128.7, 132.9, 136.7, 147.5, 147.9, 151.8, 168.9; HRMS (ESI+) m/z calcd for $(C_{21}H_{21}NO_4)^+$ [(M + Na)$^+$] 374.1368, found 374.1375. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.66; H, 5.94; N, 4.03.

Ethyl 1-Amino-6-methylnaphthalene-2-carboxylate (2f). Yield: 81% (0.186g, 0.811 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 1078, 1222, 1239, 1257 1605, 1663, 3352, 3453; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (t, J = 7.1 Hz, 3H), 2.54 (s, 3H), 4.37 (q, J = 7.1 Hz, 2H), 7.02 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 22.0, 60.2, 104.9, 116.1, 120.9, 123.4, 125.7, 128.4, 130.4, 134.6, 134.9, 147.9, 168.9; HRMS (ESI+) m/z calcd for $(C_{14}H_{15}NO_2)^+$ [(M + Na)$^+$] 252.1000, found 252.0992. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.26; H, 6.52; N, 6.01.

Ethyl 1-Amino-6-fluoronaphthalene-2-carboxylate (2g). Yield: 88% (0.205g, 0.870 mmol); gum; IR ($CHCl_3$, cm^{-1}) υ_{max} 767, 1249, 1604, 1673, 2987, 3347, 3447; ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (t, J = 7.2 Hz, 3H), 4.37 (q, J = 7.2 Hz, 2H), 6.99 (d, J = 8.9 Hz, 1H), 7.15−7.24 (m, 1H), 7.34 (dd, J = 2.5, 7.1 Hz, 1H), 7.86 (d, J = 9.2 Hz, 1H), 7.9 (d, J = 8.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 60.2, 104.1, 111.8 (d, J = 20.8 Hz), 114.7 (d, J = 25.4 Hz), 115.1 (d, J = 3.9 Hz), 120.0, 124.2 (d, J = 10.0 Hz), 128.1, 138.0 (d, J = 9.2 Hz), 148.8, 162.2 (d, J = 249.7 Hz), 168.6; HRMS (ESI+) m/z calcd for $(C_{13}H_{12}FNO_2)^+$ [(M + Na)$^+$] 256.0750, found 256.0743. Anal. Calcd for $C_{13}H_{12}FNO_2$: C, 66.94; H, 5.19; N, 6.01. Found: C, 67.03; H, 5.13; N, 5.89.

Ethyl 1-Amino-6-nitronaphthalene-2-carboxylate (2h). Yield: 91% (0.237g, 0.911 mmol); Red solid; mp 176−177 °C; IR ($CHCl_3$, cm^{-1}) υ_{max} 1243, 1345, 1602, 1674, 3352, 3446; ^1H NMR (200 MHz,

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$CDCl_3$) δ 1.45 (t, J = 7.0 Hz, 3H), 4.41 (q, J = 7.0 Hz, 2H), 6.90 (s, 2H), 7.23 (d, J = 8.8 Hz, 1H), 8.02 (t, J = 8.8 Hz, 1H), 8.18 (d, J = 2.3 Hz, 1H), 8.20 (d, J = 2.3, 1H), 8.65 (d, J = 2.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 60.8, 107.2, 116.9, 118.3, 123.4, 124.5, 125.7, 129.1, 135.7, 147.1, 148.3, 168.2; HRMS (ESI+) m/z calcd for $(C_{13}H_{12}N_2O_4)^+$ [$(M + Na)^+$] 283.0695, found 283.0687. Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.95; H, 4.51; N, 10.65.

Ethyl 5-Aminonaphtho[2,3-*d*][1,3]dioxole-6-carboxylate (2i). Yield: 82% (0.213g, 0.822 mmol); gum; IR ($CHCl_3$, cm^{-1}) υ_{max} 1243, 1345, 1602, 1674, 3352, 3446; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (t, 3H, J = 7.0 Hz), 4.35 (q, J = 7.0 Hz, 2H), 6.05 (s, 2H), 6.90 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H), 7.16 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 60.0, 98.7, 101.3, 104.5, 104.9, 115.6, 119.0, 125.5, 134.0, 147.4, 147.8, 149.2, 168.8; HRMS (ESI+) m/z calcd for $(C_{14}H_{13}NO_4)^+$ [$(M + Na)^+$] 282.0742, found 282.0747. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.79; H, 5.12; N, 5.46.

Ethyl 1-Amino-6,7-dimethoxy-5-methylnaphthalene-2-carboxylate (2j). Yield: 81% (0.234g, 0.809 mmol); yellow solid; mp 135−137 °C; IR ($CHCl_3$, cm^{-1}) υ_{max} 798, 865, 964, 1063, 1205, 1232, 1250, 1462, 1482, 1513, 1602, 1674, 2980, 3352, 3471; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (t, J = 7.1 Hz, 3H), 2.50 (s, 3H), 4.02 (s, 6H), 4.36 (q, J = 7.1 Hz, 2H), 7.11 (s, 1H), 7.13 (s, 1H), 7.61 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 18.9, 55.3, 55.4, 59.8, 101.7, 103.5, 103.6, 118.1, 120.1, 124.8, 131.5, 146.3, 148.0, 150.5, 168.7; HRMS (ESI+) m/z calcd for $(C_{16}H_{19}NO_4)^+$ [$(M + Na)^+$] 312.1212, found 312.1217. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.47; H, 6.48; N, 4.78.

Ethyl 1-Aminophenanthrene-2-carboxylate (2k). Yield: 71% (0.188g, 0.709 mmol); yellow oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 791, 845, 964, 1052, 1215, 1239, 1240, 1412, 1472, 1533, 1664, 2970, 3332, 3451; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.11 (d, J = 8.6, 1H), 7.49−7.64 (m, 3H), 7.73 (d, J = 8.7, 1H), 7.88 (dd, J = 9.0, 1.6, 1H), 8.05 (d, J = 8.5, 1H), 9.19 (d, J = 8.2, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 60.4, 108.2, 116.7, 119.1, 124.5, 125.6, 126.5, 127.0, 128.3, 129.1, 129.6, 130.8, 132.8, 137.1, 151.0, 169.1; HRMS (ESI+) m/z calcd for $(C_{17}H_{15}NO_2)^+$ [$(M + Na)^+$] 288.1000, found 288.1009. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.71; H, 5.51; N, 5.22.

(*E*)-Ethyl 4-(3,4-Dimethoxyphenyl)but-2-enoate (5). IR ($CHCl_3$, cm^{-1}) υ_{max} 856, 965, 1054, 1144, 1163, 1241, 1263, 1312, 1456, 1714, 2864; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 3.45 (dd, J = 1.5, 6.6, Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.18 (q, J = 7.2 Hz, 2H), 5.78 (td, J = 1.6, 15.5 Hz, 1H), 6.65−6.72 (m, 2H), 6.78−6.82 (m, 1H), 7.06 (td, J = 6.6 15.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 37.8, 55.5, 55.6, 59.9, 111.2, 111.7, 120.6, 121.8, 129.8, 147.3, 147.6, 148.8, 166.1; HRMS (ESI+) m/z calcd for $(C_{14}H_{18}O_4)^+$ [$(M + Na)^+$] 273.1103, found 273.1108.

Experimental Procedure for the Preparation of (*E*)-Ethyl 4-(2-Cyano-4,5-dimethoxyphenyl)but-2-enoate (6). Potassium osmate dehydrate (36 mg, 0.1 mmol) and *N*-methylmorpholine *N*-oxide (2.3g, 20 mmol) were added to a solution of 2-allyl-4,5-dimethoxybenzonitrile (2.03g, 10 mmol) in acetone/H_2O (30 mL, 1:1 ratio) and stirred at room temperature until all of the starting material had been consumed by TLC (12 h). CH_2Cl_2 was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). Organic extracts combined, dried over anhydrous Na_2SO_4, and concentrated to give the crude diol, which was then directly taken for the next step without purification.

To a vigorously stirred suspension of silica gel-supported $NaIO_4$ reagent (2.1g, 10 mmol) in CH_2Cl_2 was added a solution of the crude vicinal diol in CH_2Cl_2. The reaction was monitored by TLC until disappearance of the starting material. The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with CH_2Cl_2. The organic extract was washed with brine and dried over anhydrous Na_2SO_4, and the crude aldehyde was used immediately in the Wittig reaction.

To a stirred solution of above crude aldehyde in CH_2Cl_2 at room temperature was added Wittig reagent (3.8g, 11.1 mmol), and the resulting mixture was stirred for the 2 h at the same temperature. After the completion of the reaction, CH_2Cl_2 was distilled out to give the crude product. Chromatographic purification of crude product [silica gel (230−400 mesh) and petroleum ether/ethyl acetate (80:20) as eluent] afforded the unsaturated esters **6** in pure form (1.7g, 0.6 mmol, 62% yield). Yield: 62% (1.7g, 0.6 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 893, 964, 1051, 1142, 1163, 1241, 1263, 1456, 1712,2213, 2965; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 3.57 (dd, J = 1.6, 6.3 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.17 (q, J = 7.0 Hz, 2H), 5.74 (td, J = 1.6, 15.5 Hz, 1H), 6.86 (s, 1H), 7.01 (s 1H), 7.02 (td, J = 6.4, 15.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 38.1, 56.0, 56.1, 60.9, 102.6, 107.3, 113.7, 118.0, 125.2, 129.1, 134.7, 148.7, 152.8, 171.1; HRMS (ESI+) m/z calcd for $(C_{15}H_{17}NO_4)^+$ [$(M + Na)^+$] 298.1055, found 298.1049.

Experimental Procedure for the Preparation of (*E*)-Ethyl 4-(3,4-Dimethoxyphenyl)but-3-enoate (7). (*E*)-Ethyl 4-(3,4-dimethoxyphenyl)but-2-enoate **5** (0.25g, 1 mmol) was taken in dry DMF (10 mL) and was heated at 150 °C under N_2 for 12 h. The reaction mixture was then cooled to room temperature and diluted with water (30 mL) and EtOAc (25 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude product that was purified by column chromatography [silica gel (230−400 mesh) and petroleum ether/EtOAc (9:1) as an eluent] to give (*E*)-ethyl 4-(3,4-dimethoxyphenyl)but-3-enoate **7** along with **5** (0.19g, 0.77 mmol, 89% yield). Yield: 89% (0.19g, 0.77 mmol); colorless liquid; IR ($CHCl_3$, cm^{-1}) υ_{max} 882, 978, 1045, 1148, 1175, 1248, 1275, 1390, 1412, 1718, 2890; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 3.21 (dd, J = 1.3, 7.1, Hz, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 4.17 (q, J = 7.2 Hz, 2H), 6.07−6.25 (m, 1H), 6.33−6.46 (m, 1H), 6.76−6.80 (m, 1H), 6.85−6.92 (m, 2H); HRMS (ESI+) m/z calcd for $(C_{14}H_{18}O_4)^+$ [$(M + Na)^+$] 273.1103, found 273.1107.

Experimental Procedure for the Preparation of (*E*)-Ethyl 4-(2-Bromo-4,5-dimethoxyphenyl)but-3-enoate (8). Same as described for compound **7**. Yield: 87% (0.285g, 0.870 mmol); colorless liquid; IR ($CHCl_3$, cm^{-1}) υ_{max} 893, 964, 1051, 1142, 1163, 1241, 1263, 1456, 1712, 2965; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3H), 3.31 (dd, J = 1.3,5.6 Hz, 2H), 3.90 (s, 6H), 4.20 (q, J = 7.0 Hz, 2H), 5.74 (td, J = 7.0, 15.7 Hz, 1H), 6.78 (td, J = 1.2, 15.7 Hz, 1H), 6.98 (s 1H), 7.05 (s, 1H); HRMS (ESI+) m/z calcd for $(C_{14}H_{17}BrO_4)^+$ [$(M + Na)^+$] 351.0208, found 351.0214.

Experimental Procedure for the Preparation of (*E*)-Ethyl 4-(2-Cyano-4,5-dimethoxyphenyl)but-3-enoate (9). Same as described for compound **7**. Yield: 83% (0.198g, 0.689 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 848, 1092, 1219, 1268, 1485, 1514, 2212, 1714, 2961; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3H), 3.31 (dd, J = 7.0, 1.4 Hz, 2H), 3.90 (s, 3H), 3.96 (s, 3H), 4.20 (q, J = 7.0 Hz, 2H), 6.40 (td, J = 15.8, 7.0 Hz,1H), 6.78 (d, J = 15.8 Hz, 1H), 6.98 (s, 1H), 7.05 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) of compound **9** + compound **6** δ 14.2, 36.4, 38.1, 56.1, 60.3, 60.8, 102.6, 103.8, 107.3, 112.2, 113.6, 114.2, 117.9, 123.8, 125.2, 129.0, 134.6, 135.7, 144.6, 148.1, 148.7, 152.7, 165.8, 170.9. HRMS (ESI+) m/z calcd for $(C_{15}H_{17}NO_4)^+$ [$(M + Na)^+$] 298.1055, found 298.1051.

Experimental Procedure for the Preparation of 2-((*E*)-3-Cyanoallyl)-4,5-dimethoxybenzonitrile (11). Same as described for compound **7**. Yield: 71% (0.199g, 0.71 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 1031, 1164, 1218, 1381, 1440, 1506, 2218, 2840, 2932, 3008; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.89 (s, 3H), 3.90 (d, J = 11.3 Hz, 2H), 3.93 (s, 3H), 5.48 (d, J = 10.8 Hz, 1H), 6.65 (td, J = 7.5, 10.8 Hz, 1H), 6.80 (s, 1H), 7.04 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.1, 56.1, 56.2, 101.4, 103.5, 112.3, 114.2, 115.5, 117.7, 135.0, 148.4, 150.3, 153.2; HRMS (ESI+) m/z calcd for $(C_{13}H_{12}N_2O_2)^+$ [$(M + Na)^+$] 251.0796, found 251.0791.

Experimental Procedure for the Preparation of Compound 13. To a stirred solution of 1-bromo-4,5-dimethoxy-2-((*E*)-2-methoxyvinyl)benzene **4c** (1.3g, 5.0 mmol) in THF (10 mL) was added 1 N DCl/D_2O (2 mL) at room temperature. The resulting solution was heated at 150 °C for 3 h. After evaporation of the organic solvent *in vacuo*, EtOAc was added to the mixture, and acid was

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neutralize by adding $NaHCO_3$. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The obtained crude aldehydes were immediately used for the next reaction without purification because of their instability to air and moisture. To a stirred solution of the above crude aldehydes in CH_2Cl_2 (5 mL) at room temperature was added a Wittig reagent (1.9g, 5.5 mmol), and the resulting mixture was stirred for 2 h at the same temperature. After the completion of reaction, CH_2Cl_2 was distilled out to give the crude product. Chromatographic purification of crude product [silica gel (230−400 mesh) and petroleum ether/ethyl acetate (80:20) as eluent] afforded the deuterated unsaturated esters **13** in pure form (0.271g, 0.81 mmol, 82%). Yield: 82% (0.271g, 0.81 mmol); colorless oil; IR ($CHCl_3$, cm^{-1}) υ_{max} 895, 978, 1024, 1050, 1142, 1188, 1245, 1276, 1477, 1714, 2965; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 3.48 (d, J = 1.3, 6.4 Hz, 0.42H), 3.85 (s, 3H), 3.86 (s, 3H), 4.18 (q, J = 7.0 Hz, 2H), 5.74 (d, J = 15.6 Hz, 0.38 H), 6.66 (s, 1H), 6.98 (d, 15.6 Hz, 1H), 7.01 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 34.0, 34.2, 34.4, 34.6, 34.8, 55.9, 56.1, 59.9, 113.4, 114.0, 115.5, 119.7, 119.9, 120.2, 130.9, 146.5, 146.7, 148.3, 148.6, 166.2; HRMS (ESI+) m/z calcd for $(C_{14}H_{15}D_2BrNO_4)^+$ [(M + Na)$^+$] 353.0333, found 353.0337.

Experimental Procedure for the Preparation of Deuterated Compound 2c. The deuterated (*E*)-ethyl 4-(2-bromo-4,5-dimethoxyphenyl)but-2-enoate **13** (1 mmol) was taken in dry DMF (10 mL), CuCN (3 mmol) was added to it, and the entire solution was refluxed under N_2 atmosphere for 12 h. The reaction mixture was then cooled to room temperature, the ^2H NMR spectrum was recorded for crude product in DMF, and the presence of dideuterium on nitrogen (ND_2) in product **2c** was observed. The product deuterated compound of **2c** was further confirmed by comparing the deuterium NMR spectrum of deuterated product **2c** in DMF. It is notable that the benzylic deuterium was not observed in the ^1H NMR spectrum of product **2c**, which confirms the isomerization in our proposed mechanism.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H NMR and ^{13}C NMR spectra for all new substances and X-ray crystallographic data for **2h**. 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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