Pd-catalyzed One-Pot Multicomponent Coupling Reaction for the High Regioselective
Synthesis of Polysubstituted Benzenes

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Experimental Section

All reactions involving organometallic compounds were carried out using standard schlenk tube under nitrogen. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. The alkynes were purchased from commercial sources and used as received. 2-bromoacrylate¹ was prepared according to the literature. ¹H NMR and ¹³C NMR spectra were recorded on JEOL AL-300MHZ NMR spectrometer.

A General procedure for the reaction of alkynes 1 and 2-haloacrylate 2.

Formation of 2'-(1-methoxycarbonyl-vinyl)-[1,1';3',1'']terphenyl-5'-carboxylic acid methyl ester (4a). To a stirred mixture of 220 μ L (2.0mmol) of methyl 2-bromoacrylate (**2a**), 1.0mg (0.01mmol) of CuCl, and 23mg (0.02mmol) of Pd(PPh₃)₄, 280 μ L (2.0mmol) of triethylamine in 5mL of THF was added 240 μ L (2.2mmol) of ethynyl-benzene (**1a**). The mixture was stirred for 12 h at 50°C. Then it was quenched with 2N HCl, and extracted with 20 mL ether for 3 times. The extract was washed with NaCl aq, dried over Na₂SO₄, and concentrated in vacuo. Column chromatography on silica gel (dichloromethane/petroleum ether = 1 / 2) afforded 316mg(85% isolated yield) of (**4a**) as white solid. ¹H-NMR δ 3.38 (s, 3H), 3.92 (s, 3H), 5.32 (s, 1H), 6.21 (s, 1H), 7.32-7.29 (m, 10H), 8.02 (m, 2H); ¹³C NMR δ 51.8, 52.2, 127.2, 128.0, 128.2, 128.5, 129.5, 130.1, 131.8, 139.1, 139.2, 140.6, 142.5, 166.6, 166.7. HRMS calcd for C₂₄H₂₀O₄ 372.1362, found. 372.1357.

3,5-Dihexyl-4-(1-methoxycarbonyl-vinyl)-benzoic acid methyl ester (4b). Isolatd yield 68%. ¹H NMR δ 0.87 (t, *J* = 6.9Hz, 6H), 1.27-1.32 (m, 8H), 1.48-1.50 (m, *J* = 7.9Hz, 8H), 2.42-2.51 (m, *J* = 7.5 Hz, 4H), 3.73 (s, 3H), 3.91(s, 3H), 5.62 (d, *J* = 1.7Hz,

1H), 6.71(d, $J = 1.7\text{Hz}$, 1H), 7.75 (s, 2H); ^{13}C NMR δ 14.1, 22.6, 29.3, 30.9, 31.7, 33.7, 52.0, 52.3, 127.4, 129.4, 129.8, 138.7, 140.5, 141.5, 166.8, 167.3. HRMS calcd for $\text{C}_{24}\text{H}_{36}\text{O}_4$ 388.2614, found 388.2620.

3,5-Dibutyl-4-(1-methoxycarbonyl-vinyl)-benzoic acid methyl ester (4c). Isolated yield 72%. The NMR data of this compound are consistent with literature.²

2'-(1-Methoxycarbonyl-vinyl)-4,4''-dimethyl-[1,1';3',1'']terphenyl-5'-carboxylic acid methyl ester (4d). Isolated yield 81%. ^1H NMR δ 2.35 (s, 6H), 3.39 (s, 3H), 3.90 (s, 3H), 5.31 (d, $J = 0.7\text{Hz}$, 1H), 6.22 (d, $J = 1.4\text{Hz}$, 1H), 7.15 (d, 8H), 8.00 (d, 2H); ^{13}C NMR δ 21.1, 51.7, 52.1, 128.6, 129.3, 129.9, 131.6, 136.8, 137.7, 139.1, 139.2, 142.4, 166.6, 166.8. HRMS calcd for $\text{C}_{26}\text{H}_{24}\text{O}_4$ 400.1675, found 400.1679.

4-(1-Ethoxycarbonyl-vinyl)-3,5-dipentyl-benzoic acid ethyl ester (4e)

Isolated yield 78%. ^1H NMR δ 0.87 (t, $J = 6.9\text{ Hz}$, 6H), 1.22-1.40(m, 18H), 2.42-2.53 (m, 4H), 4.20 (q, $J = 7.3\text{Hz}$, 2H), 4.31 (q, $J = 7.3\text{ Hz}$, 2H), 5.61 (d, $J = 1.1\text{ Hz}$, 1H), 6.70 (d, $J = 1.7\text{ Hz}$, 1H), 7.74 (s, 2H); ^{13}C NMR δ 14.0, 14.2, 14.4, 22.5, 30.6, 31.8, 33.7, 60.8, 61.1, 127.3, 129.5, 129.6, 139.0, 140.5, 141.4, 166.3, 166.9. HRMS calcd for $\text{C}_{24}\text{H}_{36}\text{O}_4$ 388.2614, found 388.2611.

2'-(1-Ethoxycarbonyl-vinyl)-[1,1';3',1'']terphenyl-5'-carboxylic acid ethyl ester (4f). Isolated yield 79%. ^1H NMR δ 0.99 (t, $J = 6.9\text{Hz}$, 3H), 1.38 (t, $J = 7.2\text{Hz}$, 3H), 3.85 (q, $J = 7.2\text{Hz}$, 2H), 4.39 (q, $J = 6.9\text{Hz}$, 2H), 5.31 (s, 1H), 6.21 (s, 1H), 7.33-7.31 (m, 10H), 8.03 (d, $J = 1.7\text{Hz}$, 2H); ^{13}C NMR δ 13.9, 14.3, 60.7, 61.1, 127.1, 127.9, 129.5, 129.8, 130.0, 131.5, 139.1, 139.6, 140.7, 142.4, 166.2, 166.2, HRMS calcd for

C₂₆H₂₄O₄ 400.1675, 400.1679.

3,5-Dibutyl-4-(1-ethoxycarbonyl-vinyl)-benzoic acid ethyl ester (4g). Isolated yield 66%. ¹H NMR δ 0.90 (t, *J* = 7.2Hz, 6H), 1.51-1.21 (m, 15H), 2.51 (m, *J* = 7.2Hz, 3H), 4.22 (q, *J* = 7.2Hz, 2H), 4.39 (q, *J* = 7.2Hz, 2H), 5.62 (d, *J* = 1.4Hz, 1H), 6.71 (d, *J* = 1.4Hz, 1H), 7.75 (s, 2H); ¹³C NMR δ 13.8, 14.0, 14.3, 22.6, 33.0, 33.3, 60.7, 61.0, 127.2, 129.4, 129.5, 139.0, 140.5, 141.3, 166.2, 166.8. HRMS calcd for C₂₂H₃₂O₄ 360.2301, found 360.2296.

Reference

1. Dachon, J. Goedken, V.; Walborsky, H. M. *J. Org. Chem.*, **1989**, *54*, 1006-1012.
2. Saito, S.; Chounan, Y.; Nogami, T.; Fukushi, T.; Tsuboya, N.; Yamada, Y.; Kitahara, H.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 5350-5354.

X-ray data of compound 4a

Table 1. Details of Data Collection, Processing and Structure Refinement

Sample code	4a		
Molecular formula	C ₂₄ H ₂₀ O ₄		
Molecular weight	372.40		
Color and habit	colorless block		
Crystal size	0.2 × 0.5 × 0.5 mm		
Crystal system	triclinic		
Space group	P1̄ (No. 2)		
Unit cell parameters	a = 9.0452(12) Å α = 67.639(12)° b = 10.6117(18) Å β = 79.657(13)° c = 11.2674(18) Å γ = 84.959(13)° V = 983.7(3) Å ³ Z = 2 F(000) = 392		
Density (calcd)	1.257 g/cm ³		
Diffractometer	Bruker P4		
Radiation	graphite-monochromatized Mo K _α , λ = 0.71073 Å		
Temperature	295±2K		
Scan type	ω-scan		
Data collection range	-1 < h < 10, -11 < k < 11, -13 < l < 13; θ _{max} = 25°		
Reflections measured	Total: 4090	Unique (n): 3389	Observed [I ≥ 2σ(I)]: 2459
Absorption coefficient	0.085 mm ⁻¹		
No. of variables, p	253		
Weighting scheme	$w = \frac{1}{\sigma^2(F_o^2) + (0.001P)^2 + 0.4000P} \quad P = (F_o^2 + 2F_c^2)/3$		
$R1 = \frac{\sum F_o - F_c }{\sum F_o }$ (for all reflections)	0.0574	0.0415 (for observed data)	
$wR2 = \sqrt{\frac{\sum [w(F_o^2 - F_c^2)^2]}{\sum w(F_o^2)^2}}$ (for all reflections)	0.0893	0.0808 (for observed data)	
$Goof = S = \sqrt{\frac{\sum [w(F_o^2 - F_c^2)^2]}{n - p}}$	1.034		
Largest and mean Δ/σ	0.000, 0.000		

Table 2. Atomic coordinates and equivalent isotropic temperature factors* ($\text{\AA}^2$)

Atoms	x	y	z	$U_{eq.}$
O(1)	0.11771(19)	0.85624(14)	0.04880(14)	0.0737(4)
O(2)	0.22675(19)	0.86915(14)	-0.14936(14)	0.0764(5)
O(3)	0.3508(2)	0.03500(16)	0.31418(17)	0.0924(5)
O(4)	0.40804(16)	0.24949(14)	0.27458(13)	0.0639(4)
C(1)	0.1801(2)	0.65132(18)	0.00978(18)	0.0504(4)
C(2)	0.2520(2)	0.59157(19)	-0.07541(18)	0.0528(5)
C(3)	0.2752(2)	0.45123(19)	-0.03553(17)	0.0491(4)
C(4)	0.2225(2)	0.36798(18)	0.09419(17)	0.0488(4)
C(5)	0.1429(2)	0.42842(19)	0.17939(17)	0.0498(4)
C(6)	0.1245(2)	0.56854(19)	0.13628(18)	0.0526(5)
C(7)	0.1693(2)	0.8008(2)	-0.0254(2)	0.0568(5)
C(8)	0.2282(4)	1.0164(2)	-0.1906(3)	0.1025(10)
C(9)	0.2520(2)	0.21782(19)	0.14328(19)	0.0547(5)
C(10)	0.2063(3)	0.1362(2)	0.0936(2)	0.0751(6)
C(11)	0.3395(2)	0.1553(2)	0.2531(2)	0.0602(5)
C(12)	0.4864(3)	0.2014(3)	0.3850(2)	0.0894(8)
C(13)	0.3594(2)	0.39711(19)	-0.13353(17)	0.0503(4)
C(14)	0.4882(2)	0.3181(2)	-0.1120(2)	0.0649(6)
C(15)	0.5684(3)	0.2730(3)	-0.2059(2)	0.0773(7)
C(16)	0.5198(3)	0.3074(3)	-0.3227(2)	0.0774(7)
C(17)	0.3925(3)	0.3860(3)	-0.3465(2)	0.0754(6)
C(18)	0.3123(2)	0.4314(2)	-0.25267(19)	0.0629(5)
C(19)	0.0771(2)	0.34576(19)	0.31604(18)	0.0539(5)
C(20)	-0.0219(2)	0.2416(2)	0.3440(2)	0.0646(5)
C(21)	-0.0872(3)	0.1707(2)	0.4708(2)	0.0786(7)
C(22)	-0.0550(3)	0.2028(3)	0.5704(2)	0.0868(8)
C(23)	0.0437(3)	0.3049(3)	0.5448(2)	0.0847(7)
C(24)	0.1092(3)	0.3770(2)	0.4178(2)	0.0684(6)

* $U_{eq.}$ defined as one third of the trace of the orthogonalized $\mathbf{U}$ tensor.

Table 3. Bond lengths (Å) and bond angles (°)

O(1)-C(7)	1.204(2)	C(5)-C(19)	1.493(3)
O(2)-C(7)	1.335(2)	C(9)-C(10)	1.322(3)
O(2)-C(8)	1.451(3)	C(9)-C(11)	1.494(3)
O(3)-C(11)	1.203(2)	C(13)-C(14)	1.376(3)
O(4)-C(11)	1.337(2)	C(13)-C(18)	1.387(3)
O(4)-C(12)	1.442(3)	C(14)-C(15)	1.386(3)
C(1)-C(2)	1.383(2)	C(15)-C(16)	1.369(3)
C(1)-C(6)	1.387(3)	C(16)-C(17)	1.366(3)
C(1)-C(7)	1.481(3)	C(17)-C(18)	1.388(3)
C(2)-C(3)	1.391(3)	C(19)-C(20)	1.390(3)
C(3)-C(4)	1.409(3)	C(19)-C(24)	1.390(3)
C(3)-C(13)	1.494(2)	C(20)-C(21)	1.383(3)
C(4)-C(5)	1.411(2)	C(21)-C(22)	1.374(4)
C(4)-C(9)	1.491(3)	C(22)-C(23)	1.376(4)
C(5)-C(6)	1.382(3)	C(23)-C(24)	1.388(3)
C(7)-O(2)-C(8)	116.21(17)	C(4)-C(9)-C(11)	118.82(17)
C(11)-O(4)-C(12)	116.48(18)	O(3)-C(11)-O(4)	123.2(2)
C(2)-C(1)-C(6)	119.01(17)	O(3)-C(11)-C(9)	125.0(2)
C(2)-C(1)-C(7)	122.69(17)	O(4)-C(11)-C(9)	111.82(17)
C(6)-C(1)-C(7)	118.15(17)	C(14)-C(13)-C(18)	118.02(18)
C(1)-C(2)-C(3)	121.48(17)	C(14)-C(13)-C(3)	121.95(17)
C(2)-C(3)-C(4)	119.22(16)	C(18)-C(13)-C(3)	119.96(17)
C(2)-C(3)-C(13)	117.39(16)	C(13)-C(14)-C(15)	121.2(2)
C(4)-C(3)-C(13)	123.38(16)	C(16)-C(15)-C(14)	119.9(2)
C(3)-C(4)-C(5)	119.25(17)	C(17)-C(16)-C(15)	119.9(2)
C(3)-C(4)-C(9)	121.13(16)	C(16)-C(17)-C(18)	120.2(2)
C(5)-C(4)-C(9)	119.61(16)	C(13)-C(18)-C(17)	120.6(2)
C(6)-C(5)-C(4)	119.57(17)	C(20)-C(19)-C(24)	118.73(19)
C(6)-C(5)-C(19)	118.32(16)	C(20)-C(19)-C(5)	121.40(18)
C(4)-C(5)-C(19)	122.11(17)	C(24)-C(19)-C(5)	119.80(18)
C(5)-C(6)-C(1)	121.36(17)	C(21)-C(20)-C(19)	120.4(2)
O(1)-C(7)-O(2)	122.95(19)	C(22)-C(21)-C(20)	120.3(2)
O(1)-C(7)-C(1)	124.58(19)	C(21)-C(22)-C(23)	120.2(2)
O(2)-C(7)-C(1)	112.46(17)	C(22)-C(23)-C(24)	119.9(2)
C(10)-C(9)-C(4)	123.5(2)	C(23)-C(24)-C(19)	120.5(2)
C(10)-C(9)-C(11)	117.7(2)		

Table 4. Anisotropic thermal parameters* ($\text{\AA}^2$)

Atoms	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	0.0972(12)	0.0568(9)	0.0704(9)	-0.0315(8)	-0.0089(9)	0.0089(8)
O(2)	0.1084(13)	0.0485(8)	0.0632(9)	-0.0170(7)	0.0013(9)	-0.0025(8)
O(3)	0.1109(14)	0.0522(10)	0.0944(12)	-0.0051(9)	-0.0177(11)	-0.0006(9)
O(4)	0.0690(9)	0.0643(9)	0.0567(8)	-0.0190(7)	-0.0127(7)	-0.0020(7)
C(1)	0.0518(11)	0.0480(10)	0.0537(11)	-0.0213(9)	-0.0094(9)	-0.0001(8)
C(2)	0.0568(11)	0.0536(11)	0.0482(10)	-0.0196(9)	-0.0067(9)	-0.0025(9)
C(3)	0.0479(10)	0.0540(11)	0.0513(10)	-0.0260(9)	-0.0078(8)	-0.0007(8)
C(4)	0.0475(10)	0.0508(11)	0.0524(10)	-0.0240(9)	-0.0072(8)	-0.0023(8)
C(5)	0.0496(11)	0.0520(11)	0.0504(10)	-0.0225(9)	-0.0052(8)	-0.0032(8)
C(6)	0.0536(11)	0.0543(11)	0.0538(11)	-0.0269(9)	-0.0042(9)	0.0007(9)
C(7)	0.0595(12)	0.0541(12)	0.0590(12)	-0.0228(10)	-0.0130(10)	0.0034(9)
C(8)	0.152(3)	0.0476(13)	0.0879(18)	-0.0134(12)	0.0025(18)	-0.0004(15)
C(9)	0.0564(11)	0.0502(11)	0.0588(11)	-0.0256(9)	0.0020(9)	-0.0062(9)
C(10)	0.0842(16)	0.0612(14)	0.0862(16)	-0.0364(12)	-0.0051(13)	-0.0099(12)
C(11)	0.0592(12)	0.0523(12)	0.0603(12)	-0.0173(10)	0.0037(10)	-0.0002(10)
C(12)	0.0934(19)	0.110(2)	0.0609(14)	-0.0234(14)	-0.0227(13)	0.0032(16)
C(13)	0.0506(11)	0.0537(11)	0.0505(10)	-0.0247(9)	-0.0039(8)	-0.0041(9)
C(14)	0.0569(12)	0.0868(15)	0.0608(12)	-0.0388(11)	-0.0122(10)	0.0069(11)
C(15)	0.0658(14)	0.0980(18)	0.0782(15)	-0.0487(14)	-0.0111(12)	0.0200(13)
C(16)	0.0750(16)	0.1011(19)	0.0699(14)	-0.0531(14)	-0.0017(12)	0.0053(14)
C(17)	0.0803(16)	0.1012(18)	0.0551(12)	-0.0408(13)	-0.0124(11)	0.0027(14)
C(18)	0.0618(13)	0.0753(14)	0.0555(12)	-0.0294(10)	-0.0118(10)	0.0065(11)
C(19)	0.0541(11)	0.0528(11)	0.0522(11)	-0.0210(9)	0.0002(9)	0.0021(9)
C(20)	0.0611(13)	0.0633(13)	0.0640(13)	-0.0203(11)	-0.0026(10)	-0.0044(10)
C(21)	0.0688(15)	0.0708(15)	0.0770(16)	-0.0123(13)	0.0058(12)	-0.0087(12)
C(22)	0.0874(18)	0.0861(18)	0.0608(14)	-0.0112(13)	0.0143(13)	0.0041(15)
C(23)	0.106(2)	0.0913(18)	0.0547(13)	-0.0319(13)	0.0022(13)	0.0018(16)
C(24)	0.0793(15)	0.0700(14)	0.0570(12)	-0.0289(11)	0.0002(11)	-0.0051(12)

The exponent takes the form: $-2\pi^2 \sum \sum U_{ij} h_i h_j \mathbf{a}_i^ \mathbf{a}_j^*$

Table 5. Coordinates and isotropic temperature factors* ($\text{\AA}^2$) for H atoms

Atoms	x	y	z	$U_{eq.}$
H(2A)	0.2856	0.6465	-0.1613	0.063
H(6A)	0.0738	0.6081	0.1933	0.063
H(8A)	0.2718	1.0553	-0.2806	0.154
H(8B)	0.2866	1.0404	-0.1394	0.154
H(8C)	0.1271	1.0509	-0.1790	0.154
H(10A)	0.1527	0.1719	0.0244	0.090
H(10B)	0.2277	0.0432	0.1279	0.090
H(12A)	0.5304	0.2770	0.3916	0.134
H(12B)	0.5640	0.1371	0.3741	0.134
H(12C)	0.4168	0.1579	0.4627	0.134
H(14A)	0.5221	0.2944	-0.0329	0.078
H(15A)	0.6550	0.2195	-0.1895	0.093
H(16A)	0.5734	0.2772	-0.3858	0.093
H(17A)	0.3594	0.4091	-0.4258	0.090
H(18A)	0.2261	0.4854	-0.2699	0.075
H(20A)	-0.0444	0.2194	0.2771	0.078
H(21A)	-0.1532	0.1010	0.4887	0.094
H(22A)	-0.1000	0.1553	0.6554	0.104
H(23A)	0.0664	0.3256	0.6126	0.102
H(24A)	0.1749	0.4466	0.4006	0.082

*The exponent takes the form: $-8\pi^2 U \sin^2 \theta / \lambda^2$

ORTEP drawing of $C_{24}H_{20}O_4$ (**4a**) with 35% probability ellipsoids, showing the atomic numbering scheme.

040525-ahh116H-single_pulse.2
single_pulse

040525-ahh116C-4ppm, pulse dec, 2
single pulse decoupled gated NOE

040527-ahb124H-single_pulse.2
single_pulse

040577-ahh124C-4pmh.pulse dec.2
single pulse decoupled gated NOE

041117-ohet204-h-single_pulse.2
single_pulse

041117-ahb204C-sipha pulve dec.2
single pulse decoupled gated NOE

040527-ahsh128H-single_pulse.2
single_pulse

040577-ahh178C-4pmh.pulse dec.2
single pulse decoupled gated NOE

040407-ahb-87-3H-single_pulse4
single_pulse

646324-dmbs7-2-CARBON4
chsh

64407-dab02_PROTON4
ch01

X : Parts per Million : 1H