Heck Reaction of Amino Acid Derived Vinyl Substrates in the Synthesis of Homotyrosinol Derivatives

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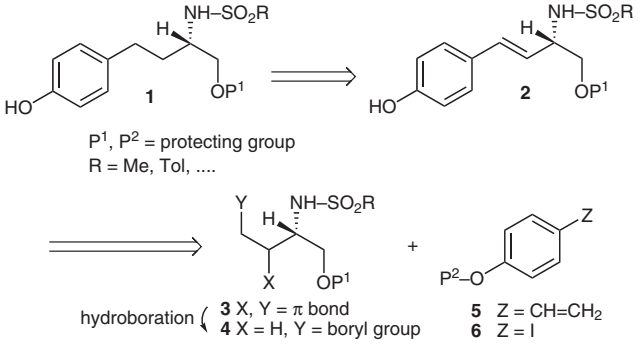
Abstract: An avenue to homotyrosinol derivatives through a Heck coupling of 4-iodophenyl acetate with a vinylglycinol derivative required extensive screening of catalysts and conditions. The use of $Pd(OAc)_2$ and *N*-phenylurea as the ligand ultimately provided excellent results.

Key words: coupling, Heck reaction, homotyrosine, palladium, *N*-phenylurea

Ongoing efforts centering on the application of the oxidative amidation of phenols[1] in alkaloid synthesis unveiled the desirability of a practical route to homotyrosinol sulfonamides such as **1** (Scheme 1). Past avenues to such educts have relied on commercial, but expensive, homotyrosine as the starting material.[2] The high cost of that amino acid[3] prompted us to seek alternatives. Important work by Göbel[4] suggested that the desired product **1** might be accessible from vinylglycinol[5] **3** by Mizoroki–Heck arylation[6] with **6**, followed by hydrogenation of the intermediate **2**. Plausible alternatives included an olefin cross-metathesis reaction[7] of **3** with styrene **5**, also followed by hydrogenation, and a Suzuki coupling[8] of boronic acid **4** with an O-protected 4-iodophenol **6**.

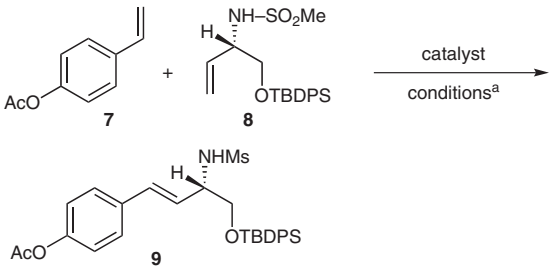
The implementation of a Suzuki approach required an initial hydroboration of **3**. Such a reaction is documented for BOC-protected vinylglycinols.[9] In contrast, attempts to hydroborate **3** with various reagents, including 9-borabicyclo[3.3.1]nonane (9-BBN), catecholborane, and pinacolborane in the presence of Wilkinson's catalyst,[10] met with failure.[11] Thus, the hydroboration of sulfonamide analogs appears to be problematic. Attempts to induce cross-metathesis of **7** with **8** also ran into difficulties. As seen in Table 1, the reaction stalled at about 40% conversion when either Grubbs II[12] or Hoveyda II[13] catalysts were used, and the desired product **2** was isolated in no more than 21% yield. Use of first-generation catalysts[14] was even less satisfactory.



Scheme 1

These disappointments induced us to concentrate on the Heck approach. The 'ligandless' procedure of Göbel (Table 2) afforded excellent results in the coupling of **8** with **10** on scales up to about 400 mg of **8**, but reactions run with larger quantities of substrate proceeded in only 40–50% yield. The formation of a black precipitate (pre-

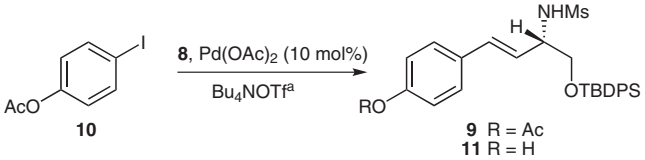
Table 1 Attempted Cross-Metathesis Reaction of **3** with **5**[a]



Entry	Catalyst	Conversion (%)	Yield (%)
1	Grubbs I	15	8
2	Grubbs II	40	12
3	Hoveyda I	25	11
4	Hoveyda II	35	21

[a] Reaction conditions: **7** (0.6 mmol), **8** (0.5 mmol), 0.2 M in CH_2Cl_2, r.t. or in toluene at 100 °C (sealed tube); catalyst: 5, 10, 30 or 100 mol%.

Table 2 The Göbel 'Ligandless' Heck Reaction of **8** with **10**[a]



Mass of **8** (mg)	Yield of **9** (%)	Yield of **11** (%)
403	63	21
2000	not detected	46

[a] Conditions as described by Suhartono et al.[4]

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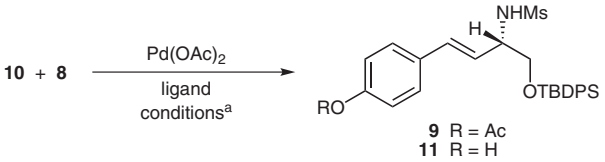
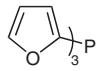
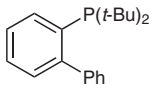
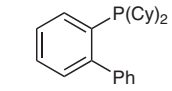
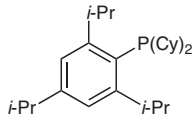
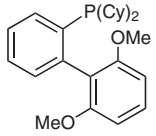
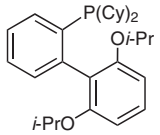
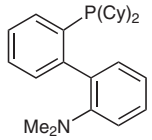
sumably, finely divided Pd) indicated that the use of a suitable ligand that might stabilize intervening organometallic species was desirable. A screen of various phosphines (Table 3) identified SPhos[15] as the best such ligand. Thus, the desired product **9** emerged in 91% yield (after chromatography) from a reaction run on a scale of 100 mg of **8** that employed 20 mol% of $Pd(OAc)_2$ and 40 mol% of ligand. Scaling up of the process resulted in formation of variable amounts of the deacetylated product **11**. For instance, **9** and **11** emerged in 52 and 34% yield (purified by chromatography), respectively, upon scale-up to 4.3 g of **8**, while keeping all other reaction parameters unchanged. Since **11** is the ultimate desired product, its formation is inconsequential.

Optimization of the reaction defined the best combination of aryl and vinyl substrates and the ideal source of Pd, and minimized the amount of metal and ligand required, both of which are costly. The combination of variants of **8** and **10** under a constant set of conditions (Table 4) produced inferior results. Consequently, further refinement focused

Table 3 Heck Reaction of **8** with **10** in the Presence of Various Palladium–Phosphine Complexes[a]



Entry	Ligand	Time (h)	Yield of **9** (%)	Yield of **11** (%)
1	PPh_3	4.5	31	9
2	PBu_3	4	87 (100 mg of **8**) 58 (2.7 g of **8**)	– –
3		7	<10	<5
4	 (JohnPhos)	9	19	–
5	 (cyclohexyl JohnPhos)	9	22	–
6	 (XPhos)	4	58	24
7	 (SPhos)	4	91 (100 mg of **8**) 52 (4.7 g of **8**)[b]	– 34[b]
8		4	55	5
9	 (DavePhos)	5 (only 72% conversion)	24	20

[a] Reaction conditions: **8** (0.5 mmol), 0.35 M in degassed (Ar) DMF, $Pd(OAc)_2$ (20 mol%), ligand (40 mol%), **10** (1.2 equiv), K_2CO_3 (1.2 equiv), 105 °C, yields of chromatographically purified products.
[b] Reaction carried out with 1.5 mmol of **8**.

exclusively on the union of **8** and **10**. The best source of Pd (Table 5) was $Pd(OAc)_2$ and best results were obtained when the reaction was carried out with 3 mol% each of $Pd(OAc)_2$ and SPhos.

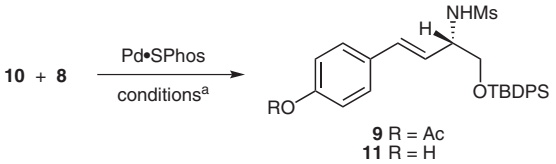
For preparative work, the mixture of **9** and **11** thus obtained was directly subjected to deacetylation, affording the desired product **11** in about 85% yield.

Table 4 Heck Reaction of Variants of the Aryl and Vinyl Components[a]

Entry	R	X	P	Yield (R = Ac) (%)[b]	Yield (R = H) (%)[b]
1	Ac	I	OAc	41	0
2	Ac	I	TBS	0	21
3	Ac	Br	TBDPS	15	0
4	H	I	TBDPS	0	10
5	H	I	H	0	36

[a] Reaction conditions: **8** (0.5 mmol), 0.35 M in degassed (Ar) DMF, **10** (1.2 equiv), $Pd(OAc)_2$ (10 mol%), SPhos (20 mol%), K_2CO_3 (1.2 equiv), 105 °C, 4 h; NMR monitoring.
[b] Yields of chromatographically purified products.

Table 5 Heck Reaction of **8** with **10** in the Presence of SPhos Complexes of Palladium[a]

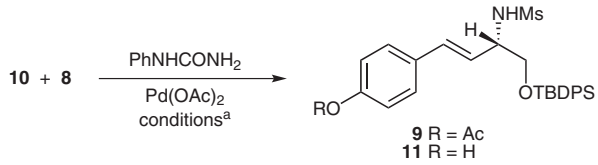


Entry	Pd source	Pd (mol%)	Pd/ligand	Yield of **9** (%)	Yield of **11** (%)
1	$Pd_2(dba)_3$	10	1:2	40	0[b]
2	$Pd(PPh_3)_4$	10	1:2	9	0[c]
3	$PdCl_2(PPh_3)_2$	10	1:2	49	0[d]
4	$Pd(OAc)_2$	10	1:2	73	11
5	$Pd(OAc)_2$	10	1:1	21	62
6	$Pd(OAc)_2$	5	1:2	43	4
7	$Pd(OAc)_2$	3	1:1	34	52
8	$Pd(OAc)_2$	1	1:2	31	21[e]

[a] Reaction conditions: **8** (0.5 mmol), 0.35 M in degassed (Ar) DMF, **10** (1.2 equiv), K_2CO_3 (1.2 equiv), 105 °C, 4 h; yields of chromatographically purified products.
[b] 80% conversion after 4 h.
[c] 30% conversion after 4 h.
[d] 65% conversion after 4 h.
[e] 70% conversion after 9 h.

The high price of SPhos translated into a significant financial investment even at a 3 mol% catalyst load. Recent work by Guo describes the use of inexpensive *N*-phenylurea as an excellent ligand in palladium-mediated reactions.[16] This remarkable discovery encouraged us to examine that ligand in our own reaction.

Table 6 Heck Reaction of **8** with **10** in the Presence of *N*-Phenylurea Complexes of Palladium[a]

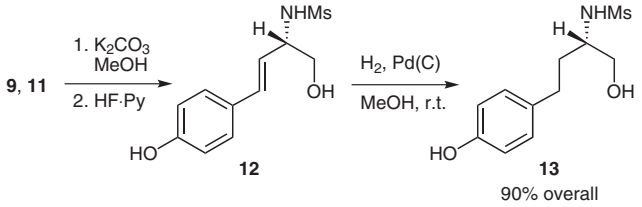


Entry	**8** (mmol)	Pd (mol%)	Base	Yield of **9** (%)	Yield of **11** (%)
1	0.5	10	K_2CO_3	38	48
2	0.5	10	$NaHCO_3$	76	13
3	0.5	10	$NaHCO_3$	84	0
4	0.5	10	Na_2HPO_3	23	0[b]
5	2.5	5	K_2CO_3	59	28
6	11.0	5	K_2CO_3	63	20[c]

[a] Reaction conditions: **8** (0.5 mmol), 0.35 M in degassed (Ar) DMF, **10** (1.2 equiv), base (1.2 equiv), $Pd(OAc)_2$/*N*-phenylurea [1:2 (mol/mol)], 105 °C, 2 h; ^{1}H NMR monitoring, yields of chromatographically purified products.
[b] 30% conversion after 4 h.
[c] Ratio calculated by integration of the ^{1}H NMR spectrum of the product.

In accord with Guo's observations, we found that *N*-phenylurea is indeed an outstanding substitute for SPhos in the Heck coupling of **8** with **10**. To wit, when **8** (0.5 mmol) in degassed DMF (1.5 mL; i.e., 0.35 M) containing $Pd(OAc)_2$ (10 mol%), *N*-phenylurea (20 mol%), **10** (0.6 mmol), and K_2CO_3 (0.6 mmol) was heated at 105 °C (reaction monitored by NMR analysis), complete consumption of **8** was detected after about two hours. Chromatographic purification of the crude product delivered **9** in 38% yield and **11** in 48% yield (86% overall, Table 6, entry 1). Replacing the base with milder $NaHCO_3$ resulted in exclusive formation of **9** in 84% yield after chromatography. It further transpired that the new ligand permitted the use of only 5 mol% of $Pd(OAc)_2$ even on substantial scales (entries 5 and 6). Clearly, use of Guo's inexpensive *N*-phenylurea afforded even better results than use of the more costly SPhos. For preparative purposes (entry 6), we favored the use of 5 mol% of metal, 10 mol% ligand, K_2CO_3 as the base, and two hours reaction time; use of these conditions afforded a mixture of **9** (63% by NMR) and **11** (20% by NMR) in 83% yield after chromatographic purification. This mixture was deacetylated (K_2CO_3 in MeOH) to furnish pure **11** directly.

All such Mizoroki–Heck reactions provided geometrically pure (within the limits of 300 MHz ^{1}H NMR spectroscopy) *trans*-isomers of the products. The enantiomeric purity was determined by the Mosher method.[17] Thus, desilylation of **9** (HF·py), esterification of the primary alcohol with (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid [(*R*)-MTPA] chloride and analysis of the resulting ester by ^{19}F NMR spectroscopy revealed the presence of a single diastereomer, signifying that no erosion of optical integrity had occurred during the synthetic sequence.

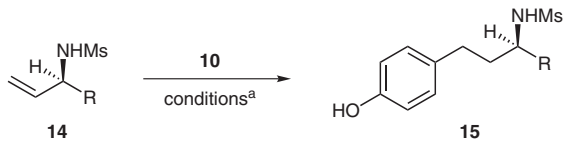


Scheme 2

The conversion of **9**–**11** into the desired final product **1** entails the hydrogenation of the olefin and the release of the protecting groups. Preliminary studies determined that it was best to fully deblock the substrate prior to hydrogenation. Thus, sequential treatment of a mixture of **9** and **11** with K_2CO_3 in MeOH (release of the phenolic acetate) and with HF·pyridine (which was superior to the use of TBAF in the present case; release of the TBDPS group), followed by hydrogenation, afforded compound **13** in 90% overall yield after chromatography (Scheme 2). In summary, the desired **13** was now available in 4.5 g batches in four steps from **8** and **10** with an overall yield of 75%.

The optimized sequence thus devised was extended to the preparation of other intermediates of current interest in our laboratory; Table 7 provides four such examples. The successful preparation of **15d** merits comment. This molecule, and its vinyl precursor **14d**, incorporate a dialkyl sulfide functionality, which may hamper the progress of transition-metal mediated reactions and/or require the use of special phosphine ligands.[18] Yet, *N*-phenylurea performed well even in this instance, wherein the overall yield of **15d** (44%) reflects the efficiency of the Heck step, in that the subsequent hydrogenation reaction was essentially quantitative.

Table 7 Heck Reaction of **10** with Amino Acid Derived Vinyl Substrates[a]



Entry	R	Overall yield (%)
a	*i*-Pr	89
b	Me	84
c	CH_2Ph	66
d	CH_2CH_2SMe	44

[a] Reaction conditions: (i) **14** (0.5 mmol), 0.35 M in degassed (Ar) DMF, **10** (1.2 equiv), base (1.2 equiv), $Pd(OAc)_2$ (5 mol%), *N*-phenylurea (10 mol%), 105 °C, 2 h; ^{1}H NMR monitoring; (ii) K_2CO_3, MeOH; (iii) HF·py; (iv) H_2, Pd/C, MeOH. Yields refer to chromatographically purified products.

In summary, this research has defined a robust method for the preparation of homotyrosinol derivatives and related intermediates through a Mizoroki–Heck coupling between an aryl iodide and appropriate amino acid derived olefins. A key aspect of the work is the use of inexpensive *N*-phenylurea as the ligand for palladium during the Heck reaction. The results obtained in the course of these studies are essential to the progress of various synthetic efforts ongoing in our laboratory.

Unless otherwise indicated, ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR (Bruker 300 Ultrashield™) spectra were recorded at r.t. from $CDCl_3$ solutions. Chemical shifts (δ) are reported as ppm and coupling constants (*J*) are reported in Hz. Multiplicities are described as s (singlet), d/dd/ddd (doublet/doublet of doublets/doublet of doublet of doublets), t (triplet), q (quartet), m (multiplet). Infrared (IR) spectra (cm^{-1}) were recorded with a Perkin–Elmer model 1710 Fourier transform spectrophotometer from films deposited on NaCl plates. Optical rotations were measured with a Jasco P-1010 polarimeter at the sodium D line (589 nm). Unless otherwise stated, low-resolution mass spectra (*m*/*z*) were obtained, in the electrospray (ESI) mode or the atmospheric pressure chemical ionization (APCI) mode on a Waters Micromass ZQ mass spectrometer. High-resolution mass spectra (*m*/*z*) were recorded in the ESI or APCI mode with a Micromass LCT mass spectrometer. Melting points (uncorrected) were measured with a Mel-Temp apparatus. Elemental analyses were measured on Carlo Erba Elemental Analyzer EA 1108. All reagents and solvents were commercial products and were used without further purification, except for THF (freshly distilled from Na/benzophenone under Ar) and CH_2Cl_2 (freshly distilled from CaH_2 under Ar). Flash chromatography was performed on Silicycle 230–400 mesh silica gel. All reactions were performed under anhydrous Ar in flame- or oven-dried flasks equipped with Teflon™ stirbars. All flasks were fitted with rubber septa for the introduction of substrates, reagents, and solvents via syringe.

(*S*,*E*)-*N*-[1-(*tert*-Butyldiphenylsilyloxy)-4-(4-hydroxyphenyl)but-3-en-2-yl]methanesulfonamide (11); General Procedure for Heck Coupling

Solid $Pd(OAc)_2$ (139 mg, 0.6 mmol, 5 mol%) was added to a degassed (Ar), well stirred DMF (35 mL) solution of 4-iodophenyl acetate (**7**; 3.9 g, 14.9 mmol), vinylglycinol derivative **8** (5.0 g, 12.4 mmol), and *N*-phenylurea (168 mmg, 1.2 mmol, 10 mol%) containing suspended K_2CO_3 (2.1 g, 14.9 mmol). The mixture was heated to 100–105 °C under argon. The progress of the reaction was monitored by ^{1}H NMR analysis. The reaction was complete after 2 h, whereupon the mixture was cooled to r.t., neutralized with aq sat. NH_4Cl (15 mL) and extracted with EtOAc (2 × 20 mL). The combined extracts were sequentially washed with aq sat. NH_4Cl (3 × 15 mL) and aq sat. NaCl (2 × 10 mL), dried (Na_2SO_4) and evaporated. The crude residue was redissolved in MeOH (30 mL) containing K_2CO_3 (1.7 g, 12.4 mmol), and the mixture was stirred at r.t. After 3 h, the reaction was complete. The solution was diluted with EtOAc (20 mL) and filtered through Celite. The filtrate was sequentially washed with aq sat. NH_4Cl (3 × 10 mL) and aq sat. NaCl (2 × 10 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue (EtOAc–hexanes, 3:1) afforded **11**.

Yield: 4.9 g (9.9 mmol, 80% yield over 2 steps); light-yellow oil; $[\alpha]_D^{21}$ –3.8 (*c* 1.75, acetone).

IR (NaCl): 3295, 2931, 1362, 1152 cm^{-1}.

^1H NMR: δ = 7.70–7.61 (m, 4 H), 7.48–7.34 (m, 6 H), 7.16 (d, *J* = 8.6 Hz, 2 H), 6.78 (d, *J* = 8.6 Hz, 2 H), 6.54 (d, *J* = 15.4 Hz, 1 H), 5.98–5.85 (m, 2 H), 5.01 (d, *J* = 6.5 Hz, 1 H), 4.24–4.13 (m, 1 H), 3.89–3.67 (m, 2 H), 2.95 (s, 3 H), 1.09 (s, 9 H).

^{13}C NMR: δ = 155.9, 135.58, 135.56, 132.9, 132.65, 132.63, 130.07, 130.03, 128.5, 127.97, 127.94, 127.91, 123.4, 115.6, 66.5, 57.8, 42.2, 26.9, 19.3.

ESI-MS: *m*/*z* = 518 $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{33}NO_4SSi$: 518.1797; found: 518.1797.

Anal. Calcd for $C_{27}H_{33}NO_4SSi$: C, 65.42; H, 6.71; N, 2.83. Found: C, 65.23; H, 6.36; N, 2.69.

(*S*,*E*)-*N*-[1-(*tert*-Butyldiphenylsilyloxy)-4-(4-acetoxyphenyl)but-3-en-2-yl]methanesulfonamide (9)

A sample of **9** was obtained by flash chromatographic purification of the Heck product (EtOAc–hexanes, 3:1) prior to K_2CO_3/MeOH treatment.

Light-yellow oil; $[\alpha]_D^{20}$ –16.6 (*c* 1.17, CH_2Cl_2).

IR (NaCl): 3288, 1750, 1324, 1156 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.68–7.60 (m, 4 H), 7.49–7.31 (m, 8 H), 7.06 (d, *J* = 8.6 Hz, 2 H), 6.62 (d, *J* = 15.7 Hz, 1 H), 6.07 (dd, *J* = 15.7, 7.5 Hz, 1 H), 4.93 (d, *J* = 6.7 Hz, 1 H), 4.25–4.15 (m, 1 H), 3.90–3.68 (m, 2 H), 2.93 (s, 3 H), 2.31 (s, 3 H), 1.08 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 169.4, 150.4, 135.56, 135.54, 133.7, 132.5, 132.3, 130.07, 130.04, 127.95, 127.90, 127.50, 126.5, 121.8, 66.4, 57.4, 42.2, 26.8, 21.1, 19.2.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{35}NO_5SSiNa$: 560.1903; found: 560.1894.

Anal. Calcd for $C_{29}H_{35}NO_5SSi$: C, 64.77; H, 6.56; N, 2.60. Found: C, 64.50; H, 6.52; N, 2.79.

(*S*,*E*)-*N*-[1-Hydroxy-4-(4-hydroxyphenyl)but-3-en-2-yl]methanesulfonamide (12)

Commercial HF-pyridine solution (70% HF, 7 mL) was added dropwise to a cold (0 °C) solution of **11** (4.9 g, 9.9 mmol) in THF (30 mL) under Ar, with good stirring. The mixture was stirred overnight, during which time it warmed to r.t., then was neutralized with solid $NaHCO_3$ added in small portions, with good stirring, until no more bubbling ensued (**CAUTION!** foaming). The mixture was then filtered through Celite and evaporated. Chromatographic purification of the residue (EtOAc–hexanes, 3:1) afforded pure **12**.

Yield: 2.4 g (9.4 mmol, 95%); light-yellow solid; mp 142–143 °C; $[\alpha]_D^{23}$ –63.6 (*c* 0.79, acetone).

IR (NaCl): 3426, 1644 cm^{-1}.

^1H NMR (acetone-d_6): δ = 8.46 (br, 1 H), 7.30 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 6.65 (d, *J* = 16 Hz, 1 H), 6.17–6.06 (m, 2 H), 4.21–4.06 (m, 2 H), 3.76–3.62 (m, 2 H), 2.96 (s, 3 H).

^{13}C NMR (acetone-d_6): δ = 157.2, 131.7, 128.3, 127.7, 124.5, 115.4, 65.1, 58.3, 41.0.

ESI-MS: *m*/*z* = 280 $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{15}NO_4SNa$: 280.0619; found: 280.0616.

Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.75; H, 5.80; N, 5.49.

(*S*)-*N*-(Methanesulfonyl)homotyrosinol (13)

Hydrogen gas was bubbled into a well-stirred solution of **10** (1 mmol) in MeOH (5 mL) containing suspended K_2CO_3 (138 mg, 1 mmol) and 10% Pd/C (53 mg, 5 mol%). Upon completion of the reaction, the mixture was filtered through a 2-inch silica pad using EtOAc as eluent. The filtrate was concentrated to afford **13**.

Yield: 2.3 g (8.9 mmol, 95%); light-yellow solid; mp 112.5–113.5 °C; $[\alpha]_D^{23}$ –6.0 (*c* 0.63, acetone).

IR (NaCl): 3417, 1644 cm^{-1}.

^1H NMR (acetone-d_6): δ = 8.08 (br, 1 H), 7.07 (d, *J* = 8.5 Hz, 2 H), 6.75 (d, *J* = 8.5 Hz, 2 H), 5.94 (d, *J* = 8.5 Hz, 1 H), 3.99 (br, 1 H), 3.63 (d, *J* = 5.5 Hz, 2 H), 3.49–3.38 (m, 1 H), 2.98 (s, 3 H), 2.81–2.56 (m, 2 H), 1.98–1.65 (m, 2 H).

^{13}C NMR (acetone-d_6): δ = 155.4, 132.7, 129.2, 115.1, 64.7, 55.8, 40.8, 34.4, 30.9.

ESI-MS: *m*/*z* = 282 $[M + Na]^+$.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{17}NO_4SNa$: 282.0776; found: 282.0778.

Anal. Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40. Found: C, 50.98; H, 6.59; N, 5.39.

(*R*)-*N*-[1-(4-Hydroxyphenyl)-4-methylpent-3-yl]methanesulfonamide (15a)

Chromatographic purification (EtOAc–hexanes, 1:1).

Pale-yellow oil; $[\alpha]_D^{17}$ –2.3 (*c* 0.97, acetone).

IR (NaCl): 3256, 1706, 1359, 1220 cm^{-1}.

^1H NMR (acetone-d_6): δ = 7.07 (d, *J* = 8.6 Hz, 2 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 3.32–3.23 (m, 1 H), 2.94 (s, 3 H), 2.80–2.52 (m, 2 H), 2.01–1.66 (m, 3 H), 0.95 (dd, *J* = 9.1, 6.7 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 154.1, 133.1, 129.3, 115.4, 59.4, 42.0, 34.3, 31.6, 31.4, 18.5, 17.6.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{21}NO_3SNa$: 294.1140; found: 294.1143.

(*S*)-*N*-[1-(4-Hydroxyphenyl)but-3-yl]methanesulfonamide (15b)

Chromatographic purification (EtOAc–hexanes, 1:1).

Pale-yellow oil; $[\alpha]_D^{17}$ –1.9 (*c* 0.85, acetone).

IR (NaCl): 3421, 1285, 1127 cm^{-1}.

^1H NMR (acetone-d_6): δ = 8.11 (br, 1 H), 7.07 (d, *J* = 8.1 Hz, 2 H), 6.76 (d, *J* = 8.1 Hz, 2 H), 5.94 (d, *J* = 8.2 Hz, 1 H), 3.54–3.39 (m, 1 H), 2.92 (s, 3 H), 2.75–2.55 (m, 2 H), 1.88–1.68 (m, 2 H), 1.28 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (acetone-d_6): δ = 155.4, 132.6, 129.2, 115.0, 49.5, 40.6, 39.7, 31.2, 21.7.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{17}NO_3SNa$: 266.0827; found: 266.0821.

(*R*)-*N*-[1-(4-Hydroxyphenyl)-4-phenylbut-3-yl]methanesulfonamide (15c)

Chromatographic purification (EtOAc–hexanes, 1:2).

Pale-yellow oil; $[\alpha]_D^{18}$ –6.1 (*c* 0.96, acetone).

IR (NaCl): 3313, 1297, 1137 cm^{-1}.

^1H NMR (acetone-d_6): δ = 8.13 (br, 1 H), 7.38–7.17 (m, 5 H), 7.03 (d, *J* = 8.3 Hz, 2 H), 6.74 (d, *J* = 8.3 Hz, 2 H), 6.10 (d, *J* = 8.9 Hz, 1 H), 3.71–3.55 (m, 1 H), 2.99–2.54 (m, 4 H), 2.45 (s, 3 H), 1.93–1.68 (m, 2 H).

^{13}C NMR (acetone-d_6): δ = 155.4, 139.1, 132.6, 129.7, 129.1, 128.3, 126.3, 115.1, 56.0, 41.9, 40.2, 37.9, 31.0.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{17}H_{21}NO_3SNa$: 342.1140; found: 342.1138.

(*R*)-*N*-[5-(4-Hydroxyphenyl)-1-(methylthio)but-3-yl]methanesulfonamide (15d)

^{1}H NMR ($CDCl_3$): δ = 7.02 (d, *J* = 7.9 Hz, 2 H), 6.76 (d, *J* = 7.9 Hz, 2 H), 3.58–3.50 (m, 1 H), 2.97 (s, 3 H), 2.64–2.57 (m, 4 H), 2.11 (s, 3 H), 1.93–1.74 (m, 4 H).

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