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Tandem Blaise/Palladium-Catalyzed Ullmann Coupling for the One-Pot Synthesis of Enamino Ester-Functionalized Biaryls from Nitriles

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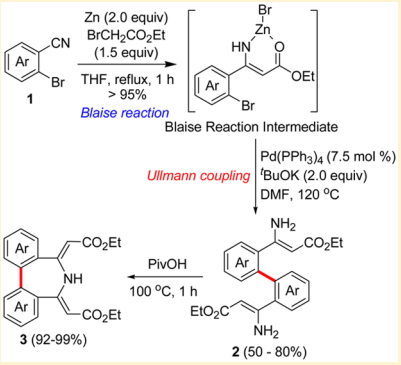
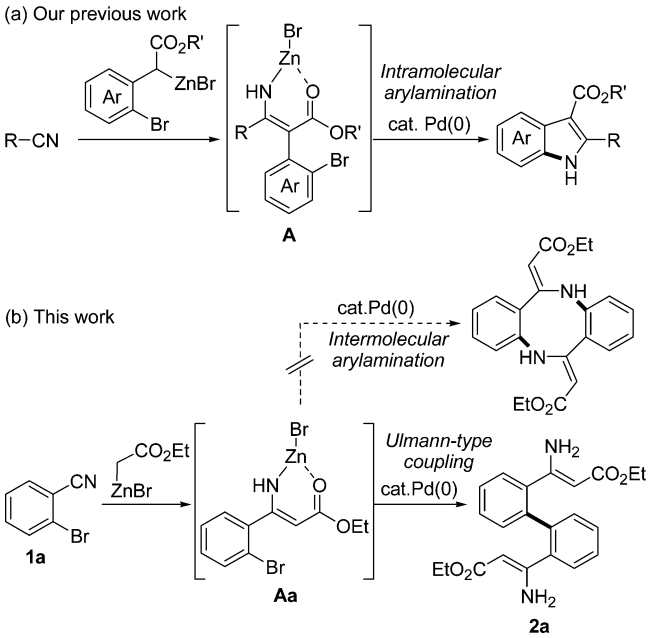
Supporting Information

ABSTRACT: A novel Pd-catalyzed Ullmann-type homocoupling reaction of the Blaise reaction intermediate generated by the reaction of 2-bromo arylnitriles and a Reformatsky reagent has been developed for one-pot synthesis of enamino ester-functionalized biaryls **2** in good yields. The 2,2′-substituted enamine moieties of the coupling products could be cyclized under acidic conditions through the conjugate addition/deamination cascade to afford the seven-membered *N*-heterocyclics **3** with biaryl backbone in excellent yields.



Sequential tandem one-pot transformations can deliver substantial increases in molecular complexity and minimize waste generation. Moreover, the intermediates involved do not need to be stable enough for isolation, and in certain cases, their reaction profiles are different from those that have been isolated creating new reaction pathways. Given these advantages, the design and implementation of tandem reactions has increasingly become an important and valuable endeavor.[1] During our ongoing studies on the tandem use of a Blaise reaction intermediate,[2] a zinc bromide complex of β-enamino esters, we previously reported that the α-2-bromoaryl substituted intermediate **A** could undergo the Pd-catalyzed redox-neutral intramolecular aryl-amination to result in indole derivatives (Scheme 1a).[2f] Along this line, we have been interested in Pd-catalyzed intermolecular aryl amination with the Blaise reaction intermediate **Aa** formed from 2-bromo benzonitrile **1a** and a Reformatsky reagent generated in situ from ethyl bromo acetate and zinc to form the benzo-fused eight-membered diazocine derivatives. To our surprise, when the tandem reaction of **Aa** was carried out in the presence of 7.5 mol % of $Pd(PPh_3)_4$ at 120 °C in DMF, the Ullmann-type homocoupled biaryl **2a** was isolated in 12% yield (see entry 1, Table 1). Given the importance of biaryl compounds and the novelty of this reaction, we attempted to further optimize the reaction conditions (Table 1). Herein, we report Pd-catalyzed Ullmann-type coupling of the Blaise reaction intermediate for one-pot synthesis to access 2,2-enamino ester-functionalized biaryls **2** starting from 2-bromoarylnitriles (Scheme 1b). A significant finding is that the ortho positioned chelated ZnBr complex moiety acts as a directing auxiliary to facilitate the Ullmann coupling of the intermediates, showing superior coupling efficiency when compared with the coupling of the intermediates formed from *m*- or *p*-bromoarylnitriles (ortho effects).

Scheme 1. Pd-Catalyzed Couplings of the Blaise Reaction Intermediates



The Ullmann coupling, a copper-mediated reductive homocoupling of aryl halides, has long been employed for the synthesis of biaryls, which are ubiquitous in natural

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Table 1. Optimization of Conditions[a]

entry	base (equiv)	sol	time (h)	**2a** (yield)[b]
1		DMF	10	12%
2	^{t}BuOK (1.0)	DMF	6	53%
3	^{t}BuOK (2.0)	DMF	6	80%
4[c]	^{t}BuOK (2.0)	DMF	10	53%
5[d]	^{t}BuOK (2.0)	DMF	10	60%
6[e]	^{t}BuOK (2.0)	DMF	10	43%
7	K_3PO_4 (2.0)	DMF	24	12%
8	K_2CO_3 (2.0)	DMF	24	58%
9	Cs_2CO_3 (2.0)	DMF	24	36%
10	^{t}BuOK (2.0)	DMA	6	69%
11	^{t}BuOK (2.0)	NMP	6	61%

[a]Intermediate **Aa** was generated by the reaction of **1a** (2.0 mmol) with ethyl bromoacetate (3.0 mmol, 1.5 equiv) and zinc (4.0 mmol, 2.0 equiv) in THF under reflux. After complete conversion of **1a** to **Aa** (by GC and TLC), solvent (THF/sol = 1/10 v/v), $Pd(PPh_3)_4$ (7.5 mol %), and base were added at room temperature, and the reaction was conducted at 120 °C. [b]Isolated yield after silica gel chromatography. [c]Reaction using 5.0 mol % of $Pd(PPh_3)_4$. [d]Used 7.5 mol % of $Pd[P(^tBu)_3]_2$ catalyst. [e]Reaction using $Pd_2(dba)_3$ (7.5 mol %)/PPh_3 (15 mol %). DMA = *N*,*N*-dimethylacetamide. NMP = *N*-methyl-2-pyrrolidone.

products, pharmaceuticals, conducting materials, and asymmetric catalysts.[3] However, the relatively harsh reaction conditions for classical Ullmann coupling reactions limits their application for the synthesis of biaryls having labile functional groups. Although the recent development of catalytic Ullmann couplings involving Pd,[4] Ni,[5] and Co[6] catalysts made it possible to conduct the reaction in milder conditions, only a few examples of tandem Ullmann-type reactions, mostly based on the copper-catalyzed azide−alkyne cycloaddition (CuAAC), have been developed.[7] Therefore, the development of tandem Blaise/Ullmann coupling could expand the utility of both reactions.

It has been found that the coupling efficiency was largely dependent on the base, source of Pd(0), and reaction solvents. Thus, upon the addition of 1.0 equiv of ^{t}BuOK, biaryl **2a** was formed in 53% yield (entry 2, Table 1). To our delight, the reaction with 2.0 equiv of ^{t}BuOK afforded **2a** with the highest yield of 80% (entry 3, Table 1). The yield was decreased to 53% when reducing the loading amount of catalyst to 5.0 mol % (entry 4, Table 1). The use of other Pd catalysts, such as $Pd[P(^tBu)_3]_2$ or $Pd_2(dba)_3/PPh_3$, did not improve the yield (entries 5 and 6, Table 1). In addition, low yields were noted when other bases were used (entries 7−9, Table 1) and also when the solvent was changed to DMA, NMP (entries 10 and 11, Table 1), or others, such as toluene (8%), DMSO (48%), and dioxane (26%). The structure of **2a** was unambiguously determined by NMR, HR-MS, and X-ray spectroscopic analyses (Figure 1).[8]

Utilizing the optimized conditions (entry 3, Table 1), various enamino ester-functionalized biaryls were synthesized from the corresponding 2-bromoaryl nitriles (Table 2). The 2-bromobenzonitriles (**1b−1e**), having electron-donating methyl, methoxy, and dioxolane substituents, afforded the corresponding biaryls **2b−2e** in good yields ranging from 67 to 76%. The electron-withdrawing fluorine-, chlorine-, and trifluoromethyl-substituted benzonitriles were also well-tolerated under the reaction conditions, affording the corresponding biaryls **2f−2j** in moderate to good yields (50−73%). However, when the

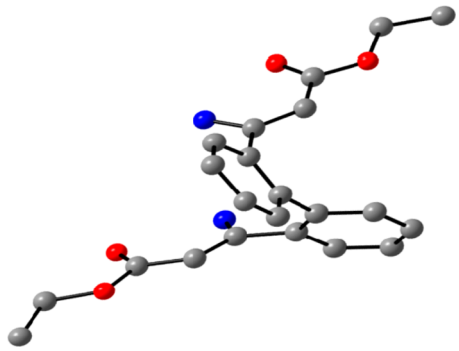
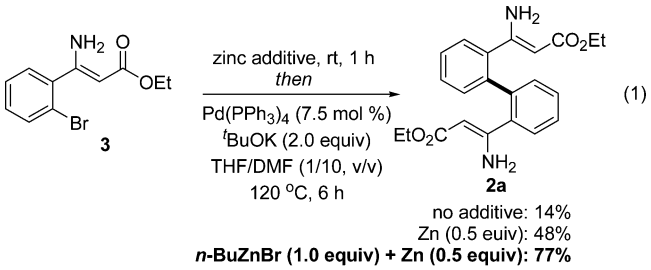
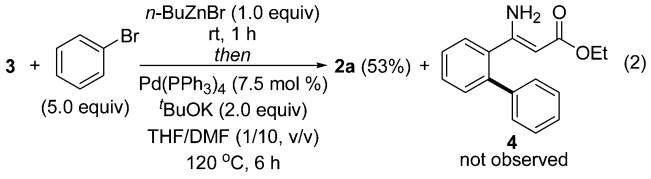


Figure 1. X-ray structure of **2a**. For clarity, hydrogens and disordered atoms were omitted.

same tandem coupling reactions were carried out with the sterically less demanding intermediates generated from *m*- (**1k**) and *p*-bromobenzonitriles (**1l**), much lower yields of the coupling products **2k** (41%) and **2l** (33%) were formed. In general, the Ullmann coupling with sterically less demanding *m*- and *p*-halogenated aryls provides high yields of the coupling products.

To determine the role of the zinc bromide complex in facilitating the Pd-catalyzed homocoupling of the intermediate formed from *o*-bromo arylnitriles, we investigated the effects of zinc additives on the isolated *β*-enamino ester **3** (eq 1). In the





absence of a zinc additive, only 14% of **2a** was isolated. The addition of 0.5 equiv of zinc increased the yield to 48%, suggesting that the zinc left over from the Blaise reaction could partially act as a reducing agent for Pd(II) species to the catalytically active Pd(0).[9] Although it is also known that DMF could also reduce Pd(II) to Pd(0) in the presence of base,[10] the lower yield of the coupling product suggested that the chelated ZnBr complex may play a crucial role in the catalytic cycle. Interestingly, the coupling efficiency was dramatically increased when **3** was pretreated with 1.0 equiv of *n*-BuZnBr, affording **2a** in 77% yield.[11] However, other zinc additives, such as $Zn(OAc)_2$ (42%) or Et_2Zn (54%), did not improve the yield. In addition, the Pd-catalyzed coupling of **3** after pretreatment with *n*-BuZnBr with excess amounts of bromobenzene also afforded homocoupled **2a** in 53% yield along with biphenyl, but cross-coupled product **4** was not observed (eq 2). These results suggest that the chelated ZnBr in intermediate **A** may participate in the catalytic cycle to facilitate the homocoupling of the intermediates derived from the *o*-bromoarylnitriles.

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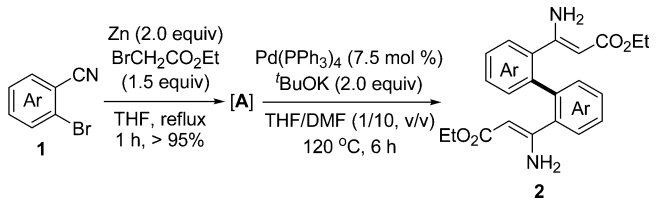
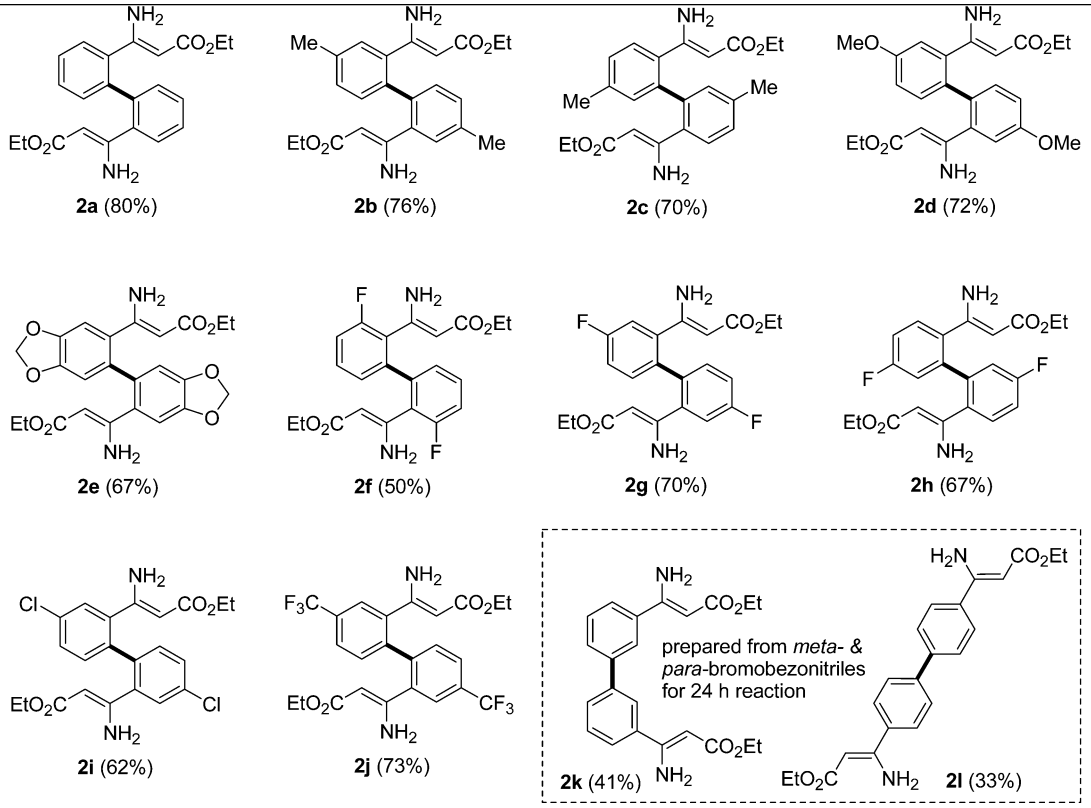
Table 2. Synthesis of Biaryls through Tandem Blaise/Pd-Catalyzed Ullmann Coupling[a]

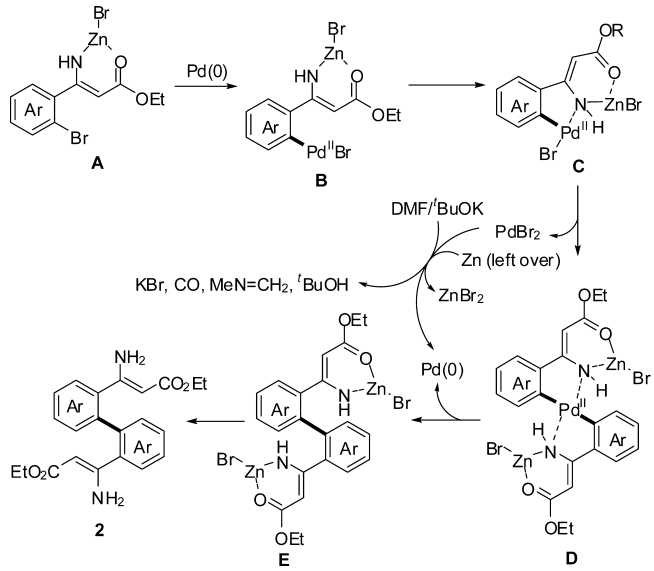




[a]Intermediate **A** was generated by the reaction of **1** (2.0 mmol) with ethyl bromoacetate (3.0 mmol, 1.5 equiv) and zinc (4.0 mmol, 2.0 equiv) in THF (1.0 mL) under reflux. After complete conversion of **1** to **A** (by GC and TLC), a solvent (THF/sol = 1/10 v/v), $Pd(PPh_3)_4$ (7.5 mol %), and ^tBuOK (2.0 equiv) were added at room temperature, and the reaction was conducted at 120 °C. Yields are isolated yields.

On the basis of these results, a plausible reaction mechanism for the Pd-catalyzed Ullmann coupling of Blaise reaction intermediate **A** is depicted in Scheme 2. The Pd(II) bromide complex **B**, formed by oxidative addition of Pd(0) to **A**, may be stabilized through coordination with the *o*-positioned nitrogen atom to form **C**. In Pd-catalyzed Ullmann coupling of aryl halides, it is generally considered that the oxidatively formed ArPd(II)X may be in equilibrium with Ar-Pd-Ar and PdX_2.[4,9] Likewise, the Pd(II) complex **C** could be converted to the coordinatively stabilized **D** with release of $PdBr_2$. Reductive elimination of **D** to form an Ar−Ar bond with regeneration of Pd(0) could afford **E**, giving coupling product **2** after hydrolytic workup. $PdBr_2$ can also be reduced to Pd(0) by the actions of leftover Zn[9] and/or DMF/base.[10] On the basis of this mechanistic rationale, the high coupling efficiency of the Blaise reaction intermediate generated from the 2-bromoarylnitriles is ascribed to the facile formation of intermediate **C** and **D** with the aid of the ortho-positioned enamino ester moiety. The chelated ZnBr not only increased electron-density facilitating coordination to form **C** and **D**, but also may act as an *N*-protecting group to prevent the formation of catalytically inactive Pd complexes.

Scheme 2. Proposed Reaction Mechanism



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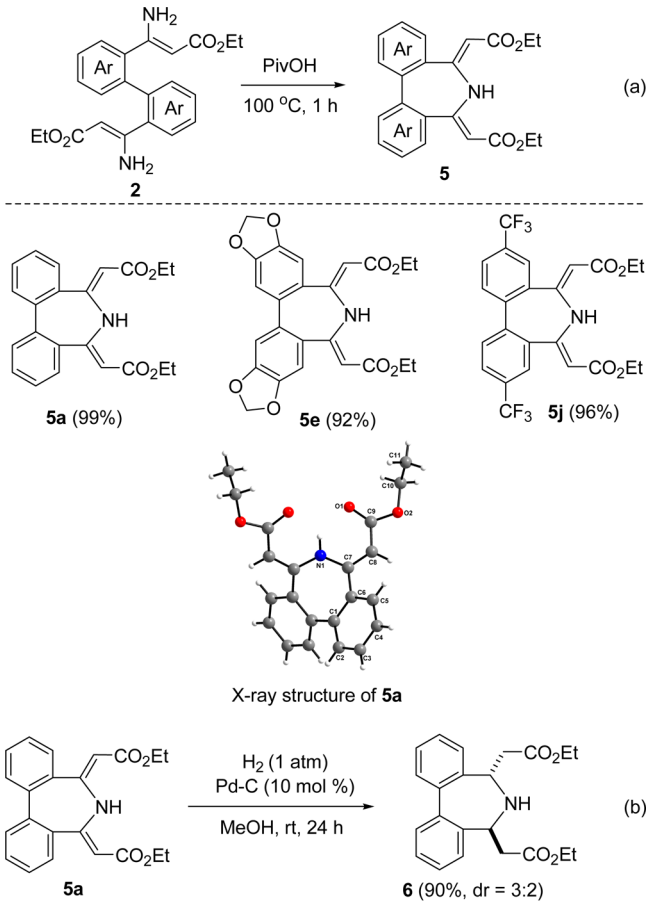
As an example of the potential application of biaryls **2**, we successfully transformed homocoupled product **2a** into 6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine derivative **6**, which could be a useful amine organocatalyst.[12] It was found that the 2,2′-substituted enamine moieties of **2** could be cyclized intramolecularly under acidic conditions through the conjugate addition/deamination cascade to afford **5** in almost quantitative yields (Scheme 3a). The structure of **5** was determined unambiguously by X-ray analysis of **5a**.[8] Through the catalytic hydrogenation of **5a** in the presence of Pd−C, the C_2-symmetric amine **6** could easily be synthesized in 90% yield with dr = 3:2 (Scheme 3b).

Scheme 3. Application of 2 for the Synthesis of Heterocyclic Compounds



In summary, we have developed an unprecedented tandem Pd-catalyzed Ullmann-type homocoupling reaction of the Blaise reaction intermediate generated by the reaction of *o*-bromo arylnitriles and a Reformatsky reagent for the one pot synthesis of enamino ester-functionalized biaryls in good yields. In this tandem catalytic transformation, the chelated ZnBr may be responsible for the ortho effect, exhibiting higher Ullmann coupling efficiency with the Blaise reaction intermediates formed from *o*-bromoarylnitriles than those of the intermediates formed from *m*- or *p*-bromoarylnitriles. The easy transformation of the coupling adduct to C_2-symmetric amines with biaryl backbones would also provide an opportunity to develop new chiral organocatalysts.

EXPERIMENTAL SECTION

All reactions were performed under a nitrogen atmosphere using standard Schlenk techniques. Reaction flasks were flame-dried under a stream of nitrogen. All purchased reagents were used without further purification. Anhydrous solvent was transferred by an oven-dried syringe. The NMR spectra were recorded at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C. HRMS data were obtained by electron ionization and fast atom bombardment with a magnetic sector-electronic sector double focusing mass analyzer.

General Procedure for Synthesis of Biaryls 2. To a stirred suspension of commercial zinc dust (10 μm, 254 mg, 4.0 mmol) in THF (1.0 mL) was added a solution of methanesulfonic acid in THF (1.0 M, 0.2 mL) at 80 °C (bath temperature). After stirring for 10 min, nitrile **1** (2.0 mmol) was added all at once. While maintaining the same temperature, ethyl bromoacetate (3.0 mmol) was added over 1 h using a syringe pump, and then the reaction mixture was further stirred for 1 h. After confirmed conversion of nitrile **1** (>95%) to the Blaise reaction intermediate **A** by gas chromatography, the reaction mixture was cooled to room temperature. To the reaction mixture were added $Pd(PPh_3)_4$ (7.5 mol %), potassium *tert*-butoxide (2.0 equiv), and 10 mL of anhydrous DMF. Then, the mixure was stirred for 6 h at 120 °C. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl solution. The organic compounds were extracted with ethyl acetate (50 mL × 3). The combined organic layer was dried with anhydrous Na_2SO_4, filtered through a pad of Celite 545, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography to afford pure **2**.

Diethyl (2*Z*,2′*Z*)-3,3′-Biphenyl-2,2′-diylbis(3-aminoprop-2-enoate) (2a). Yield: 80% (304 mg). Eluent: *n*-hexane/ethyl acetate = 6/1. White solid; mp 82−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 6H), 4.05 (q, J = 7.1 Hz, 4H), 4.48 (s, 2 H), 6.15 (brs, 4H), 7.30−7.33 (m, 2H), 7.35−7.47 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.6, 58.8, 87.8, 128.1, 128.7, 129.3, 130.9, 137.2, 138.5, 160.6, 170.1. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{22}H_{24}N_2O_4$, 380.1736; found, 380.1734.

Diethyl (2*Z*,2′*Z*)-3,3′-(4,4′-Dimethylbiphenyl)-2,2′-diylbis(3-aminoprop-2-enoate) (2b). Yield: 76% (311 mg). Eluent: *n*-hexane/ethyl acetate = 6/1. White solid; mp 52−54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, J = 7.1 Hz, 6H), 2.35 (s, 6H), 4.02 (q, J = 7.1 Hz, 4H), 4.51 (s, 2 H), 6.19 (brs, 4H), 7.17−7.23 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.4, 20.9, 58.5, 87.1, 129.2, 129.8, 130.7, 135.2, 136.9, 137.5, 161.1, 169.9. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{24}H_{28}N_2O_4$, 408.2049; found, 408.2050.

Diethyl (2*Z*,2′*Z*)-3,3′-(5,5′-Dimethylbiphenyl)-2,2′-diylbis(3-aminoprop-2-enoate) (2c). Yield: 70% (286 mg). Eluent: *n*-hexane/ethyl acetate = 6/1. White solid; mp 116−118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 6H), 2.38 (s, 6H), 4.05 (q, J = 7.1 Hz, 4H), 4.49 (s, 2 H), 6.12 (brs, 4H), 7.1 (s, 2H), 7.17 (dd, J = 7.9 Hz, 1.1 Hz, 2H), 7.26−7.35 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.6, 21.3, 58.7, 87.3, 128.6, 128.8, 131.5, 134.4, 138.5, 139.3, 160.9, 170.2. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{24}H_{28}N_2O_4$, 408.2049; found, 408.2047.

Diethyl (2*Z*,2′*Z*)-3,3′-(4,4′-Dimethoxylbiphenyl)-2,2′-diylbis(3-aminoprop-2-enoate) (2d). Yield: 72% (317 mg). Eluent: *n*-hexane/ethyl acetate = 6/1. Yellow solid; mp 110−112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, J = 7.1 Hz, 6H), 3.84 (s, 6H), 4.07 (q, J = 7.1 Hz, 4H), 4.52 (s, 2 H), 6.15 (brs, 4H), 6.91−6.97 (m, 4H), 7.18−7.21 (d, J= 8.4 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.6, 55.5, 58.8, 87.4, 113.8, 115.1, 130.3, 132.3, 138.4, 159.0, 160.9, 170.1. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{24}H_{28}N_2O_6$, 440.1947; found, 440.1945.

Diethyl (2*Z*,2′*Z*)-3,3′-(4,5−4′5′-Dibenzodioxole)-2,2′-diylbis(3-aminoprop-2-enoate) (2e). Yield: 67% (314 mg). Eluent: *n*-hexane/ethyl acetate = 4/1−2/1. Yellow solid; mp 82−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 6H), 4.05 (q, J = 7.1 Hz, 4H), 4.46 (s, 2H), 6.01 (s, 4H), 6.19 (brs, 4H), 6.71 (s, 2H), 6.88 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.5, 58.8, 87.4, 101.8, 108.9, 110.9, 131.0, 132.3, 147.3, 148.2, 160.4, 170.1. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{24}H_{24}N_2O_8$, 468.1533; found, 468.1535.

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Diethyl (2*Z*,2′*Z*)-3,3′-(3,3′-Difluorobiphenyl)-2,2′-diylbis(3-aminoprop-2-enoate) (2f). Yield: 50% (208 mg). Eluent: *n*-hexane/ethyl acetate = 6/1. Yellow solid; mp 138−140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, J = 7.1 Hz, 6H), 4.03 (q, J = 7.1 Hz, 4H), 4.49 (s, 2 H), 6.32 (brs, 4H), 7.11 (t, J = 7.9 Hz, 4H), 7.28−7.36 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.5, 59.0, 89.3, 115.5 (d, J = 22.7 Hz), 125.0 (d, J = 15.9 Hz), 126.6 (d, J = 3.0 Hz), 129.9 (d, J = 8.3 Hz), 139.5 (t, J = 2.3 Hz), 153.7, 159.3 (d, J = 249.2 Hz), 169.6. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{22}H_{22}F_2N_2O_4$, 416.1548; found, 416.1544.

Diethyl (2*Z*,2′*Z*)-3,3′-(4,4′-Difluorobiphenyl)-2,2′-diylbis(3-aminoprop-2-enoate) (2g). Yield: 70% (292 mg). Eluent: *n*-hexane/ethyl acetate = 4/1. Yellow solid; mp 110−112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 6H), 4.06 (q, J = 7.1 Hz, 4H), 4.42 (s, 2 H), 6.14 (brs, 4H), 7.09−7.19 (m, 4H), 7.24−7.29 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.5, 59.0, 88.4, 115.7 (d, J = 22.7 Hz), 116.3 (d, J = 21.1 Hz), 132.8 (d, J = 7.6 Hz), 133.6 (d, J = 3.8 Hz), 139.1 (d, J = 8.3 Hz), 158.9 (158.90), 158.9 (158.92), 162.2 (d, J = 249.2 Hz), 169.8. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{22}H_{22}F_2N_2O_4$, 416.1548; found, 416.1548.

Diethyl (2*Z*,2′*Z*)-3,3′-(5,5′-Difluorobiphenyl)-2,2′-diylbis(3-aminoprop-2-enoate) (2h). Yield: 67% (279 mg). Eluent: *n*-hexane/ethyl acetate = 4/1. Yellow solid; mp 102−104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 6H), 4.05 (q, J = 7.1 Hz, 4H), 4.41 (s, 2 H), 6.14 (brs, 4H), 7.03 (dd, J = 9.1 Hz, 2.6 Hz, 2H), 7.06−7.13 (m, 2H), 7.41−7.46 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.6, 59.0, 88.5, 115.5 (d, J = 21.1 Hz), 117.7 (d, J = 22.7 Hz), 130.7 (d, J = 9.1 Hz), 133.4 (d, J = 3.8 Hz), 139.8 (d, J = 8.3 Hz), 159.1, 162.7 (d, J = 251.4 Hz), 169.9. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{22}H_{22}F_2N_2O_4$, 416.1548; found, 416.1547.

Diethyl (2*Z*,2′*Z*)-3,3′-(4,4′-Dichlorobiphenyl)-2,2′-diylbis(3-aminoprop-2-enoate) (2i). Yield: 62% (279 mg). Eluent: *n*-hexane/ethyl acetate = 6/1. White solid; mp 140−142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 6H), 4.06 (q, J = 7.1 Hz, 4H), 4.43 (s, 2 H), 6.15 (brs, 4H), 7.21−7.24 (d, J = 8.2 Hz, 2H), 7.37−7.45 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.6, 59.1, 88.6, 128.8, 129.5, 132.2, 134.3, 135.9, 138.7, 158.7, 169.8. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{22}H_{22}{}^{35}Cl_2N_2O_4$, 448.0957; found, 448.0958; $[M]^+$ calcd for $C_{22}H_{22}{}^{37}Cl_2N_2O_4$, 450.0932; found, 450.0915.

Diethyl (2*Z*,2′*Z*)-3,3′-(4,4′-Trifluoromethylbiphenyl)-2,2′-diylbis(3-aminoprop-2-enoate) (2j). Yield: 73% (377 mg). Eluent: *n*-hexane/diethyl ether = 4/1. Yellow solid; mp 82−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 6H), 4.06 (q, J = 7.1 Hz, 4H), 4.44 (s, 2 H), 6.17 (brs, 4H), 7.46 (d, J = 8.0 Hz, 2H), 7.69−7.74 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.5, 59.2, 89.3, 123.7 (q, J = 272.6 Hz), 125.9 (q, J = 3.8 Hz), 126.2 (q, J = 3.8 Hz), 131.0 (q, J = 33.2 Hz), 131.3, 137.9, 141.0, 158.2, 169.7. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{24}H_{22}F_6N_2O_4$, 516.1484; found, 516.1485.

Diethyl (2*Z*,2′*Z*)-3,3′-Biphenyl-3,3′-diylbis(3-aminoprop-2-enoate) (2k). Yield: 41% (156 mg). Eluent: *n*-hexane/ethyl acetate = 4/1. Pale yellow solid; mp 118−120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 6H), 4.20 (q, J = 7.1 Hz, 4H), 5.03 (s, 2H), 7.48−7.57 (m, 4H), 7.64−7.75 (m, 2H), 7.75 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.7, 59.2, 85.2, 125.2, 125.6, 129.1, 129.6, 138.6, 141.2, 160.3, 170.5. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{22}H_{24}N_2O_4$, 380.1736; found, 380.1736.

Diethyl (2*Z*,2′*Z*)-3,3′-Biphenyl-4,4′-diylbis(3-aminoprop-2-enoate) (2l). Yield: 33% (126 mg). Eluent: *n*-hexane/ethyl acetate = 4/1. Pale yellow solid; mp 164−166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 6H), 4.29 (q, J = 7.1 Hz, 4H), 5.03 (s, 2 H), 7.63 (s, 8H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.7, 59.1, 88.9, 126.9, 127.5, 137.1, 142.0, 159.9, 170.5. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{22}H_{24}N_2O_4$, 380.1736; found, 380.1733.

General Procedure for the Synthesis of Compound 5. A solution of **2** (0.125 mmol) in pivalic acid (1.25 mL) was stirred for 1 h at 100 °C. The reaction mixture was cooled to room temperature and neutralized with saturated aqueous Na_2CO_3 solution. The organic compounds were extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate = 6/1 (v/v) with 2% of trimethylamine) to afford **5**.

Diethyl (2*Z*,2′*Z*)-2,2′-(5*H*-Dibenzo[*c*,*e*]azepine-5,7(6*H*)-diylidene)diethanoate (5a). Yield: 99% (45 mg). White solid; mp 168−170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, J = 7.1 Hz, 6H), 4.22 (q, J = 7.1 Hz, 4H), 5.46 (s, 2H), 7.34−7.41 (m, 2H), 7.46−7.50 (m, 6H), 11,85 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.5, 27.3, 59.9, 98.3, 128.4, 129.6, 130.4 (130.36), 130.4 (130.41), 136.9, 137.8, 154.6, 168.2. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{22}H_{21}NO_4$, 363.1471; found, 363.1469.

Diethyl (2*Z*,2′*Z*)-2,2′-(2,3-2′,3′-Dibenzodioxole-5*H*-[*c*,*e*]-azepine-5,7(6*H*)-diylidene)diethanoate (5e). Yield: 92% (52 mg). Yellow solid; mp 178−180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, J = 7.1 Hz, 6H), 4.21 (q, J = 7.1 Hz, 4H), 5.36 (s, 2H), 6.02 (d, J = 1.3 Hz, 2H), 6.03 (d, J = 1.3 Hz, 2H), 6.86 (s, 2H), 6.92 (s, 2H), 11.79 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.6, 59.8, 97.9, 102.0, 109.1, 110.3, 130.6, 132.4, 147.6, 149.5, 154.2, 168.1. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{24}H_{21}NO_8$, 451.1267; found, 451.1264.

Diethyl (2*Z*,2′*Z*)-2,2′-(2,2′-Trifluoromethyl-5*H*-dibenzo[*c*,*e*]-azepine-5,7(6*H*)-diylidene)diethanoate (5j). Yield: 96% (60 mg). Yellow solid; mp 164−168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, J = 7.1 Hz, 6H), 4.24 (m, 4H), 5.52 (s, 2H), 7.66 (d, J = 8.6 Hz, 2H), 7.79−7.81 (m, 4H), 11.76 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.5, 60.3, 123.6 (q, J = 273 Hz), 127.1 (q, J = 3.8 Hz), 127.6 (q, J = 3.8 Hz), 130.4, 131.5 (q, J = 33.2 Hz), 137.7, 139.9, 152.2, 167.73. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{24}H_{19}F_6NO_4$, 499.1218; found, 499.1218.

Synthesis of 6. A solution of **5a** (36.3 mg, 0.1 mmol), Pd/C (10 wt %, 10.6 mg, 10 mol % based on Pd contents) in anhydrous methanol (1.0 mL) was stirred for 24 h at room temperature under hydrogen atmosphere (1 atm, balloon). The reaction mixture was diluted with ethyl acetate, filtered through a pad of Celite 545, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate = 4/1 to 2/1 with 2% of trimethylamine) to afford **6** (33 mg, 90%) with a trans/cis = 3:2 ratio. Diastereomer ratio = 3:2. Major: ^{1}H NMR (300 MHz, D_2O+HCl): δ 1.01 (t, J = 7.2 Hz, 6H), 3.07−3.19 (m, 2H), 3.38 (dd, J = 17 Hz, 8.8 Hz, 2H), 3.92−4.02 (m, 4H), 5.00 (t, J = 7.8 Hz, 2H), 7.38−7.59 (m, 8H). Minor: ^{1}H NMR (300 MHz, D_2O+HCl): δ 0.90 (t, J = 7.2 Hz, 6H), 1.95−2.03 (m, 2H), 2.38 (dd, J = 16.5 Hz, 7.5 Hz, 2H), 3.76−3.86 (m, 4H), 4.27 (dd, J = 9.2 Hz, 5.7 Hz, 2H), 7.38−7.59 (m, 8H). Resonance signals overlapped: ^{13}C NMR (75.5 MHz, D_2O +HCl): δ 13.0 (12.96), 13.0 (13.01), 33.4, 33.6, 37.0, 51.8, 52.2, 57.4, 62.1, 62.4, 125.5, 125.7, 129.0, 129.1, 129.2 (129.20), 129.2 (129.24), 129.5, 130.0, 130.7, 131.1, 131.2 (131.15), 131.2 (131.21), 138.4, 140.2, 140.4, 171.1, 171.2. HRMS (EI) (m/z): $[M]^+$ calcd for $C_{22}H_{25}NO_4$, 367.1784; found, 367.1781.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystal data of **2a** and **5a** and copies of ^{1}H and ^{13}C NMR spectra for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01375.

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Notes

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