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Advanced Synthesis & Catalysis

Bis(cycloocta-1,5-diene)nickel-Catalyzed Carbon Dioxide Fixation for the Stereoselective Synthesis of 3-Alkylidene-2-indolinones

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Abstract: A bis(cycloocta-1,5-diene)nickel-catalyzed highly regio- and (*E*)-stereoselective hydrocarboxylation of 2-alkynylanilines under very mild conditions has been developed to afford (*E*)-[2-(*o*-aminophenyl)]acrylic acids, which could easily be converted to (*E*)-3-alkylidene-2-indolinones with important potential bioactivity. The stereoselective syntheses of two biologically active molecules, (*E*)-3-benzylidene-2-indolinone (chemo-preventive potential in inducing NQO1 activity) and (*E*)-3-(3-methylbutylidene)-2-indolinone (a natural product isolated from *Cimicifuga foetida* with cytotoxic activity against HL-60 cells) are presented as examples.

Keywords: acrylic acids; 2-alkylanilines; bis(cycloocta-1,5-diene)nickel [Ni(COD)$_2$]; carbon dioxide; hydrocarboxylation

Introduction

3-Alkylidene-2-indolinones and their derivatives are important frameworks existing in various drugs and biologically active molecules (Figure 1).[1] Previous pharmaceutical research has indicated that in many cases different steric configurations of the C=C bond in 3-alkylidene-2-indolinones may lead to different biological activities.[2] However, from a synthetic aspect, stereospecific syntheses toward 3-alkylidene-2-indolinones are still under developed: the established approaches including Knoevenagel condensation[3] and Pd-catalyzed carbonyl insertion reactions[4] usually led to a mixture of stereoisomers with unsatisfactory *E*/*Z* ratios [Scheme 1, Eq. (1)].

Recently much attention has been focused on the fixation of inert, non-toxic, yet very cheap CO_2.[5] The key is to activate the rather unreactive C=O bonds. Under the catalysis of transition metals, CO_2 has been developed as a useful reagent for the construction of the carboxylic acid unit.[6] We reasoned that the amide unit in the compounds listed in Figure 1 may be formed by the lactamization of a carboxylic acid with an amine. In 2011, our group reported an

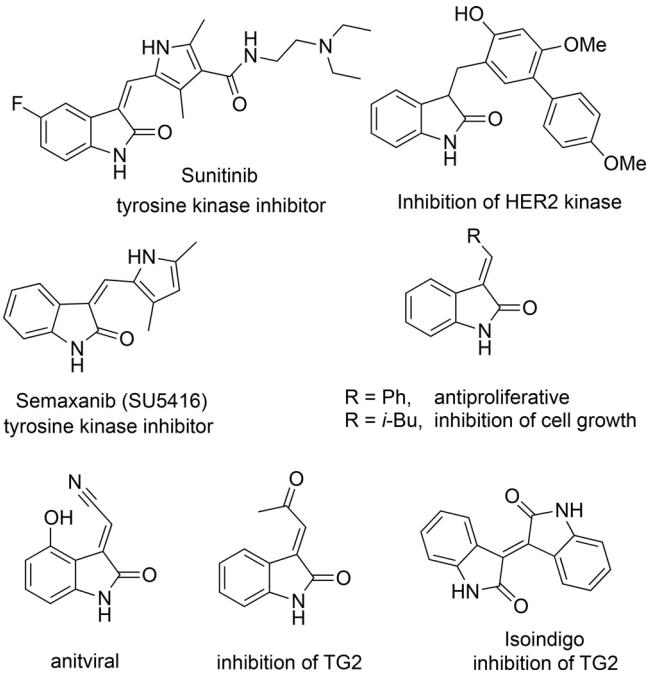
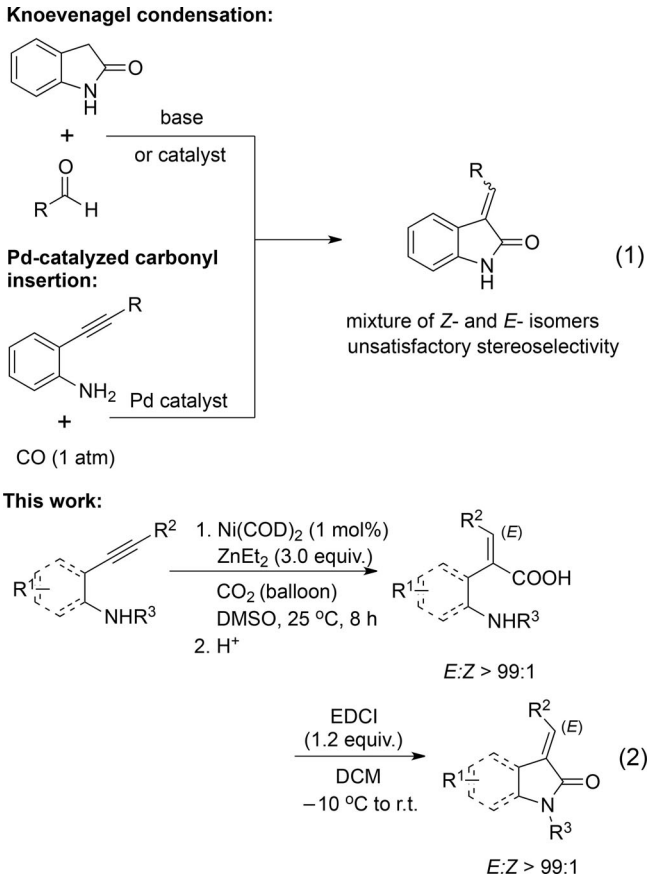


Figure 1. Bioactive 3-alkylidene-2-indolinone derivatives.

$Ni(COD)_2$-catalyzed *syn*-hydrocarboxylation reaction of simple alkynes with CO_2 under very mild conditions.[7–9] However, we observed that the regioselectivity is rather poor for unsymmetrical alkynes. We observed that the amide unit in 2-alkynylanilines **1** may act as a directing group to dictate the regioselectivity of their *syn*-hydrocarboxylation, thus forming (*E*)-2-[*o*-(*N*-tosylamino)phenyl]acrylic acids *E*-**2** with exclusive regio- and (*E*)-stereoselectivities from **1**. Herein we would like to present our comprehensive study on the $Ni(COD)_2$-catalyzed *syn*-hydrocarboxylation reaction of 2-alkynylanilines with carbon dioxide and its application in the stereoselective syntheses of two bioactive(*E*)-3-alkylidene-2-indolinones.

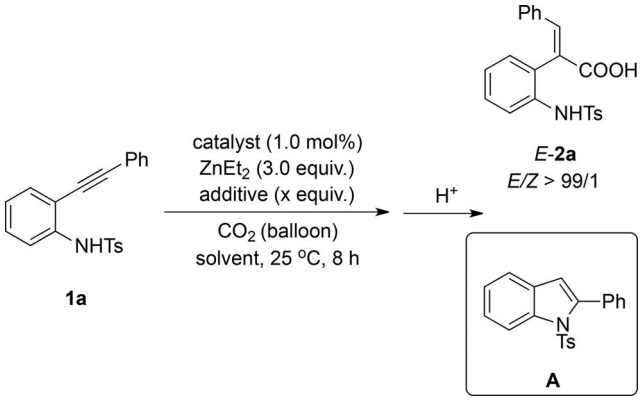


Scheme 1. Stereoselective problems in the synthesis of 3-alkylidene-2-indolinones.

Results and Discussion

The hydrocarboxylation reaction was first conducted with 2-(2-phenylethynyl)aniline **1a** and 3.0 equiv. of $ZnEt_2$ at room temperature with a CO_2 balloon by using 1.0 mol% of $Cu(OAc)_2$ as the catalyst. However, only the cycloisomerization product indole **A** was formed in 53% yield (Table 1, entry 1). Omitting the catalyst led to a high recovery of **1a** together with 16% of indole **A** (Table 1, entry 2). Luckily, we found that *E*-**2a** was afforded in >99% yield with no regio- or stereoisomer being observed as judged by ^1H NMR analysis on using 1.0 mol% of $Ni(COD)_2$ as the catalyst (Table 1, entry 3). Either reducing the equivalents of $ZnEt_2$ or raising the temperature cause diminished yields (Table 1, entries 4 and 7). The use of other solvents led to complicated results (Table 1, entries 5 and 6). Additives such as LiCl[10] and CsF[7,11] are not required (Table 1, entries 8–10). The reactions with 0.1 mol% of $Ni(COD)_2$ are incomplete (Table 1, entries 11–13).

Table 1. Optimization of the reaction conditions.[a]

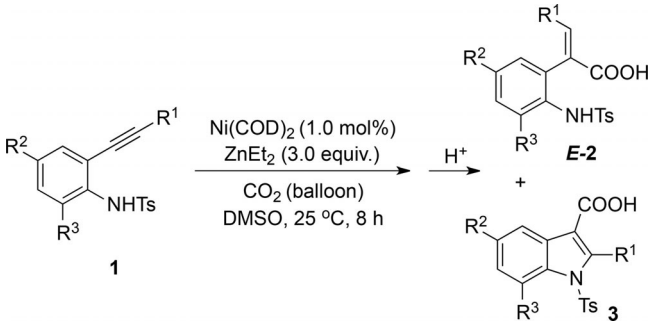


Entry	Catalyst	Solvent	Additive (equiv.)	Yield [%][b] *E*-**2a**	**A**	**1a**
1	$Cu(OAc)_2$	DMSO	–	n.d.	53	12
2	–	DMSO	–	n.d.	16	81
3	$Ni(COD)_2$	DMSO	–	>99	n.d.	n.d.
4[c]	$Ni(COD)_2$	DMSO	–	80	n.d.	n.d.
5	$Ni(COD)_2$	DMF	–	n.d.	n.d.	76
6	$Ni(COD)_2$	CH_3CN	–	n.d.	n.d.	66
7[d]	$Ni(COD)_2$	DMSO	–	85	n.d.	n.d.
8	$Ni(COD)_2$	DMSO	CsF (0.5)	>99	n.d.	n.d.
9	$Ni(COD)_2$	DMSO	CsF (1.0)	96	n.d.	n.d.
10	$Ni(COD)_2$	DMSO	LiCl (1.0)	>99	n.d.	n.d.
11	$Ni(COD)_2$[e]	DMSO	–	8	14	70
12	$Ni(COD)_2$[e]	DMSO	CsF (1.0)	–	21	73
13	$Ni(COD)_2$[e]	DMSO	LiCl (1.0)	8	34	52

[a] The reaction was conducted with 0.5 mmol of **1a**, $Ni(COD)_2$ (1.0 mol%) and 1.5 mmol of $ZnEt_2$ (1.5 M in toluene, 1.0 mL) in 3 mL of anhydrous solvent with a CO_2 balloon.
[b] Determined by ^1H NMR analysis of the crude reaction mixture.
[c] 2.0 equiv. of $ZnEt_2$ were used.
[d] The reaction was conducted at 60 °C.
[e] The reaction was conducted with 0.1 mol% of $Ni(COD)_2$.

Based on the standard reaction conditions shown in entry 3 of Table 1, the substrate scope and the functional group tolerance of the reaction were carefully investigated. Different substituents including aryl (Table 2, entries 1, 2 and 4), heterocyclic aryl (Table 2,

Table 2. $Ni(COD)_2$-catalyzed hydrocarboxylation of 2-alkynylanilines.[a]



Entry	1			Yield of	
	R^1	R^2	R^3	**2** [%][b]	**3** [%][c]
1	Ph	H	H (**1a**)	99 (*E*-**2a**)	n.d.
2[d]	Ph	H	H (**1a**)	94 (*E*-**2a**)	n.d.
3	2-thienyl	H	H (**1b**)	97 (*E*-**2b**)	n.d.
4	1-naphthyl	H	H (**1c**)	92 (*E*-**2c**)	n.d.
5	cyclopropyl	H	H (**1d**)	92 (*E*-**2d**)	n.d.
6	*t*-Bu	H	H (**1e**)	92 (*E*-**2e**)	n.d.
7	*n*-Bu	H	H (**1f**)	80 (*E*-**2f**)	16 (**3f**)
8	*n*-Bu	F	H (**1g**)	84 (*E*-**2g**)	8 (**3g**)
9	*n*-Bu	Cl	H (**1h**)	88 (*E*-**2h**)	6 (**3h**)
10	*n*-Bu	Br	H (**1i**)	90 (*E*-**2i**)	4 (**3i**)
11	*n*-Bu	CF_3	H (**1j**)	71 (*E*-**2j**)	20 (**3j**)
12	*n*-Bu	MeOOC	H (**1k**)	80 (*E*-**2k**)	16 (**3k**)
13	*n*-Bu	MeO	H (**1l**)	91 (*E*-**2l**)	n.d.
14	*n*-Bu	Cl	F (**1m**)	98 (*E*-**2m**)	n.d.
15	4-NCC_6H_4	H	H (**1n**)	88 (*E*-**2n**)	n.d.
16[e]	4-HOC_6H_4	H	H (**1o**)	86 (*E*-**2o**)	n.d.

[a] The reaction was conducted with 1.0 mmol of **1**, 0.01 mmol of $Ni(COD)_2$, and 3.0 mmol of $ZnEt_2$ (1.5 M in toluene, 2.0 mL) in 6 mL of anhydrous DMSO at room temperature with a CO_2 balloon.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude reaction mixture.
[d] The reaction was conducted with 4.5 mmol of **1a**, 0.0045 mmol of $Ni(COD)_2$, and 13.5 mmol of $ZnEt_2$ (1.5 M in toluene, 9.0 mL) in 27 mL of anhydrous DMSO at room temperature with a CO_2 balloon.
[e] 4.0 equiv. of $ZnEt_2$ were used.

entry 3), alkyl (Table 2, entries 6 and 7) and cycloalkyl groups (Table 2, entry 5) on the terminal position of the alkynes moiety were tested to afford the corresponding acrylic acids *E*-**2** in very good yields and specific regio- and (*E*)-stereoselectivities. The reaction could easily be conducted on a 4.5 mmol scale and the catalyst loading could be further reduced to 0.1 mol% affording a 97% yield (1.66 g) of *E*-**2a** (Table 2, entry 2). Both electron-donating and electron-withdrawing groups on the aryl ring did not affect the yield (Table 2, entries 8–16). In some cases, cyclic *anti*-azacarboxylation products **3** were also observed when R^1 is *n*-Bu (Table 2, entries 7–12).[12] Reactive functional groups including sp^2 C–Br, cyano and ester groups were well tolerated (Table 2, entries 10, 12 and 15). Furthermore, 2-alkynylaniline **1o** bearing a free hydroxy group in the phenyl group provided *E*-**2o** in 86% yield (Table 2, entry 16).

The steric configurations of *E*-**2** were confirmed by the X-ray diffraction study of *E*-**2e** (Figure 2).[13]

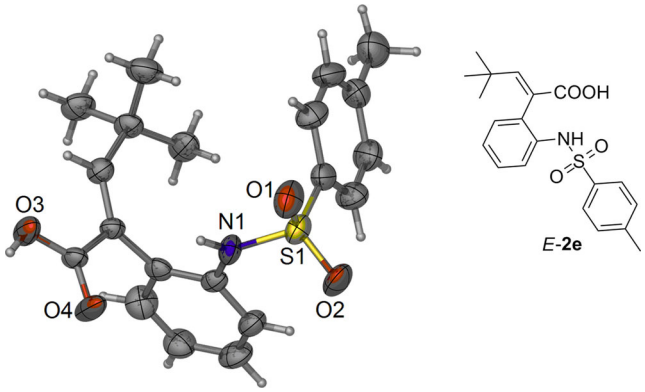
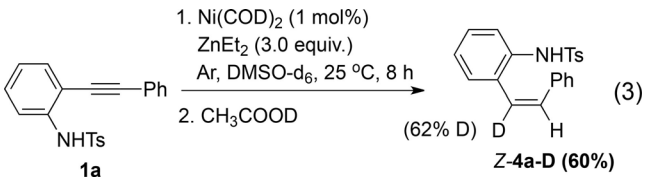


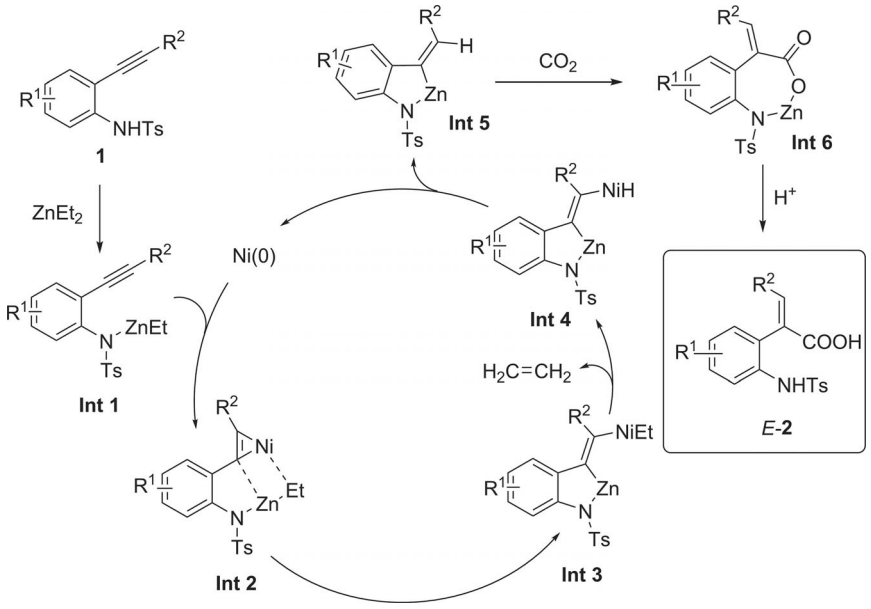
Figure 2. ORTEP representation of *E*-**2e**.

To understand the mechanism, the reaction of **1a** was conducted in DMSO-d_6 for 8 h under an argon atmosphere and quenched by DOAc. (*Z*)-*N*-(2-Styrylphenyl)-4-methylbenzenesulfonamide *Z*-**4a-D**, was isolated in 60% with 62% of D-incorporation to the olefinic carbon atom connected to the benzene ring with –NHTs [Eq. (3)].

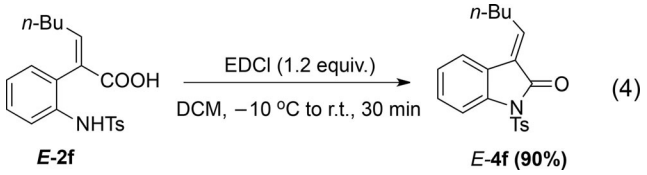


Thus, a possible mechanism was proposed as shown in Scheme 2. Deprotonation of 2-alkynylaniline **1** with $ZnEt_2$ forms **Int 1**. The oxidative addition of Ni(0) species with the C≡C triple bond would form metacyclopropene **Int 2**, which would undergo intramolecular transmetallation to form **Int 3**. **Int 5** is generated after β-hydrogen elimination and reductive elimination and regeneration of Ni(0) to complete the catalytic cycle. **Int 5** reacts with carbon dioxide to form **Int 6**, which then generates *E*-**2** after being quenched with protons.[14] Comparing the low regioselectivity of simple alkynes,[7a,8] we reasoned that the amide group is responsible for the observed specific regio- and (*E*)-stereoselectivity.

Due to the bio-importance of 3-alkylidene-2-indolinones, the (*E*)-[2-(*o*-amino)phenyl]acrylic acid *E*-**2f** thus prepared was transformed to *E*-**4f** with the aid of EDCI under very mild conditions[15] as shown in Eq. (4).



Scheme 2. Hypothesis on the reaction mechanism.

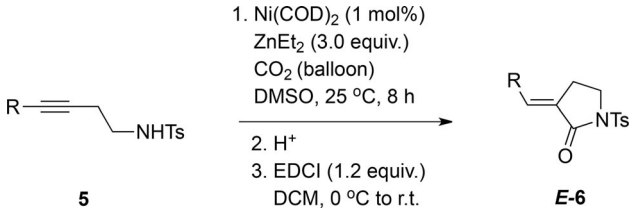


Furthermore, such a strategy was applied to prepare the non-benzo-fused lactams **6**. It was observed that the phenyl moiety is ***not*** necessary in this reaction: *N*-Ts substituted homopropargyl amines **5** may also undergo the *syn*-hydrocarboxylation reactions highly regio- and stereoselectively under the typical conditions followed by a direct intramolecular amidation to afford α-alkylidene-γ-butyrolactam *E*-**6** in very high yields, exclusively! Both aryl and alkyl groups were tolerated (Table 3, entries 1–4) and the reaction allows functionalities including halogen and ester (Table 3, entries 2 and 3).

In consideration of the difficulty in removing the *N*-tosyl group, several easily removable protecting groups were then screened. The introduction of acetyl and trifluoroacetyl groups on the amino group did not affect the yield or the selectivity: the corresponding acids *E*-**2p** and *E*-**2q** were also successfully afforded in greater than 80% yields (Scheme 3).

To further illustrate the potential of this approach in medicinal chemistry, gram-scale syntheses of two bioactive 3-alkylidene-2-indolinones were carried out. (*E*)-3-Benzylidene-2-indolinone *E*-**9a** is a widely investigated compound with chemopreventive potential in inducing NQO1 activity.[16] The Sonogashira coupling of 2-iodoaniline with phenylacetylene afforded **7a** in 95% yield followed by protection of the amino group with trifluoroacetic anhydride to afford **1r**. The hydrocarboxylation proceeded smoothly under the typical conditions, the acrylic acid *E*-**2r** was obtained in 96% yield. However, we observed that the conden-

Table 3. Synthesis of α-alkylidene-γ-butyrolactams ***E*-6**.[a]



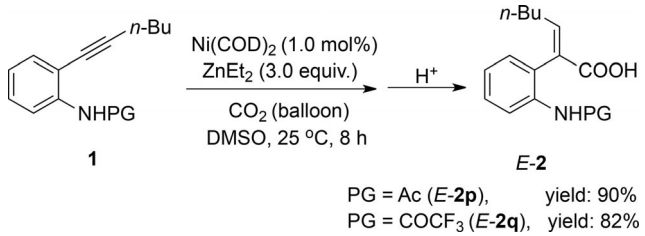
Entry	R	Yield of ***E*-6** [%][b]
1	Ph (**5a**)	99 (***E*-6a**)
2	*p*-BrC_6H_4 (**5b**)	92 (***E*-6b**)
3	*p*-$EtOOCC_6H_4$ (**5c**)	87 (***E*-6c**)
4[c]	*n*-C_5H_{11} (**5d**)	77 (***E*-6d**)
5	*n*-C_5H_{11} (**5d**)	59 (***E*-6d**)[d]

[a] The hydrocarboxylation reaction was conducted with 1.0 mmol of **5**, 0.01 mmol of $Ni(COD)_2$, and 3.0 mmol of $ZnEt_2$ (1.5 M in toluene, 2.0 mL) in 6 mL of DMSO at room temperature with a CO_2 balloon followed by the amidation with 1.2 mmol of EDCI in 20 mL of DCM.

[b] Isolated yield.

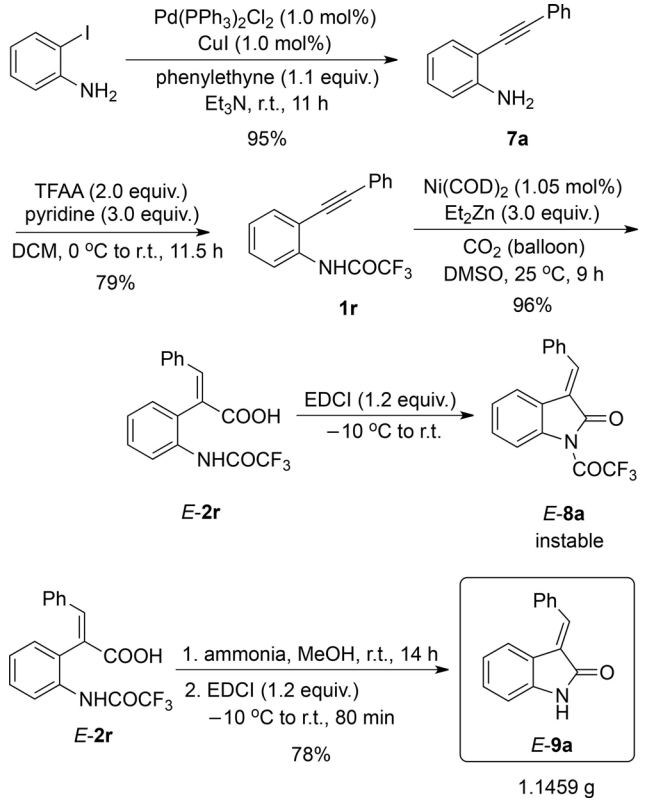
[c] The hydrocarboxylation reaction was conducted with 0.5 mmol of **5d**, 0.015 mmol of $Ni(COD)_2$, 0.1 mmol of CsF, and 1.5 mmol of $ZnEt_2$ (1.5 M in toluene, 2.0 mL) in 3 mL of DMSO at room temperature in 6 h with a CO_2 balloon followed by the amidation with 0.6 mmol of EDCI in 10 mL of DCM.

[d] Determined by ^1H NMR analysis of the crude reaction mixture.



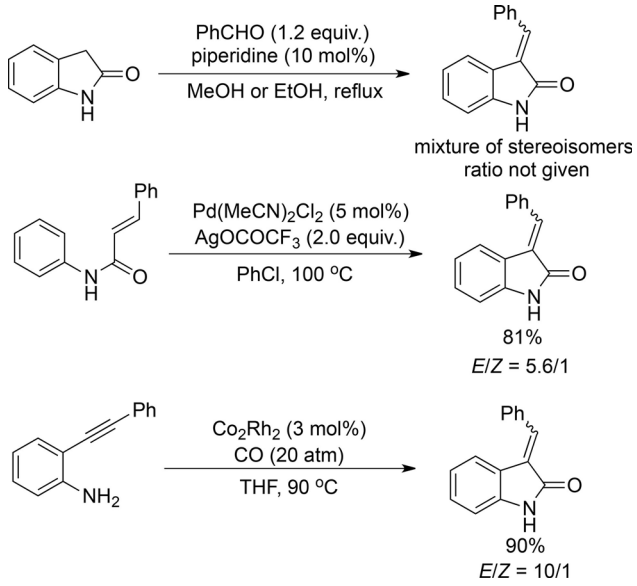
Scheme 3. Screening of the protecting groups.

sation product *E*-**8a** was highly unstable, and thus, could not be separated *via* column chromatography on silica gel. Thus, we revised the synthetic route: after removal of the protecting group, i.e., $COCF_3$ of *E*-**2r** on the amino group[17] and an intramolecular lactam formation reaction with EDCI, the (*E*)-3-benzylidene-2-indolinone *E*-**9a** was afforded in a total yield of 56% (1.15 g) after 4 steps (Scheme 4).

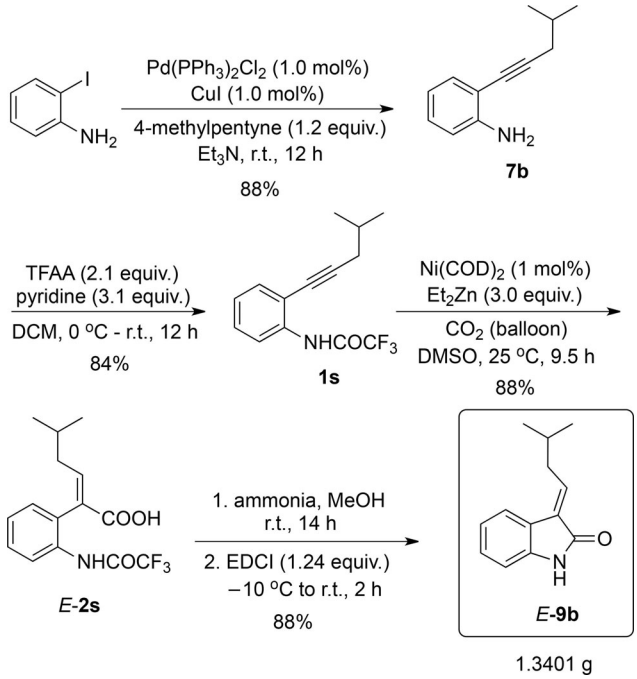


Scheme 4. Synthesis of (*E*)-3-benzylidene-2-indolinone *E*-**9a**.

As a comparison, most of the reported approaches yielded a mixture of the stereoisomers (Scheme 5).[4,18] A similar synthetic route was also utilized in the first synthesis of (*E*)-3-(3-methylbutylidene)-2-indolinone, a natural product isolated from *Cimicifuga foetida* which exhibited cytotoxic activity against HL-60 cells.[19] *E*-**9b** (1.34 g) was prepared from the simple starting materials 2-iodoaniline and 4-methylpentyne in a total yield of 57% after 4 steps (Scheme 6).



Scheme 5. Comparison with the reported approaches.



Scheme 6. Synthesis of (*E*)-3-(3-methylbutylidene)-2-indolinone *E*-**9b**.

Conclusions

In summary, a highly regio- and (*E*)-stereoselective *syn*-hydrocarboxylation of 2-alkynylanilines at room temperature with 1 atm of CO_2 was reported to afford (*E*)-[2-(*o*-amino)phenyl]acrylic acids in very high yields, which provided a very convenient approach for the stereospecific synthesis of various biologically active (*E*)-3-alkylidene-2-indolinones. The

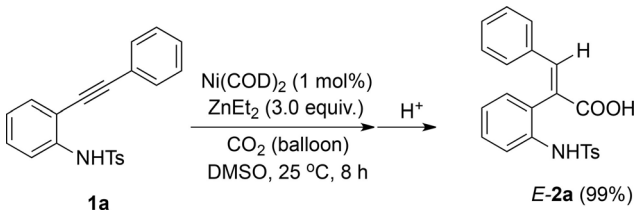
reaction presents very wide substrates scope and sensitive functional groups such as Br, cyano, ester or even a hydroxy group were well tolerated. Further studies on the synthesis of other bioactive molecules shown in Figure 1 are being actively pursued in our group.

Experimental Section

General Information

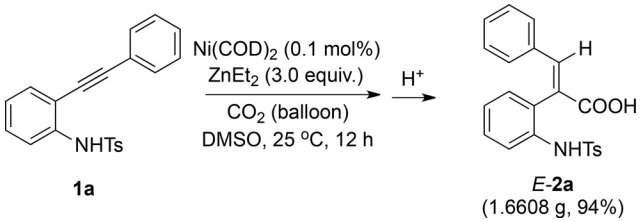
All reactions were carried out in 50-mL Schlenk tubes. 2-Alkynylanilines **1a–1q** and **4a–4d** were prepared according to the literature methods.[20] $Ni(COD)_2$ was purchased from Strem. $ZnEt_2$ (1.5 M in toluene) was purchased from Acros. CsF was purchased from Alfa-Aesar. DMSO and DCM were dried over CaH_2 and distilled right before use. The purity of CO_2 was 99.995% and it used without further treatment. All the temperatures are referred to the bath temperature. NMR spectra were taken using TMS (^1H, $\delta=0$), DMSO-d_6 (^1H, $\delta=2.5$), $CDCl_3$ (^{13}C CPD, $\delta=77.0$), DMSO-d_6 (^{13}C CPD, $\delta=29.5$) and $CFCl_3$ (^{19}F CPD, $\delta=0$) as the internal standards.

Synthesis of (*E*)-2-[2-(*N*-Tosylamino)phenyl]-3-phenylacrylic Acid (*E*-2a)



Typical Procedure I: To an oven-dried 50-mL Schlenk tube was added **1a** (347.2 mg, 1.0 mmol) under an argon atmosphere. $Ni(COD)_2$ (2.9 mg, 0.01 mmol) was added inside a glove box and then 6 mL of DMSO were added under argon. The mixture was frozen with a liquid nitrogen bath and the argon inside was completely replaced with CO_2 by using a CO_2 balloon (about 1 L). Then the reaction flask was allowed to stand until the mixture thawed. To the resulting suspension was added $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol) *via* a syringe with stirring. Then the resulting mixture was stirred at room temperature for 8 h. After that, the resulting mixture was quenched with 10 mL of 3 M aqueous solution HCl. The aqueous layer was extracted with ethyl acetate (10 mL × 5) and the combined organic layer was washed with 30 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 20/1) to afford *E*-**2a** as a white solid; yield: 390.1 mg (99%); mp 207–208 °C (petroleum ether/ethyl acetate) (Lit.[7] mp: 207–208 °C, petroleum ether/ethyl acetate); ^1H NMR (400 MHz, DMSO-d_6): $\delta=12.54$ (bs, 1H, COOH), 9.49 (s, 1H, NH), 7.78 (s, 1H, HC=), 7.65 (d, $J=8.0$ Hz, 2H, ArH), 7.27–7.17 (m, 4H, ArH), 7.16–7.04 (m, 4H, ArH), 7.03–6.95 (m, 3H, ArH), 2.29 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=168.1$, 142.9, 140.6, 137.6, 135.8, 134.4, 131.3, 131.0, 130.3, 130.2, 129.5, 129.0, 128.5, 128.1, 126.9, 125.2, 122.6, 21.0; MS (ESI): $m/z=457$ $[M+MeCN+Na]^+$, 416 $[M+Na]^+$; IR (neat): $\nu=3500$–2200 (br), 1695, 1671, 1615, 1600, 1573, 1489, 1449, 1427, 1405, 1377, 1341, 1322, 1294, 1268, 1226, 1208, 1188, 1163, 1121, 1093, 1045 cm^{-1}.

Gram-Scale Synthesis of (*E*)-2-[2-(*N*-Tosylamino)-phenyl]-3-phenylacrylic Acid (*E*-2a)

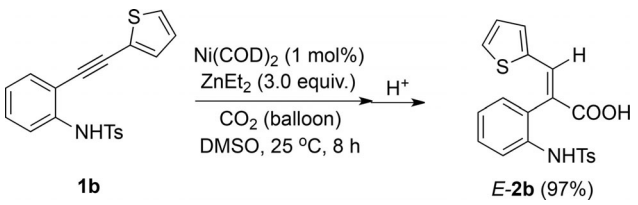


To an oven-dried 250-mL Schlenk flask was added **1a** (1.5635 g, 4.5 mmol) under an argon atmosphere. $Ni(COD)_2$ (1.2 mg, 0.0045 mmol) was added inside a glove box and then 27 mL of DMSO were added under argon. The mixture was frozen with a liquid nitrogen bath and the argon inside was completely replaced with CO_2 by using a CO_2 balloon. Then the reaction flask was allowed to stand until the mixture thawed. To the resulting suspension was added $ZnEt_2$ (1.5 M in toluene, 9.0 mL, 13.5 mmol) a syringe with stirring. Then the resulting mixture was stirred at 25 °C for 12 h. After that, the resulting mixture was quenched with 45 mL of aqueous solution of 3 M HCl. The aqueous layer was extracted with ethyl acetate (45 mL × 5) and the combined organic layer was washed with 135 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 20/1) to afford *E*-**2a** as a white solid; yield: 1.6608 g (94%). ^1H NMR (400 MHz, DMSO-d_6): $\delta=12.55$ (bs, 1H, COOH), 9.53 (s, 1H, NH), 7.75 (s, 1H, HC=), 7.63 (d, $J=8.4$ Hz, 2H, ArH), 7.27–7.17 (m, 4H, ArH), 7.13 (t, $J=7.6$ Hz, 2H, ArH), 7.09–7.02 (m, 2H, ArH), 7.01–6.94 (m, 3H, ArH), 2.30 (s, 3H, CH_3).

The following compounds were prepared according to this Typical Procedure I.

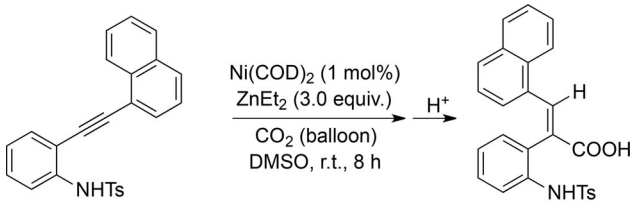
Synthesis of (*E*)-2-[2-(*N*-Tosylamino)phenyl]-3-(2-thienyl)acrylic Acid (*E*-2b)

The reaction of **1b** (353.5 mg, 1.0 mmol), $Ni(COD)_2$ (2.8 mg, 0.01 mmol), $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2b**[7] (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/



MeOH = 30/1) as a white solid; yield: 385.6 mg (97%); mp 200–201 °C (petroleum ether/ethyl acetate) (Lit.[7] mp 200–201 °C, petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.39 (bs, 1H, COOH), 9.47 (s, 1H, NH), 7.98 (s, 1H, HC=), 7.59 (d, J = 8.1 Hz, 2H, ArH), 7.44 (d, J = 5.1 Hz, 1H, ArH), 7.35–6.94 (m, 8H, ArH), 2.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.8, 142.9, 138.3, 137.4, 136.2, 134.4, 133.8, 131.6, 131.5, 129.3, 129.1, 128.9, 126.8, 126.6, 126.4, 125.1, 121.7, 21.1; MS (ESI): m/z = 819 $[2M-2H+Na]^-$, 398 $[M-H]^-$; IR (neat): ν = 3700–2200 (br), 1691, 1667, 1600, 1578, 1488, 1431, 1406, 1380, 1339, 1275, 1242, 1215, 1190, 1165, 1094, 1058 cm^{-1}.

Synthesis of (*E*)-2-[2-(*N*-Tosylamino)phenyl]-3-(1-naphthyl)acrylic Acid (*E*-2c)

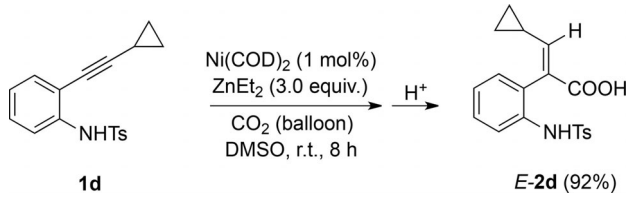


1c *E*-**2c** (92%)

The reaction of **1c** (397.5 mg, 1.0 mmol), Ni(COD)$_2$ (2.8 mg, 0.01 mmol), ZnEt$_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2c** (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 30/1) as a yellow solid; yield: 407.1 mg (92%); mp 204–205 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.71 (s, 1H, COOH), 9.51 (s, 1H, NH), 8.39 (s, 1H, HC=C), 8.16 (d, J = 8.4 Hz, 1H, ArH), 7.94 (d, J = 7.5 Hz, 1H, ArH), 7.79 (d, J = 8.1 Hz, 1H, ArH), 7.69–7.51 (m, 4H, ArH), 7.29 (d, J = 8.1 Hz, 2H, ArH), 7.16–6.97 (m, 3H, ArH), 6.92–6.81 (m, 3H, ArH), 2.33 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.0, 143.0, 137.93, 137.91, 137.5, 136.0, 133.4, 133.0, 131.7, 131.53, 131.48, 129.5, 128.7, 128.6, 128.2, 127.3, 127.0, 126.8, 126.2, 125.1, 124.9, 123.8, 122.6, 21.0; MS (ESI): m/z = 442 $(M-H)^-$; IR (neat): ν = 3500–2200 (br), 1668, 1596, 1573, 1493, 1451, 1426, 1399, 1365, 1326, 1286, 1214, 1186, 1156, 1090, 1044, 1020 cm^{-1}; Anal. calcd for $C_{26}H_{21}NO_4S$: C 70.41, H 4.77, N 3.16; found: C 70.20, H 4.75, N 3.10.

Synthesis of (*E*)-3-Cyclopropyl-2-[2-(*N*-tosylamino)-phenyl]acrylic Acid (*E*-2d)

The reaction of **1d** (311.4 mg, 1.0 mmol), Ni(COD)$_2$ (2.8 mg, 0.01 mmol), ZnEt$_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2d**[2] (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 30/1) as a white solid; yield: 327.2 mg (92%); mp 157–158 °C (petroleum ether/ethyl acetate) (Lit.[7] mp 157–158 °C, petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.15 (s, 1H, COOH), 9.32 (s, 1H, NH), 7.69 (d, J = 8.4 Hz, 2H, ArH), 7.34 (d, J = 8.1 Hz, 2H, ArH), 7.20–7.03 (m, 3H, ArH), 7.00 (d, J = 4.8 Hz, 1H, ArH), 6.38 (d, J = 10.8 Hz, 1H, HC=), 2.35 (s, 3H, CH_3), 1.10–0.96 (m, 1H, CH), 0.80 (d, J = 7.5 Hz, 2H, CH_2), 0.65 (bs, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.4, 151.2, 142.9, 138.1, 135.8, 131.7, 130.5, 129.6, 128.2, 127.9, 126.8, 124.5, 122.0, 21.0, 12.8, 9.0, 8.4; MS (ESI): m/z = 735 $[2M-2H+Na]^-$, 356 $[M-H]^-$; IR (neat): ν = 3500–2200 (br), 1676, 1613, 1580, 1492, 1450, 1409, 1333, 1269, 1205, 1185, 1156, 1092, 1055, 1027, 1003 cm^{-1}.



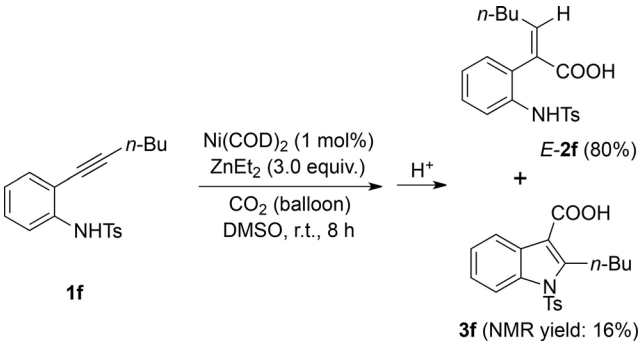
1d *E*-**2d** (92%)

Synthesis of (*E*)-4,4-Dimethyl-2-[2-(*N*-tosylamino)-phenyl]pent-2-enoic Acid (*E*-2e)

1e *E*-**2e** (92%)

The reaction of **1e** (327.5 mg, 1.0 mmol), Ni(COD)$_2$ (2.8 mg, 0.01 mmol), ZnEt$_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2e**[2] (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 30/1) as a white solid; yield: 344.3 mg (92%); mp 189–190 °C (petroleum ether/ethyl acetate) (Lit.[7] mp 188–189 °C, petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.22 (s, 1H, COOH), 9.48 (s, 1H, NH), 7.79 (d, J = 8.1 Hz, 2H, ArH), 7.36 (d, J = 7.8 Hz, 2H, ArH), 7.14–7.05 (m, 1H, ArH), 7.05–6.90 (m, 4H, ArH + HC=), 2.35 (s, 3H, CH_3), 0.87 (s, 9H, 3 × CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 168.2, 153.8, 143.0, 138.3, 136.2, 131.8, 129.7, 129.6, 127.9, 127.4, 126.8, 123.0, 119.5, 34.1, 29.3, 21.0; MS (ESI): m/z = 767 $[2M-2H+Na]^-$, 372 $[M-H]^-$; IR (neat): ν = 3500–2200 (br), 1693, 1673, 1634, 1599, 1580, 1493, 1458, 1432, 1417, 1398, 1379, 1364, 1344, 1308, 1271, 1231, 1204, 1189, 1168, 1092, 1053, 1040 cm^{-1}.

Synthesis of (*E*)-2-[2-(*N*-tosylamino)phenyl]hept-2-enoic Acid (*E*-2f)

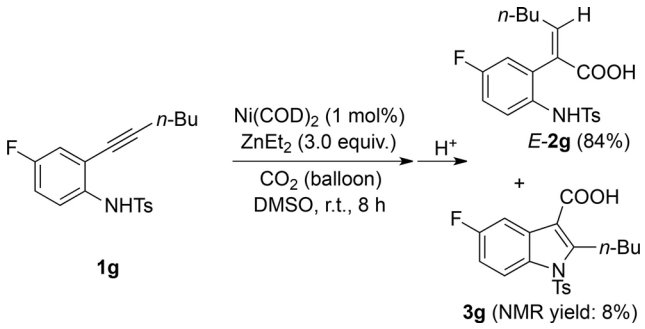


1f *E*-**2f** (80%) + **3f** (NMR yield: 16%)

The reaction of **1f** (327.5 mg, 1.0 mmol), Ni(COD)$_2$ (2.8 mg, 0.01 mmol), ZnEt$_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and

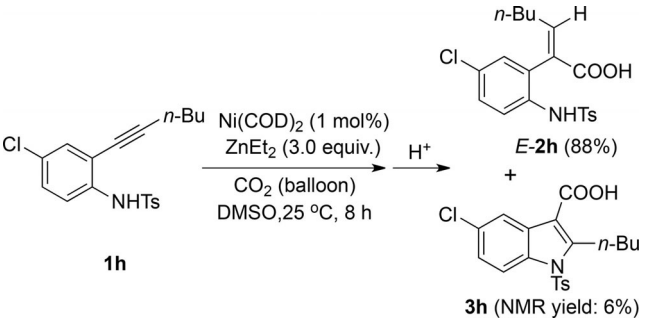
carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2f**[2] (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 30/1) as a white solid; yield: 298.0 mg (80%); mp 140–141 °C (petroleum ether/ethyl acetate) (Lit.[7] mp 140–141 °C, petroleum ether/ethyl acetate): ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.24 (s, 1H, COOH), 9.38 (s, 1H, NH), 7.67 (d, J = 8.4 Hz, 2H, ArH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 7.17–7.04 (m, 2H, ArH), 7.03–6.89 (m, 3H, ArH + HC=), 2.35 (s, 3H, CH_3), 1.89–1.60 (m, 2H, CH_2), 1.42–1.11 (m, 4H, 2×CH_2), 0.78 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.4, 145.7, 142.9, 138.1, 135.5, 131.2, 131.1, 130.9, 129.5, 127.9, 126.8, 124.6, 122.2, 30.0, 28.9, 22.0, 21.0, 13.7; MS (ESI): m/z = 396 $[M+Na]^+$; IR (neat): ν = 3500–2200 (br), 1686, 1635, 1598, 1580, 1493, 1453, 1404, 1333, 1272, 1225, 1187, 1160, 1090, 1048, 1021, 1006 cm^{-1}. **3f** (16%) was observed in the ^{1}H NMR spectrum of the crude product, and was characterized by comparison with the sample prepared previously by this group.[7]

Synthesis of (*E*)-2-[5-Fluoro-2-(*N*-tosylamino)-phenyl]-2-heptenoic Acid (*E*-2g)



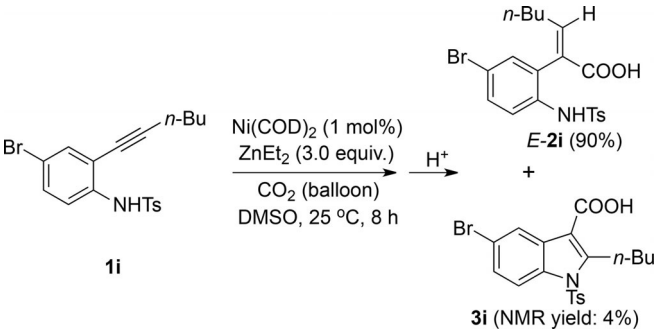
The reaction of **1g** (345.6 mg, 1.0 mmol), Ni(COD)$_2$ (2.7 mg, 0.01 mmol), $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2g** (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 30/1) as a yellow solid; yield: 329.6 mg (84%); mp 127–128 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.31 (s, 1H, COOH), 9.42 (s, 1H, NH), 7.63 (d, J = 8.4 Hz, 2H, ArH), 7.35 (d, J = 8.4 Hz, 2H, ArH), 7.06–6.77 (m, 4H, ArH + HC=), 2.36 (s, 3H, CH_3), 1.88–1.65 (m, 2H, CH_2), 1.45–1.13 (m, 4H, 2×CH_2), 0.79 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.7, 159.2 (d, $J_{C,F}$ = 241.1 Hz), 145.9, 143.0, 137.8, 134.6 (d, $J_{C,F}$ = 8.3 Hz), 131.8 (d, $J_{C,F}$ = 2.2 Hz), 130.5, 129.6, 126.8, 125.4 (d, $J_{C,F}$ = 8.8 Hz), 117.7 (d, $J_{C,F}$ = 21.9 Hz), 114.7 (d, $J_{C,F}$ = 21.9 Hz), 29.9, 28.9, 22.0, 21.0, 13.7; ^{19}F NMR (282 MHz, DMSO-d_6): δ = −117.2; MS (ESI): m/z = 418 $[M+CO-H]^-$, 390 $[M-H]^-$; IR (neat): ν = 3500–2200 (br), 1683, 1639, 1599, 1492, 1465, 1446, 1398, 1365, 1338, 1289, 1270, 1257, 1210, 1169, 1160, 1118, 1093, 1022 cm^{-1}; anal. calcd. for $C_{20}H_{22}FNO_4S$: C 61.36, H 5.66, N 3.58; found: C 61.43, H 5.79, N 3.46. **3g** (8%) was observed in the ^{1}H NMR spectrum of the crude product and was characterized by comparison with the sample prepared previously by this group.[7]

Synthesis of (*E*)-2-[5-Chloro-2-(*N*-tosylamino)-phenyl]-2-heptenoic Acid (*E*-2h)



The reaction of **1h** (362.0 mg, 1.0 mmol), Ni(COD)$_2$ (2.8 mg, 0.01 mmol), $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2h** (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 30/1) as a white solid; yield: 358.3 mg (88%); mp 176–178 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.34 (s, 1H, COOH), 9.57 (s, 1H, NH), 7.66 (d, J = 8.1 Hz, 2H, ArH), 7.36 (d, J = 8.1 Hz, 2H, ArH), 7.24 (dd, J_1 = 8.7 Hz, J_2 = 2.7 Hz, 1H, ArH), 7.05 (d, J = 2.7 Hz, 1H, ArH), 7.00–6.91 (m, 2H, ArH + HC=), 2.36 (s, 3H, CH_3), 1.85–1.64 (m, 2H, CH_2), 1.44–1.05 (m, 4H, 2×CH_2), 0.78 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.9, 146.4, 143.2, 137.7, 134.7, 132.8, 130.7, 129.9, 129.6, 128.6, 127.9, 126.8, 123.7, 29.8, 28.9, 21.9, 21.0, 13.6; MS (%): m/z = 409 $[M^+(^{37}Cl)$, 2.39], 407 $[M^+(^{35}Cl)$, 5.95], 91 (100); IR (neat): ν = 3500–2200 (br), 1682, 1634, 1598, 1483, 1423, 1403, 1364, 1340, 1278, 1244, 1172, 1116, 1092 cm^{-1}; anal. calcd. for $C_{20}H_{22}ClNO_4S$: C 58.89, H 5.44, N 3.43; found: C 58.85, H 5.46, N 3.46. **3h** (6%) was observed in the ^{1}H NMR spectrum of the crude product and was characterized by comparison with the sample prepared previously by this group.[7]

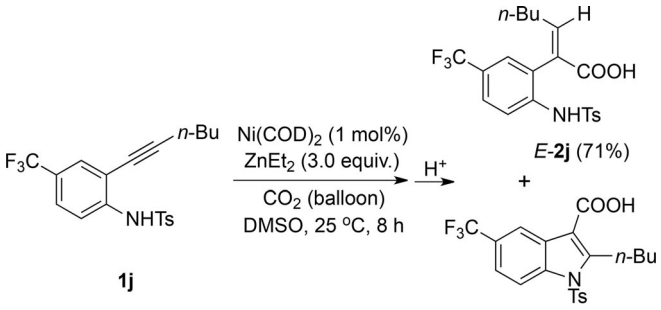
Synthesis of (*E*)-2-[5-Bromo-2-(*N*-tosylamino)-phenyl]-2-heptenoic Acid (*E*-2i)



The reaction of **1i** (406.3 mg, 1.0 mmol), Ni(COD)$_2$ (2.7 mg, 0.01 mmol), $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2i** (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 30/1) as a white solid; yield: 408.7 mg (90%); mp 183–184 °C (petroleum ether/ethyl acetate): ^{1}H NMR

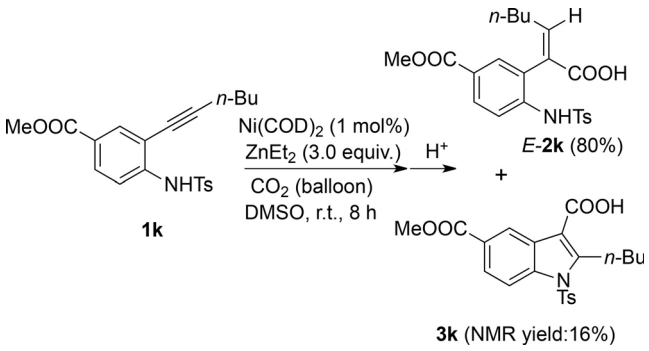
(400 MHz, DMSO-d_6): δ = 12.33 (s, 1H, COOH), 9.55 (s, 1H, NH), 7.67 (d, J = 8.4 Hz, 2H, ArH), 7.40–7.31 (m, 3H, ArH), 7.17 (d, J = 2.4 Hz, 1H, ArH), 6.99–6.89 (m, 2H, ArH + HC=), 2.35 (s, 3H, CH_3), 1.85–1.65 (m, 2H, CH_2), 1.43–1.13 (m, 4H, 2 × CH_2), 0.78 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.8, 146.4, 143.1, 137.6, 135.1, 133.5, 132.9, 130.8, 129.9, 129.6, 126.8, 123.8, 116.6, 29.8, 28.8, 21.9, 21.0, 13.6; MS (ESI): m/z = 480 [^{81}Br, M + CO − H]$^-$, 478 [^{79}Br, M + CO − H]$^-$, 452 [^{81}Br, M − H]$^-$, 450 [^{79}Br, M − H]$^-$; IR (neat): ν = 3500–2200 (br), 1681, 1634, 1597, 1568, 1481, 1420, 1401, 1363, 1341, 1276, 1244, 1229, 1211, 1172, 1123, 1109, 1092, 1065, 1049, 1017 cm^{-1}; anal. calcd for $C_{20}H_{22}BrNO_4S$: C 53.10, H 4.90, N 3.10; found: C 53.26, H 4.80, N 3.04. **3i** (4%) was observed in the ^{1}H NMR spectrum of the crude product and was characterized by comparison with the sample prepared previously in this group.[7]

Synthesis of (*E*)-2-[5-Trifluoromethyl-2-(*N*-tosylamino)phenyl]-2-heptenoic Acid (*E*-2j)



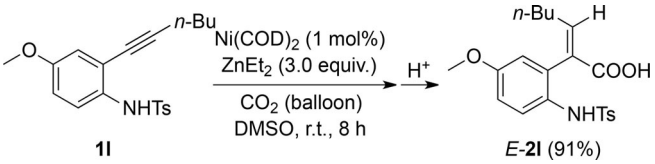
The reaction of **1j** (395.5 mg, 1.0 mmol), Ni(COD)$_2$ (2.9 mg, 0.01 mmol), ZnEt$_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2j** (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 30/1) as a white solid; yield: 315.0 mg (71%); mp 191–193 °C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.46 (s, 1H, COOH), 10.04 (s, 1H, NH), 7.76 (d, J = 8.4 Hz, 2H, ArH), 7.56 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, ArH), 7.40–7.30 (m, 3H, ArH), 7.30–7.26 (m, 1H, ArH), 7.03 (t, J = 7.8 Hz, 1H, HC=), 2.34 (s, 3H, CH_3), 1.82–1.59 (m, 2H, CH_2), 1.42–1.07 (m, 4H, 2 × CH_2), 0.73 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.9, 147.2, 143.5, 139.7, 137.6, 129.8, 129.7, 129.1, 128.0 (q, $J_{C,F}$ = 3.8 Hz), 126.9, 125.3 (q, $J_{C,F}$ = 3.8 Hz), 124.1 (q, $J_{C,F}$ = 270.2 Hz), 123.9 (q, $J_{C,F}$ = 31.9 Hz), 120.0, 29.7, 28.8, 21.8, 21.0, 13.5; ^{19}F NMR (282 MHz, DMSO-d_6): δ = −60.2; MS (ESI): m/z = 462 [M + CO − H]$^-$, 440 [M − H]$^-$; IR (neat): ν = 3500–2200 (br), 1681, 1633, 1618, 1599, 1589, 1500, 1447, 1416, 1365, 1345, 1322, 1276, 1246, 1174, 1159, 1138, 1109, 1092, 1078, 1052, 1019 cm^{-1}; anal. calcd. for $C_{21}H_{22}F_3NO_4S$: C 57.13, H 5.02, N 3.17; found: C 57.24, H 4.97, N 3.11. **3j** (20%) was observed in the ^{1}H NMR spectrum of the crude product and was characterized by comparison with the sample prepared previously in this group.[7]

Synthesis of (*E*)-2-[5-Methoxycarbonyl-2-(*N*-tosylamino)phenyl]-2-heptenoic Acid (*E*-2k)



The reaction of **1k** (385.5 mg, 1.0 mmol), Ni(COD)$_2$ (2.8 mg, 0.01 mmol), ZnEt$_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2k** (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 20/1) as a yellow solid; yield: 344.8 mg (80%); mp 187–189 °C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.42 (s, 1H, COOH), 9.99 (s, 1H, NH), 7.79–7.72 (m, 3H, ArH), 7.50 (d, J = 1.6 Hz, 1H, ArH), 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.29 (d, J = 8.8 Hz, 1H, ArH), 7.01 (t, J = 7.4 Hz, 1H, HC=), 3.77 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.82–1.71 (m, 1H, one proton of CH_2), 1.70–1.59 (m, 1H, one proton of CH_2), 1.41–1.08 (m, 4H, 2 × CH_2), 0.74 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.0, 165.6, 147.0, 143.5, 140.5, 137.5, 132.2, 129.9, 129.8, 129.3, 128.2, 126.9, 124.4, 119.3, 52.1, 29.8, 28.9, 21.9, 21.0, 13.6; MS (ESI): m/z = 430 [M − H]$^-$; IR (neat): ν = 3500–2200 (br), 1726, 1688, 1605, 1584, 1495, 1435, 1411, 1363, 1340, 1293, 1262, 1169, 1113, 1090, 1018 cm^{-1}; anal. calcd. for $C_{22}H_{25}NO_6S$: C 61.24, H 5.84, N 3.25; found: C 61.19, H 5.81, N 3.29. **3k** (16%) was observed in the ^{1}H NMR spectrum of the crude product and was characterized by comparison with the sample prepared previously by this group.[7]

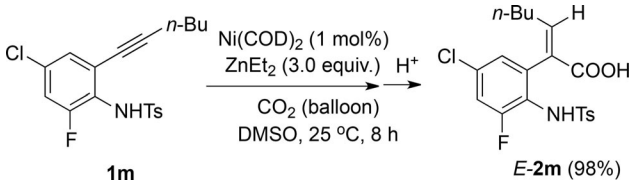
Synthesis of (*E*)-2-[5-Methoxy-2-(*N*-tosylamino)-phenyl]-2-heptenoic Acid (*E*-2l)



The reaction of **1l** (357.3 mg, 1.0 mmol), Ni(COD)$_2$ (2.9 mg, 0.01 mmol), ZnEt$_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2l** (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 20/1) as a yellow solid; yield: 365.7 mg (91%); mp 139–140 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.21 (s, 1H, COOH), 9.11 (s, 1H, NH), 7.59 (d, J = 8.1 Hz, 2H, ArH), 7.34 (d, J = 8.1 Hz, 2H, ArH), 6.89 (t, J = 7.5 Hz, 1H, ArH), 6.75–6.68 (m, 1H, ArH), 6.67–6.60 (m, 1H, ArH), 6.57 (d, J = 2.7 Hz, 1H,

HC=), 3.67 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 1.82 (q, J= 7.2 Hz, 2H, CH_2), 1.45–1.15 (m, 4H, 2×CH_2), 0.81 (t, J= 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ=167.4, 156.8, 145.2, 142.7, 138.0, 134.9, 131.5, 129.5, 128.0, 126.9, 126.1, 116.4, 112.9, 55.2, 30.1, 29.0, 22.0, 21.0, 13.8; MS (ESI): m/z=402 $[M-H]^-$, 358 $[M-CO_2-H]^-$; IR (neat): ν=3500–2200 (br), 1679, 1607, 1495, 1450, 1419, 1388, 1334, 1278, 1201, 1162, 1095, 1032, 1003 cm^{-1}; anal. calcd. for $C_{21}H_{25}NO_5S$: C 62.51, H 6.25, N 3.47; found: C 62.42, H 6.31, N 3.20.

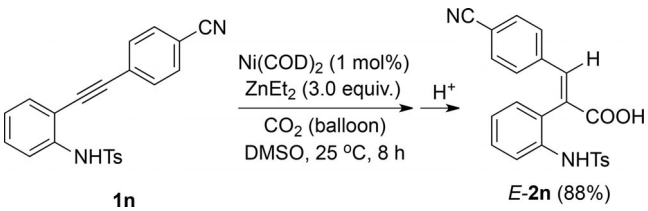
Synthesis of (*E*)-2-[5-Chloro-3-fluoro-2-(*N*-tosylamino)-phenyl]-2-heptenoic Acid (*E*-2m)



1m *E*-**2m** (98%)

The reaction of **1m** (380.1 mg, 1.0 mmol), Ni(COD)$_2$ (2.7 mg, 0.01 mmol), $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2m** (eluent: petroleum ether/ethyl acetate=5/1 to DCM/MeOH=30/1) as a white solid; yield: 418.4 mg (98%); mp 149–151 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.25 (bs, 1H, COOH), 7.75–7.56 (m, 3H, NH+ArH), 7.31 (t, J=7.5 Hz, 1H, ArH), 7.23 (d, J=8.4 Hz, 2H, ArH), 7.04–6.89 (m, 2H, ArH+HC=), 2.40 (s, 3H, CH_3), 2.23–2.05 (m, 2H, CH_2), 1.60–1.29 (m, 4H, 2×CH_2), 0.91 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.1, 159.1 ($J_{C,F}$= 253.1 Hz), 151.3, 143.6, 139.4, 137.6, 133.9 ($J_{C,F}$=10.9 Hz), 129.4, 128.5 ($J_{C,F}$=2.2 Hz), 127.1, 126.8 ($J_{C,F}$=2.9 Hz), 121.5 ($J_{C,F}$=13.9 Hz), 116.6 ($J_{C,F}$=24.0 Hz), 30.4, 30.0, 22.5, 21.5, 13.8; ^{19}F NMR (282 MHz, DMSO-d_6): δ=−115.2; MS (%): m/z=425 (M^+, 1.06), 91 (100); IR (neat): ν=3500–2200 (br), 1703, 1638, 1599, 1574, 1471, 1425, 1380, 1359, 1323, 1265, 1232, 1147, 1089, 1035 cm^{-1}; anal. calcd. for $C_{20}H_{21}ClFNO_4S$: C 56.40, H 4.97, N 3.29; found: C 56.13, H 4.93, N 3.31.

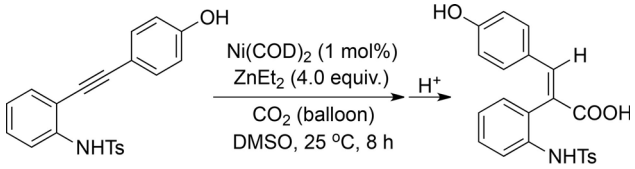
Synthesis of (*E*)-2-[2-(*N*-tosylamino)phenyl]-3-(4-cyanophenyl)acrylic Acid (*E*-2n)



1n *E*-**2n** (88%)

The reaction of **1n** (372.5 mg, 1.0 mmol), Ni(COD)$_2$ (2.8 mg, 0.01 mmol), $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2n** (eluent: petroleum ether/ethyl acetate=5/1 to DCM/MeOH=20/1) as a white solid; yield: 366.7 mg (88%); mp 190–192 °C (petroleum ether/ethyl acetate); ^{1}H NMR (300 MHz, DMSO-d_6): δ=12.76 (bs, 1H, COOH), 9.59 (s, 1H, NH), 7.77 (s, 1H, HC=), 7.60 (d, J=8.1 Hz, 4H, ArH), 7.30–7.05 (m, 6H, ArH), 7.04–6.95 (m, 2H, ArH), 2.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ=167.7, 143.0, 139.3, 138.2, 137.5, 135.5, 133.8, 131.9, 131.3, 131.0, 130.5, 129.5, 128.9, 126.9, 125.7, 123.5, 118.6, 110.9, 21.0; MS (ESI): m/z=417 $[M-H]^-$; IR (neat): ν=3500–2300 (br), 2227, 1698, 1674, 1617, 1600, 1578, 1491, 1453, 1420, 1383, 1343, 1319, 1309, 1266, 1229, 1210, 1189, 1170, 1092, 1046 cm^{-1}; anal. calcd. for $C_{23}H_{18}N_2O_4S$: C 66.01, H 4.34, N 6.69; found: C 66.04, H 4.34, N 6.52.

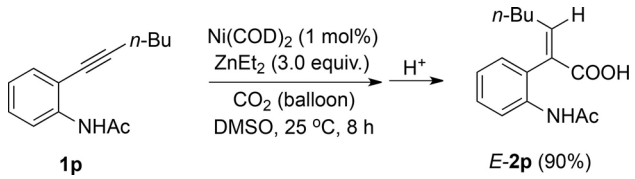
Synthesis of (*E*)-2-[2-(*N*-tosylamino)phenyl]-3-(4-hydroxyphenyl)acrylic Acid (*E*-2o)



1o *E*-**2o** (86%)

The reaction of **1o** (363.4 mg, 1.0 mmol), Ni(COD)$_2$ (2.8 mg, 0.01 mmol), $ZnEt_2$ (1.5 M in toluene, 2.7 mL, 4.05 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded *E*-**2o** (eluent: petroleum ether/ethyl acetate=5/1 to DCM/MeOH=20/1) as a yellow solid; yield: 351.7 mg (86%); mp 231–232 °C (petroleum ether/ethyl acetate): ^{1}H NMR (300 MHz, DMSO-d_6): δ=12.28 (bs, 1H, COOH), 9.84 (s, 1H, NH), 9.34 (s, 1H, OH), 7.65 (s, 1H, HC=), 7.60 (d, J= 8.1 Hz, 2H, ArH), 7.21 (d, J=8.1 Hz, 3H, ArH), 7.15–7.03 (m, 2H, ArH), 6.97 (d, J=6.9 Hz, 1H, ArH), 6.75 (d, J= 8.7 Hz, 2H, ArH), 6.48 (d, J=8.4 Hz, 2H, ArH), 2.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ=168.3, 158.6, 142.9, 141.0, 137.5, 135.8, 132.2, 131.14, 131.07, 129.4, 128.3, 126.8, 126.1, 125.3, 125.0, 121.9, 115.1, 21.0; MS (ESI): m/z= 562 $[M+3CO_2+Na-2H]^-$, 408 $[M-H]^-$; IR (neat): ν= 3600–2200 (br), 1669, 1603, 1577, 1511, 1491, 1452, 1408, 1380, 1320, 1266, 1212, 1163, 1092, 1047 cm^{-1}; anal. calcd. for $C_{22}H_{19}NO_5S$: C 64.53, H 4.68, N 3.42; found: C 64.27, H 4.70, N 3.34. The solubility of *E*-**2o** is very low even in DMSO.

Synthesis of (*E*)-2-[2-(*N*-acetylamino)phenyl]hept-2-enoic Acid (*E*-2p)

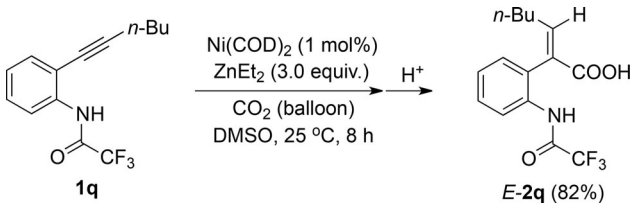


1p *E*-**2p** (90%)

To an oven-dried 50-mL Schlenk tube was added **1p** (215.3 mg, 1.0 mmol) under an argon atmosphere. Ni(COD)$_2$ (2.7 mg, 0.01 mmol) was added inside a glove box and then 6 mL of DMSO were added under argon. The mix-

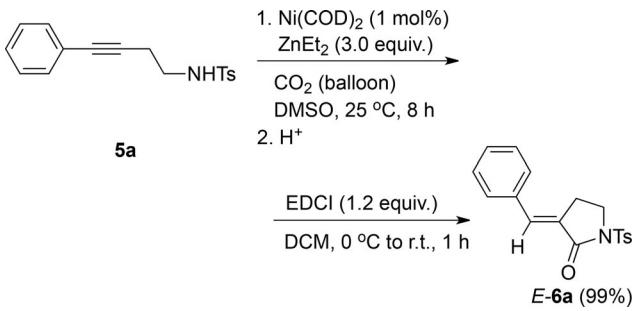
ture was frozen with a liquid nitrogen bath and the argon inside was completely replaced with CO_2 by using a CO_2 balloon (about 1 L). Then the reaction flask was allowed to stand until the mixture thawed. To the resulting suspension was added $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol) *via* a syringe with stirring. Then the resulting mixture was stirred at 25 °C for 8 h. After that, the resulting mixture was quenched with 10 mL of 3 M aqueous HCl. The aqueous layer was extracted with ethyl acetate (10 mL × 5) and the combined organic layer was washed with 30 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by recrystallization (petroleum ether/ethyl acetate) to afford *E*-**2p** as colorless crystals; yield: 236.1 mg (90%): mp 108–109 °C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.27 (bs, 1H, COOH), 9.02 (s, 1H, NH), 7.65 (d, J = 8.0 Hz, 1H, ArH), 7.26 (t, J = 7.2 Hz, 1H, ArH), 7.11 (t, J = 7.4 Hz, 1H, ArH), 7.03 (d, J = 7.2 Hz, 1H, ArH), 6.96 (t, J = 7.6 Hz, 1H, =CH), 1.98 (s, 3H, $COCH_3$), 1.91–1.80 (m, 2H, $=CCH_2$), 1.37–1.28 (m, 2H, CH_2), 1.24–1.13 (m, 2H, CH_2), 0.77 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.2, 167.6, 145.6, 136.3, 131.0, 130.6, 129.1, 127.5, 124.2, 124.0, 30.1, 28.8, 23.5, 21.9, 13.7; MS (ESI): m/z = 325 $[M+MeCN+Na]^+$, 284 $[M+Na]^+$, 262 $[M+H]^+$; IR (neat): ν = 3500–2200 (br), 1693, 1633, 1617, 1577, 1544, 1484, 1449, 1377, 1315, 1209, 1104, 1088, 1043, 1022 cm^{-1}; anal. calcd. for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36; found: C 69.07, H 7.64, N 5.20.

Synthesis of (*E*)-2-[2-(*N*-trifluoroacetylamino)-phenyl]hept-2-enoic Acid (*E*-2q)



To an oven-dried 50-mL Schlenk tube was added $Ni(COD)_2$ (2.8 mg, 0.01 mmol) inside a glove box. **1q** (269.4 mg, 1.0 mmol) and 6 mL of DMSO were added under an argon atmosphere and the mixture was frozen with a liquid nitrogen bath. The argon inside was completely replaced with CO_2 by using a CO_2 balloon (about 1 L). Then the reaction flask was allowed to stand until the mixture thawed. To the resulting suspension was added $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol) *via* a syringe with stirring. Then the resulting mixture was stirred at 25 °C for 8 h. After that, the resulting mixture was quenched with 10 mL of 3 M aqueous HCl. The aqueous layer was extracted with ethyl acetate (10 mL × 5) and the combined organic layer was washed with 30 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5/1 to DCM/MeOH = 20/1) to afford *E*-**2q** as an oil: yield: 259.6 mg (82%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.34 (bs, 1H, COOH), 10.90 (s, 1H, NH), 7.42–7.31 (m, ArH, 3H), 7.18 (d, J = 7.6 Hz, 1H, ArH), 6.91 (t, J = 7.6 Hz, 1H, =CH), 1.88 (q, J = 7.5 Hz, 2H, $=CCH_2$), 1.37–1.27 (m, 2H, CH_2), 1.26–1.13 (m, 2H, CH_2), 0.77 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.2, 154.9 (q, $J_{C,F}$ = 36.2 Hz), 145.3, 133.3, 132.4, 131.3, 130.8, 128.0, 126.8, 126.3, 116.0 (q, $J_{C,F}$ = 287.2 Hz), 30.0, 28.8, 21.9, 13.6; ^{19}F NMR (282 MHz, DMSO-d_6): δ = −73.5; MS (%): m/z = 315 (M^+, 36.62), 297 (100); IR (neat): ν = 3500–2200 (br), 1725, 1682, 1631, 1607, 1583, 1537, 1487, 1453, 1418, 1381, 1366, 1279, 1240, 1197, 1150, 1100, 1045, 1001 cm^{-1}; HR-MS (EI): m/z = 315.1085, calcd. for $C_{15}H_{16}F_3NO_3$ (M^+): 315.1082.

Synthesis of (*E*)-3-Benzylidene-1-tosylpyrrolidin-2-one (*E*-6a)

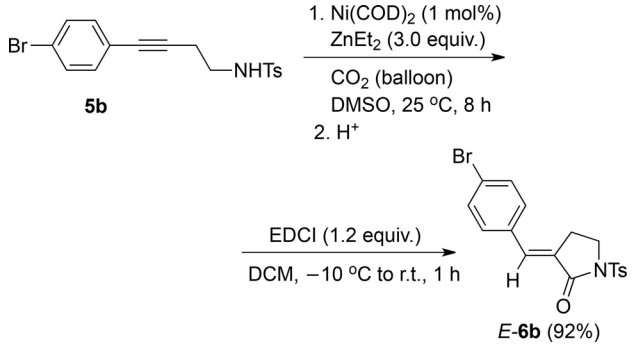


Typical Procedure II (Table 3): To an oven-dried 50-mL Schlenk tube was added **5a** (299.5 mg, 1.0 mmol) under an argon atmosphere. $Ni(COD)_2$ (2.8 mg, 0.01 mmol) was added inside a glove box and then 6 mL of DMSO were added under argon. The mixture was frozen with a liquid nitrogen bath and the argon inside was completely replaced with CO_2 by using a CO_2 balloon (about 1 L). Then the reaction flask was allowed to stand until the mixture thawed. To the resulting suspension was added $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol) with stirring. Then the resulting mixture was stirred at 25 °C for 8 h. After that, the resulting mixture was quenched with 6 mL of 3 M aqueous HCl. The aqueous layer was extracted with ethyl acetate (15 mL × 4) and the combined organic layer was washed with 30 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated in a 100-mL flask to afford the crude product acid. DCM (20 mL) was added into this flask under an argon atmosphere. The suspension was cooled to −10 °C and EDCI (230.7 mg, 1.2 mmol) was added, followed by warming up to room temperature naturally within 1 h. DCM (15 mL) was added and the resulting mixture was washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (eluent: dichloromethane/petroleum ether/ethyl acetate = 15/40/1) to afford *E*-**6a**[2] as a white solid; yield: 322.6 mg (99%); mp 166–167 °C (petroleum ether/ethyl acetate) (Lit.[7] mp 166–167 °C, petroleum ether/ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.4 Hz, 2H, ArH), 7.44–7.32 (m, 8H, ArH + HC=), 3.98 (t, J = 7.0 Hz, 2H, CH_2), 3.11 (td, J_1 = 7.0 Hz, J_2 = 2.8 Hz, 2H, CH_2), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 145.2, 135.0, 134.9, 134.5, 130.0, 129.64, 129.62, 128.8, 128.2, 128.0, 44.0, 24.2, 21.7; MS (ESI): m/z = 316 $[M+Na-2H]^-$, 294 $[M-H]^-$; IR (neat):

ν = 2968, 2909, 1711, 1646, 1596, 1486, 1445, 1403, 1355, 1289, 1234, 1165, 1127, 1086, 1060, 1001 cm^{-1}.

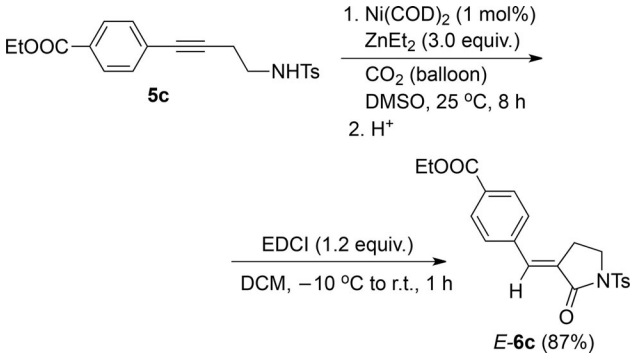
The following compounds were prepared according to this Typical Procedure II.

Synthesis of (*E*)-3-(4-Bromobenzylidene)-1-tosylpyrrolidin-2-one (*E*-6b)



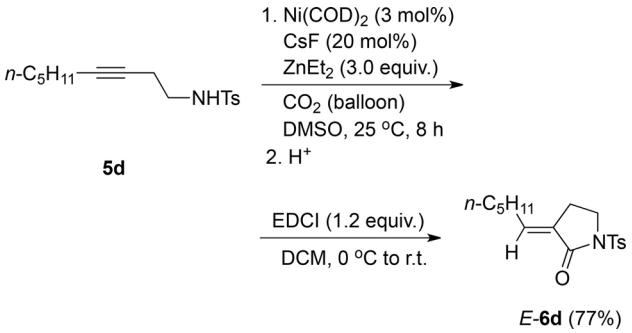
The reaction of **5b** (378.5 mg, 1.0 mmol), $Ni(COD)_2$ (2.8 mg, 0.01 mmol), $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded the crude product acid. The amidation reaction of the crude product acid with EDCI (230.1 mg, 1.2 mmol) in 20 mL of DCM afforded *E*-**6b** (eluent: dichloromethane/petroleum ether/ethyl acetate = 40/40/1) as a white solid; yield: 375.2 mg (92%); mp 253–254 °C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.4 Hz, 2H, ArH), 7.53 (d, J = 8.8 Hz, 2H, ArH), 7.35 (d, J = 8.4 Hz, 3H, ArH + HC=), 7.28 (d, J = 7.6 Hz, 2H, ArH), 3.99 (t, J = 6.8 Hz, 2H, CH_2), 3.07 (td, J_1 = 6.7 Hz, J_2 = 2.7 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 145.3, 134.8, 133.7, 133.4, 132.1, 131.3, 129.7, 128.8, 128.2, 124.0, 44.0, 24.2, 21.7; MS (%): m/z = 407 [M^+(^{81}Br), 1.09], 405 [M^+(^{79}Br), 1.00], 115 (100); IR (neat): ν = 1713, 1652, 1582, 1486, 1402, 1358, 1304, 1244, 1189, 1166, 1130, 1114, 1088, 1071, 1047, 1005 cm^{-1}; anal. calcd. for $C_{18}H_{16}BrNO_3S$: C 53.21, H 3.97, N 3.45; found: C 53.14, H 4.07, N 3.32.

Synthesis of (*E*)-3-(4-Ethoxycarbonylbenzylidene)-1-tosylpyrrolidin-2-one (*E*-6c)



The reaction of **5c** (371.5 mg, 1.0 mmol), $Ni(COD)_2$ (2.9 mg, 0.01 mmol), $ZnEt_2$ (1.5 M in toluene, 2.0 mL, 3.0 mmol), and carbon dioxide (about 1 L) in 6 mL of DMSO afforded the crude product acid. The amidation reaction of the crude product acid, EDCI (230.1 mg, 1.2 mmol) in 20 mL of DCM afforded *E*-**6c** (eluent: dichloromethane/petroleum ether/ethyl acetate = 20/20/1) as a white solid; yield: 349.1 mg (87%); mp 217–218 °C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.4 Hz, 2H, ArH), 8.00 (d, J = 8.0 Hz, 2H, ArH), 7.50–7.42 (m, 3H, ArH + HC=), 7.36 (d, J = 8.0 Hz, 2H, ArH), 4.39 (q, J = 7.1 Hz, 2H, CH_2), 4.01 (t, J = 7.0 Hz, 2H, CH_2), 3.14 (td, J_1 = 7.0 Hz, J_2 = 2.6 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.40 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 165.8, 145.3, 138.6, 134.8, 133.6, 130.9, 130.5, 129.9, 129.7, 129.6, 128.2, 61.2, 43.9, 24.2, 21.6, 14.2; MS (%): m/z = 399 (M^+, 0.40), 91 (100); IR (neat): ν = 3069, 2991, 2922, 2854, 1707, 1649, 1604, 1595, 1566, 1506, 1492, 1477, 1452, 1428, 1414, 1396, 1359, 1313, 1287, 1243, 1190, 1171, 1125, 1090, 1074, 1041, 1016 cm^{-1}; anal. calcd. for $C_{21}H_{21}NO_5S$: C 63.14, H 5.30, N 3.51; found: C 62.94, H 5.40, N 3.47.

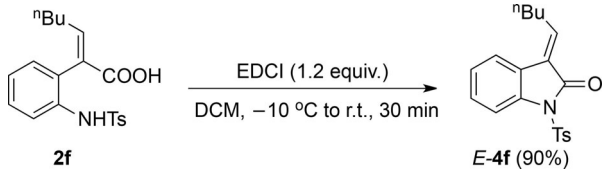
Synthesis of (*E*)-3-Hexylidene-1-tosylpyrrolidin-2-one (*E*-6d)



To an oven-dried 25-mL Schlenk tube were added $Ni(COD)_2$ (4.1 mg, 0.015 mmol) and CsF (15.6 mg, 0.1 mmol) inside a glove box. **5d** (146.6 mg, 0.5 mmol) and 3 mL of DMSO were added under an argon atmosphere and the mixture was frozen with a liquid nitrogen bath. The argon inside was completely replaced with CO_2 by using a CO_2 balloon (about 1 L), then the reaction flask was allowed to stand until the mixture thawed. To the resulting suspension was added $ZnEt_2$ (1.5 M in toluene, 1.0 mL, 1.5 mmol) with stirring. Then the resulting mixture was stirred at room temperature for 6 h. After that, the resulting mixture was quenched with aqueous 3 M HCl. The aqueous layer was extracted with ethyl acetate (5 mL × 5) and the combined organic layer was washed with water (5 mL × 2) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in a 50-mL flask to afford the crude product acid. DCM (10 mL) was added into this flask under an argon atmosphere. The suspension was cooled to −10 °C and EDCI (115.6 mg, 0.6 mmol) was added, followed by warming up to room temperature naturally within 0.5 h. The suspension was concentrated and the crude product was purified by column chromatography on silica gel to afford *E*-**6d** (eluent: dichloromethane/petroleum ether/ethyl acetate = 40/40/1) as a solid; yield: 124.4 mg (77%); mp 69–70 °C (petroleum ether/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.4 Hz, 2H, ArH), 7.33 (d, J = 8.1 Hz, 2H, ArH), 6.59

(tt, J_1=7.5 Hz, J_2=2.7 Hz, 1H, HC=), 3.89 (t, J=7.2 Hz, 2H, NCH_2), 2.75–2.64 (m, 2H, =CCH_2), 2.42 (s, 3H, CH_3 in Ts), 2.09 (q, J=7.3 Hz, 2H, =CCH_2), 1.48–1.34 (m, 2H, CH_2), 1.33–1.20 (m, 4H, 2×CH_2), 0.86 (t, J=6.8 Hz, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.1, 144.9, 139.4, 135.0, 129.4, 129.1, 128.0, 43.8, 31.2, 29.2, 27.6, 22.2, 21.48, 21.46, 13.7; MS (%): m/z=321 (M^+, 0.54), 257 (100); IR (neat): ν=2954, 2924, 2853, 1717, 1668, 1597, 1494, 1466, 1449, 1359, 1290, 1226, 1187, 1172, 1118, 1091, 1038, 1018 cm^{-1}; anal. calcd. for $C_{17}H_{23}NO_3S$: C 63.52, H 7.21, N 4.36; found: C 63.41, H 7.20, N 4.05.

Synthesis of (*E*)-3-(Pentylidene)-1-tosylindolin-2-one (*E*-4f)

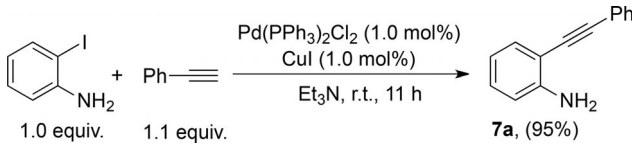


2f *E*-**4f** (90%)

To a 50-mL Schlenk flask were added **2f** (374.0 mg, 1.0 mmol) and 16 mL of DCM under an argon atmosphere. The suspension was cooled to −10 °C and EDCI [(1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl] (230.3 mg, 1.2 mmol) was added followed by warming up to room temperature naturally within 0.5 h. 20 mL of DCM were added and the mixture was washed with water (30 mL×2) and brine (30 mL) sequentially, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=10/1) to afford *E*-**4f** as an oil; yield: 320.6 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.03–7.96 (m, 3H, ArH), 7.56 (d, J=7.6 Hz, 1H, ArH), 7.38–7.27 (m, 3H, ArH), 7.18 (t, J=7.6 Hz, 1H, ArH), 7.02 (t, J=7.8 Hz, 1H, =CH), 2.62 (q, J=7.5 Hz, 2H, =CCH_2), 2.40 (s, 3H, CH_3 in Ts), 1.62–1.53 (m, 2H, CH_2), 1.47–1.37 (m, 2H, CH_2), 0.93 (t, J=7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.7, 145.4, 145.2, 138.6, 135.4, 129.6, 129.3, 127.8, 125.5, 124.4, 123.6, 122.6, 113.6, 30.4, 29.1, 22.4, 21.6, 13.7; MS (%): m/z=355 (M^+, 65.72), 158 (100); IR (neat): ν=2958, 2928, 2871, 1742, 1648, 1599, 1493, 1456, 1373, 1310, 1295, 1234, 1189, 1176, 1151, 1120, 1086, 1066, 1041, 1006 cm^{-1}; HR-MS (EI): m/z=355.1246, calcd. for $C_{20}H_{21}NO_3S$ (M^+): 355.1242.

Synthesis of (*E*)-3-Benzylidene-2-indolinone (*E*-9a)

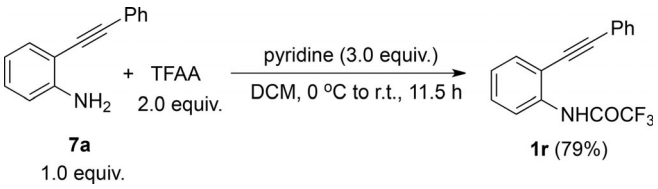
Synthesis of 2-(phenylethynyl)aniline (7a)



1.0 equiv. 1.1 equiv. **7a**, (95%)

To a 250-mL three-necked flask were added 2-iodoaniline (4.3858 g, 20.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.1400 g, 0.2 mmol), 40 mL of anhydrous Et_3N, and phenylethyne (2.4 mL, d=0.93 g mL^{-1}, 22 mmol, 2.2469 g) sequentially under an argon atmosphere. The resulting mixture was stirred at room temperature for 5 min followed by the addition of CuI (0.0383 g, 0.2 mmol). After being stirred at room temperature for 11 h as monitored by TLC, the resulting suspension was filtered under vacuum, concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate=100/1) to afford **7a**[21] as a brown solid; yield: 3.6986 g (95%); mp 86–87 °C (petroleum ether/ethyl acetate) (Lit.[21] mp 88–89 °C, petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.56–7.48 (m, 2H, ArH), 7.38–7.28 (m, 4H, ArH), 7.13 (td, J_1=8.0 Hz, J_2=1.3 Hz, 1H, ArH), 6.74–6.68 (m, 2H, ArH), 4.26 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=147.7, 132.1, 131.4, 129.7, 128.3, 128.2, 123.3, 117.9, 114.3, 107.9, 94.7, 85.9; MS (%): m/z=193 (M^+, 100); IR (neat): ν=3460, 3367, 2206, 1606, 1597, 1567, 1511, 1495, 1483, 1455, 1443, 1391, 1308, 1278, 1251, 1177, 1157, 1104, 1071, 1055, 1027 cm^{-1}.

Synthesis of *N*-Trifluoroacetyl-2-(phenylethynyl)-aniline (1r)

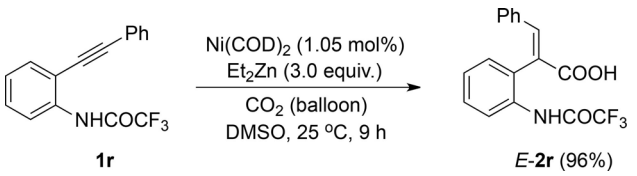


7a 1.0 equiv. **1r** (79%)

To a 100-mL three-necked flask were added **6a** (2.0520 g, 12.0 mmol), 31 mL of anhydrous DCM, and pyridine (2.8 mL, d=0.98 g mL^{-1}, 36.0 mmol, 2.8476 g) sequentially under an argon atmosphere. The resulting mixture was cooled to 0 °C and trifluoroacetic anhydride (TFAA) (3.3 mL, d=1.49 g mL^{-1}, 24.0 mmol, 5.0395 g) was added dropwise at this temperature. Then the mixture was warmed up to room temperature and stirred for 11.5 h as monitored by TLC. The resulting solution was quenched with 30 mL of water. The aqueous layer was extracted with DCM (10 mL×3) and the combined organic layer was washed with 50 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=200/1) to afford **1r**[1a] as a white solid; yield: 2.4079 g (79%); mp 113–114 °C (petroleum ether/ethyl acetate) (Lit.[20] mp 95–96 °C, hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.89 (s, 1H, NH), 8.38 (d, J=8.4 Hz, 1H, ArH), 7.60–7.49 (m, 3H, ArH), 7.46–7.37 (m, 4H, ArH), 7.22 (td, J_1=7.6 Hz, J_2=0.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.4 (q, $J_{C,F}$=37.2 Hz), 136.0, 131.7, 131.4, 129.8, 129.3, 128.7, 125.5, 121.6, 119.6, 115.7 (q, $J_{C,F}$=287.4 Hz), 113.4, 98.0, 82.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−76.3; MS (%): m/z=289 (M^+, 100); IR (neat): ν=3344, 1710, 1611, 1583, 1545, 1493, 1473, 1453, 1343, 1282, 1233, 1182, 1171, 1155, 1096, 1071, 1041, 1028 cm^{-1}; Raman: ν=2234 cm^{-1}.

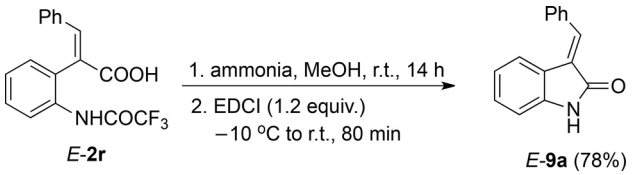
Synthesis of (*E*)-2-[*o*-(*N*-trifluoroacetylamino)-phenyl]-3-phenylacrylic Acid (*E*-2r)

To a 250-mL three-necked flask was added **1r** (2.2014 g, 7.6 mmol) under an argon atmosphere and $Ni(COD)_2$ (22.0 mg, 0.08 mmol) was then added inside a glove box. Then 47 mL of DMSO were added under an argon atmos-



phere and the mixture was frozen with a liquid nitrogen bath. The argon inside was completely replaced with CO_2 by using a CO_2 balloon. Then the reaction flask was allowed to stand until the mixture thawed. To the resulting suspension was added $ZnEt_2$ (1.5 M in toluene, 15.0 mL, 22.5 mmol) *via* a syringe with stirring. Then the resulting mixture was stirred at 25 °C for 9 h. After that, the resulting mixture was quenched with 80 mL of aqueous 3 M HCl. The aqueous layer was extracted with ethyl acetate (50 mL × 3) and the combined organic layer was washed with 200 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluent: DCM/MeOH = 40/1) to afford *E*-**2r** as a brown solid; yield: 2.4723 g (96%); mp 136–138 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.60 (bs, 1H, COOH), 10.85 (s, 1H, NH), 7.76 (s, 1H, =CH), 7.43 (d, J = 4.0 Hz, 2H, ArH), 7.34–7.26 (m, 1H, ArH), 7.26–7.14 (m, 4H, ArH), 7.10 (d, J = 6.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.8, 154.7 (q, $J_{C,F}$ = 36.1 Hz), 140.3, 134.3, 133.5, 132.4, 131.4, 130.0, 129.9, 129.1, 128.4, 128.1, 127.1, 126.5, 115.9 (q, $J_{C,F}$ = 284.1 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ = −73.4; MS (%): m/z = 335 (M^+, 49.53), 91 (100); IR (neat): ν = 3400–2100 (br), 1714, 1682, 1621, 1603, 1575, 1544, 1495, 1446, 1411, 1371, 1345, 1317, 1263, 1241, 1200, 1180, 1161, 1151, 1114, 1077, 1041, 1032 cm^{-1}; anal. calcd. for $C_{17}H_{12}F_3NO_3$: C 60.90, H 3.61, N 4.18; found: C 60.84, H 3.76, N 4.10.

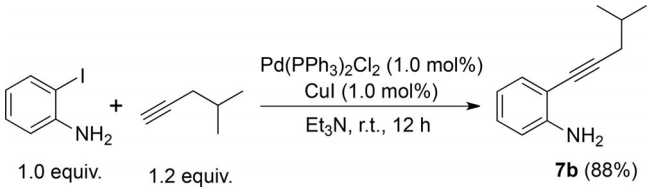
Synthesis of (*E*)-3-Benzylidene-2-indolinone (*E*-9a)



To a 500-mL of three-necked flask were added *E*-**2r** (2.2012 g, 6.5 mmol) and 198 mL of a saturated solution of ammonia in MeOH. The mixture was stirred at room temperature for 14 h and then the solvent was removed by a rotary evaporator. The residue was dissolved in 165 mL of anhydrous DCM under an argon atmosphere and EDCI (1.5360 g, 7.9 mmol) was added at −10 °C. The resulting solution was then warmed up to room temperature naturally and stirred for 80 min. After that, the resulting solution was washed with 100 mL of water and 100 mL of brine sequentially, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (eluent: DCM/MeOH = 60/1) to afford *E*-**9a**[22] as a yellow solid; yield: 1.1459 g (78%); mp 179–180 °C (petroleum ether/ethyl acetate) (Lit.[22] mp 174–176 °C, dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.50 (s, 1H, NH), 7.85 (s, 1H, ArH), 7.70–7.59 (m, 3H, ArH), 7.51–7.38 (m, 3H, ArH), 7.21 (t, J = 7.8 Hz, 1H, ArH), 6.95 (d, J = 7.6 Hz, 1H, ArH), 6.86 (t, J = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 141.8, 137.5, 134.8, 129.9, 129.6, 129.3, 128.6, 127.7, 122.9, 121.7, 121.6, 110.4; MS (%): m/z = 221 (M^+, 100); IR (neat): ν = 1612, 1591, 1575, 1490, 1462, 1445, 1416, 1362, 1328, 1295, 1269, 1232, 1204, 1143, 1092, 1074, 1028 cm^{-1}.

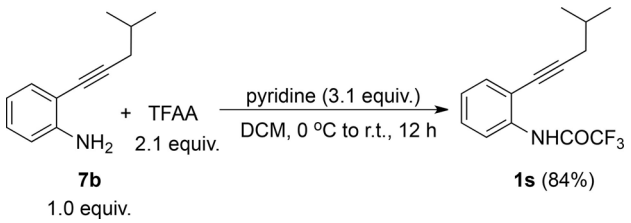
Synthesis of (*E*)-3-(3-methylbutylidene)-2-indolinone (*E*-9b)

Synthesis of 2-(4-methyl-1-pentynyl)aniline (7b)



To a 250-mL three-necked flask were added 2-iodoaniline (7.7713 g, 35.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.2491 g, 0.3 mmol), 100 mL of anhydrous Et_3N, and 4-methylpentyne (5.0 mL, d = 0.70 g mL^{-1}, 42.6 mmol, 3.4992 g) sequentially under an argon atmosphere. The mixture was stirred at room temperature for 5 min followed by the addition of CuI (0.0676 g, 0.3 mmol). After being stirred at room temperature for 12 h as monitored by TLC, the resulting suspension was filtered under vacuum, concentrated and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/1) to afford **7b**[23] as an oil; yield: 5.4148 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.10–7.04 (m, 1H, ArH), 6.70–6.63 (m, 2H, ArH), 4.16 (bs, 2H, NH_2), 2.36 (d, J = 6.4 Hz, 2H, CH_2), 1.98–1.87 (m, 1H, CH), 1.05 (d, J = 6.8 Hz, 6H, 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 132.0, 128.7, 117.8, 114.1, 109.0, 94.6, 77.8, 28.8, 28.2, 22.0; MS (%): m/z = 173 (M^+, 49.5), 130 (100); IR (neat): ν = 3473, 3377, 3028, 1612, 1572, 1492, 1455, 1426, 1384, 1367, 1343, 1305, 1263, 1245, 1157 cm^{-1}.

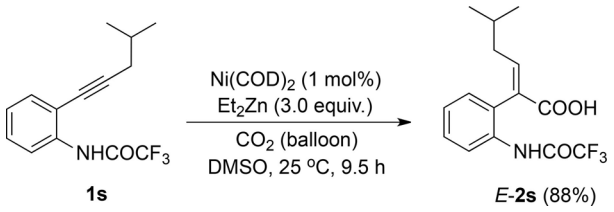
Synthesis of *N*-Trifluoroacetyl-2-(4-methyl-1-pentynyl)aniline (1s)



To a 100-mL three-necked flask were added **7b** (2.5390 g, 14.6 mmol), 42 mL of anhydrous DCM, and pyridine (4.2 mL, d = 0.98 g mL^{-1}, 45.0 mmol, 3.5595 g) sequentially under an argon atmosphere. The resulting mixture was cooled to 0 °C and trifluoroacetic anhydride (TFAA) (4.3 mL, d = 1.49 g mL^{-1}, 30.0 mmol, 6.2994 g) was added

dropwise. Then the mixture was warmed up to room temperature and stirred for 12 h as monitored by TLC. The resulted solution was quenched with 40 mL of water. The aqueous layer was extracted with DCM (40 mL×3) and the combined organic layer was washed with 200 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 60/1) to afford **1s** as an oil; yield: 3.3095 g (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (s, 1H, NH), 8.34 (d, J = 8.0 Hz, 1H, ArH), 7.46–7.41 (m, 1H, ArH), 7.38–7.32 (m, 1H, ArH), 7.15 (td, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H, ArH), 2.41 (d, J = 6.8 Hz, 2H, CH_2), 2.00–1.89 (m, 1H, CH), 1.06 (d, J = 6.8 Hz, 6H, 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4 (q, $J_{C,F}$ = 36.2 Hz), 136.1, 131.7, 129.0, 125.3, 119.3, 115.7 (q, $J_{C,F}$ = 287.4 Hz), 114.1, 98.5, 75.6, 28.6, 28.0, 21.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −76.4; MS (%): m/z = 269 (M^+, 34.82), 130 (100); IR (neat): ν = 3319, 2965, 1741, 1710, 1677, 1608, 1583, 1542, 1465, 1451, 1427, 1386, 1370, 1340, 1280, 1260, 1222, 1187, 1167, 1152, 1102, 1042 cm^{-1}; anal. calcd. for $C_{14}H_{14}F_3NO$: C 62.45, H 5.24, N 5.20; found: C 62.29, H 5.24, N 5.22.

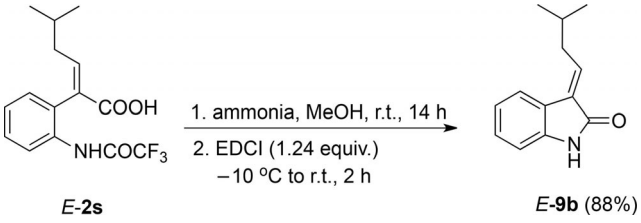
Synthesis of (*E*)-*N*-Trifluoroacetyl-2-(1-carboxy-4-methyl-1-pentenyl)aniline (*E*-2s)



1s *E*-**2s** (88%)

To a 250-mL three-necked flask was added **1s** (2.6002 g, 9.7 mmol) under an argon atmosphere and $Ni(COD)_2$ (27.6 mg, 0.10 mmol) was then added inside a glove box. Then 60 mL of DMSO were added under an argon atmosphere and the mixture was frozen with a liquid nitrogen bath. The argon inside was completely replaced with CO_2 by using a CO_2 balloon. Then the reaction flask was allowed to stand until the mixture thawed. To the resulting suspension was added $ZnEt_2$ (1.5 M in toluene, 20.0 mL, 30 mmol) with stirring. Then the resulting mixture was stirred at 25 °C for 9.5 h. After that, the resulting mixture was quenched with 100 mL of aqueous 3 M HCl. The aqueous layer was extracted with DCM (60 mL×3) and the combined organic layer was washed with 250 mL of brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1 to DCM/MeOH = 30/1) to afford *E*-**2s** as a yellow solid; yield: 2.6659 g (88%); mp 108–109 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.37 (bs, 1H, COOH), 10.87 (s, 1H, NH), 7.42–7.30 (m, 3H, ArH), 7.18 (d, J = 7.2 Hz, 1H, ArH), 6.96 (t, J = 7.4 Hz, 1H, =CH), 1.90–1.61 (m, 3H, CH + CH_2), 0.80 (d, J = 6.8 Hz, 6H, 2×CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.2, 154.9 (q, $J_{C,F}$ = 36.4 Hz), 144.1, 133.3, 132.5, 131.5, 128.1, 126.8, 126.3, 116.1 (q, $J_{C,F}$ = 287.4 Hz), 37.9, 27.5, 22.3; ^{19}F NMR (376 MHz, DMSO-d_6): δ = −73.5; MS (%): m/z = 315 (M^+, 4.93), 130 (100); IR (neat): ν = 3685, 3663, 2987, 2973, 2901, 1706, 1692, 1633, 1581, 1539, 1479, 1466, 1452, 1406, 1394, 1383, 1327, 1251, 1199, 1182, 1156, 1066, 1056 cm^{-1}; anal. calcd. for $C_{15}H_{16}F_3NO_3$: C 57.14, H 5.12, N 4.44; found: C 57.20, H 5.22, N 4.33.

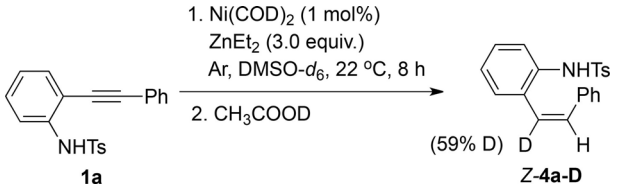
Synthesis of (*E*)-3-(3-Methylbutylidene)-2-indolinone (*E*-9b)



E-**2s** *E*-**9b** (88%)

To a 500-mL three-necked flask were added *E*-**2s** (2.3826 g, 7.5 mmol) and 250 mL of saturated solution of ammonia in MeOH. The mixture was stirred at room temperature for 14 h and then the solvent was removed by a rotary evaporator. The residue was dissolved in 230 mL of anhydrous DCM under an argon atmosphere and EDCI (1.7860 g, 9.3 mmol) was added at −10 °C. The solution was then warmed up to room temperature naturally and stirred for 110 min. After that, the resulting solution was washed with 200 mL of water and 200 mL of brine sequentially, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1 to 1/1) to afford *E*-**9b**[1a] as a yellow solid; yield: 1.3401 g (88%); mp 102–103 °C (petroleum ether/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1H, NH), 7.55 (d, J = 7.2 Hz, 1H, ArH), 7.21 (t, J = 7.8 Hz, 1H, ArH), 7.08 (t, J = 7.6 Hz, 1H, ArH), 7.01 (t, J = 7.6 Hz, 1H, ArH), 6.94 (d, J = 8.0 Hz, 1H, ArH), 2.58 (t, J = 7.2 Hz, 2H, CH_2), 2.04–1.92 (m, 1H, CH), 1.05 (d, J = 6.8 Hz, 6H, 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 141.8, 141.0, 128.8, 128.5, 123.7, 122.9, 122.0, 110.1, 38.3, 28.6, 22.6; MS (m/z) % 201 (M^+, 41.33), 145 (100); IR (neat): ν = 1702, 1648, 1614, 1593, 1464, 1420, 1368, 1349, 1320, 1294, 1260, 1216, 1164, 1154, 1093, 1050, 1027 cm^{-1}.

Synthesis of (*Z*)-4-Methyl-*N*-(2-styrylphenyl)-benzenesulfonamide (*Z*-4a-D)



1a *Z*-**4a-D**

To an oven-dried 50-mL Schlenk tube was added $Ni(COD)_2$ (2.8 mg, 0.01 mmol) inside a glove box. Then 2 mL of $ZnEt_2$ (1.5 M in toluene, 3.0 mmol) and 6 mL of DMSO-d_6 were added under an argon atmosphere and the mixture was frozen with a liquid nitrogen bath. Then **1a** (347.7 mg, 1.0 mmol) was added under an argon atmosphere. After replacing air with argon for three times under vacuum, the re-

action flask was allowed to stand until the mixture thawed to room temperature and was then stirred at 22 °C for 8 h. After that, the reaction was quenched with 1.0037 g DOAc and then 20 mL of Et_2O and 20 mL of brine were added into the mixture. The aqueous layer was extracted with Et_2O (10 mL × 3) and the combined organic layer was washed with brine (10 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1) to afford *Z*-**4a-D** as a white solid; yield: 210.3 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.51 (m, 3H, ArH), 7.22–7.19 (m, 1H, ArH), 7.19–7.10 (m, 5H, ArH), 7.10–6.97 (m, 2H, ArH), 6.93 (d, J = 7.6 Hz, 2H, ArH), 6.639 (s, 0.62H, =CH), 6.57 (s, 1H, NH), 2.34 (s, 3H, CH_3). The following signals are discernible for *Z*-**4a**: δ = 6.64 (d, J = 12.8 Hz, 0.38H, =CH), 6.12 (d, J = 11.6 Hz, 0.38H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 136.4, 135.4, 134.2, 134.02, 133.64, 133.62, 129.59, 129.57, 129.54, 129.51, 128.7, 128.5, 128.4, 128.0, 127.2, 125.1, 124.5, 121.60, 21.5. The following signals are discernible for *Z*-**4a**: δ = 134.02, 133.64, 129.57 (t, J = 4.0 Hz), 121.63; IR (neat, cm^{-1}) 3251, 1597, 1494, 1483, 1448, 1401, 1272, 1154, 1089; MS (ESI): m/z = 374 $[M(D)+Na+H]^+$, 373 $[M(D)+Na]^+$, 351 $[M(D)+H]^+$, 350 $[M(D)]^+$; HR-MS: m/z = 350.1196, calcd, for $C_{21}H_{18}DNO_2S$ $[M]^+$: 350.1199.

In addition, 26.8 mg of an unknown product were isolated and presented unique peaks in the ^{1}H NMR spectrum. This kind of structure had never been observed by comparing with all other crude ^{1}H NMR spectra described previously in this article. Further study will be continued in this group about this unknown product.

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[13] Crystal data for compound *E*-**2e**: $C_{20}H_{23}NO_4S$, MW = 373.47, triclinic, space group *P*-1, final *R* indices [$I > 2\sigma(I)$], $R1 = 0.1096$, $wR2 = 0.2978$; *R* indices (all data): $R1 = 0.1373$, $wR2 = 0.3126$; $a = 8.317(2)$ Å, $b = 9.719(2)$ Å, $c = 13.090(3)$ Å, $\alpha = 96.558(8)°$, $\beta = 102.297(6)°$, $\gamma = 107.332(8)°$, $V = 968.8(4)$ Å^3, $T = 296(2)$ K, $Z = 2$, reflections collected/unique: 10963/3369 ($R_{int} = 0.0551$), number of observations [$I > 2\sigma(I)$] 2431, parameters: 236. CCDC 1465264 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
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18 Bis(cycloocta-1,5-diene)nickel-Catalyzed Carbon Dioxide Fixation for the Stereoselective Synthesis of 3-Alkylidene-2-indolinones

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