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Synthesis of Nitrogen Heterocycles by Rhodium-Catalyzed Hydroformylation of Polymer-Attached Amino Alkenes with Syngas

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Rhodium(I) phosphite catalyzed hydroaminomethylation of resin-tethered amino alkenes with H_2/CO gives moderate to good yields of five-, eight-, ten-, and thirteen-membered heterocycles. Competing hydrogenation, dimerization, or polymerization reactions were not observed using this methodology.

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Introduction

Tandem reaction sequences are becoming increasingly more important in organic synthesis and are readily achieved through the use of metal-catalyzed reactions of difunctional molecules. We recently reported a highly enantioselective route to five- and six-membered cyclic α-amino acids by a one-pot, single-catalyst, tandem hydrogenation–hydroformylation cyclization sequence.[1] However, the formation of larger sized heterocycles by this approach can be more challenging because of competing dimerization/polymerization processes. Recently, Doyle and coworkers employed rhodium–carbenoid cyclization to obtain high yields of medium and large rings, in addition to five- and six-membered ring compounds.[2] We have previously reported the synthesis of medium and large cyclic amines by rhodium-catalyzed hydroformylation–reductive amination of amino alkenes.[3] In this tandem reaction sequence, the initially formed aldehyde reacts with the tethered amine to form an intermediate imine; this is then hydrogenated in the presence of the rhodium catalyst to give a saturated amine. This process, termed hydroaminomethylation, has recently been extensively reviewed.[4] Excellent yields of thirteen-membered ring compounds were obtained by rhodium(I)-BIPHEPHOS catalyzed reactions of *N*-benzylundec-10-enamine. Conversely, hydroaminomethylation of other amino alkenes of varying chain length gave only modest yields of cyclized product because of competing reactions such as polymerization, dimerization, and initial hydrogenation rather than hydroformylation of the alkene.[3]

To overcome the formation of dimers and polymers, we re-investigated the domino reaction sequence using resin-supported amino alkenes. Solid-phase hydroformylation of a tethered alkene was first reported by Takahashi et al. in the partial synthesis of muscone.[5] More recently, intermolecular hydroaminomethylation reactions of resin-tethered alkenes with in situ amines have afforded saturated amines in good to excellent yields.[6] One intramolecular hydroaminomethylation has also been reported. The rhodium-catalyzed reaction of an unsaturated amine tethered by a Wang linker to a PS-DVB (polystyrene divinylbenzene) resin with H_2/CO gave a thirteen-membered cyclic amine in excellent yield. It should be noted that high yields were only obtained when the reactions were stirred, and this necessitated the use of a specially modified glass vial to prevent destruction of the polymer beads.

We wish to report the preparation of additional nitrogen heterocycles with ring sizes that range from small to large by a similar intramolecular hydroaminomethylation sequence. The use of a Wang 4-(hydroxymethyl)phenoxymethyl polystyrene resin has allowed us to carry out the reaction sequence without the need for stirring. Good to excellent yields of the resultant cyclic amines were obtained.

Results and Discussion

Hydroxymethyl Wang resin **1** was reacted with *p*-carboxybenzaldehyde **2** to give the aldehyde-functionalized resin **3** (Scheme 1). The resin was reacted with unsaturated amines **4a–4d** and the resultant imines were subsequently reduced with sodium cyanoborohydride to give the solid-phase amino alkenes **5**. Rhodium(I)-BIPHEPHOS[7] catalyzed hydroformylation of these alkenes with H_2/CO gave the polymer-attached heterocycles **6**. The heterocycles were cleaved from the resin by treatment with 95% TFA (trifluoroacetic acid), and isolated as their methyl ester derivatives **7** by reaction with diazomethane.

The yields of cyclic amines **7a–7d** are given in Table 1. Modest yields of amines **7b–7d**, and an excellent yield of **7a** were obtained. Products as a result of branch-chain aldehydes were not detected. The high regioselectivity observed is in keeping with the catalyst's preference for terminal

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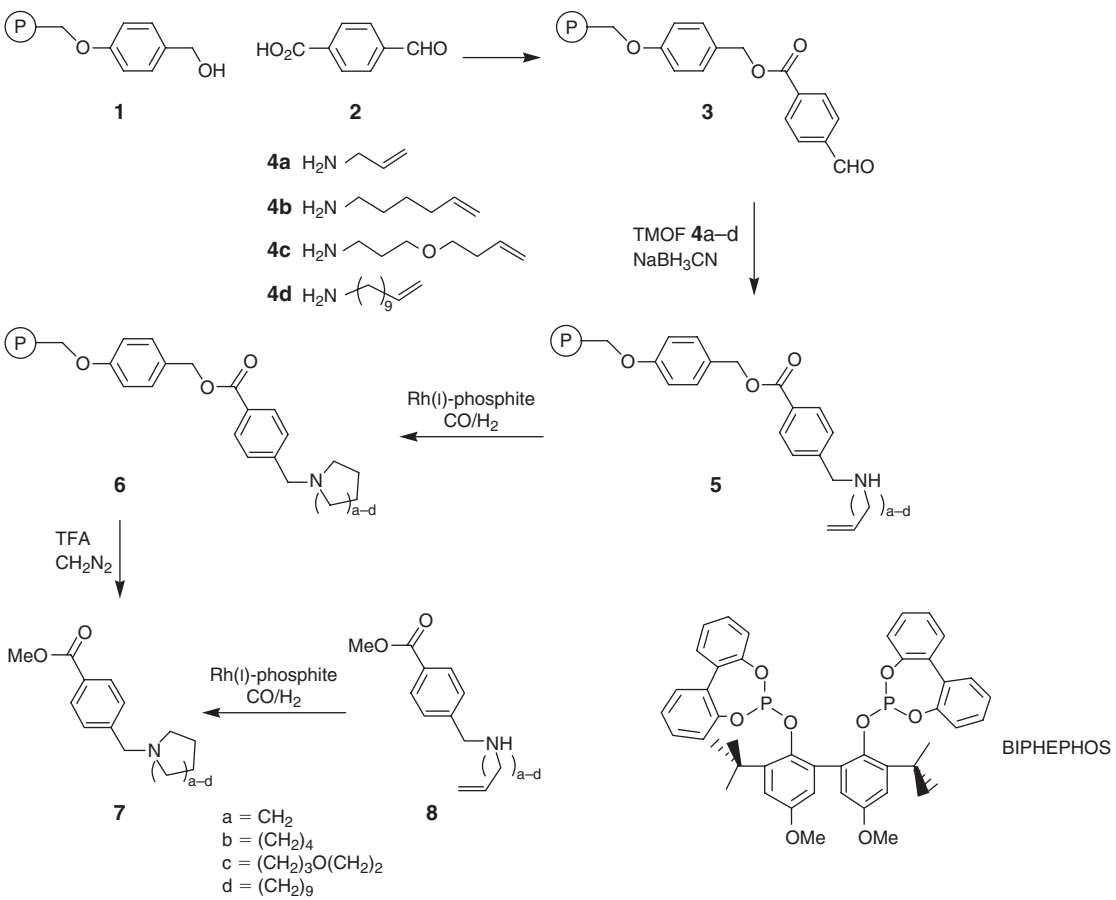

Scheme 1.

Table 1. Yields of cyclic amines[A]

Amine no.	Ring size	Isolated yields [%]	
		Resin-attached **5**	Solution of **8**
7a	5	91	25[B]
7b	8	56	44
7c	10	61	49[B]
7d	13	50	14[B]

[A] Hydroaminomethylation reactions on resin-attached amines **5** and free amines **8** were performed at 80°C for 18 h with an initial gas pressure (H_2 and CO, 1 : 1) of 2.76 MPa (400 psi) in the presence of $[Rh(OAc)_2]_2$ and BIPHEPHOS. Molar ratio of substrate to $[Rh(OAc)_2]_2$ to BIPHEPHOS was 100 : 1 : 2 for reactions that employed amines **7a**, **7b**, and **7d**. A molar ratio of 50 : 1 : 2 was used in the reaction with amine **7c**.
[B] Polymer was also obtained.

hydroformylation in the presence of the bulky phosphite ligand.[7]

Products as a result of competing hydrogenation rather than hydroformylation of the C=C double bond were not isolated, except for the reaction in which resin-tethered **5c** was involved in a 100 : 1 : 2 ratio of alkene/rhodium(I)/ligand. A higher catalyst loading was found to completely eliminate this side reaction. In all other cases only a single product was obtained; this suggests that the modest yields may arise because of insufficient cleavage from the resin or incomplete product isolation.

For the purpose of comparing solid- and solution-phase intramolecular hydroaminomethylation reactions, amines **4** were also converted into their *N*-(4-methoxycarbonyl)benzyl derivatives **8**. These amino alkenes were then subjected to the same reaction conditions used in the resin-supported examples. In every case more complex product mixtures were isolated, while in the three reactions that involved **8a**, **8c**, and **8d**, polymeric material was isolated. Surprisingly, hydroaminomethylation of the 4-methoxycarbonyl derivative of *N*-benzylundecenylamine gave only a low yield of cyclic product (14%), even though in previous solution-phase hydroaminomethylation investigations the related *N*-benzylundecenylamine afforded thirteen-membered *N*-benzylazacyclotridecane in excellent yield (85%).[3]

Conclusion

Cyclic amines of varying ring size can be prepared in moderate to excellent yields by rhodium-catalyzed hydroaminomethylation of unsaturated amines tethered to a Wang resin. Analogous reactions of untethered amines in solution gave more complex product mixtures, and in three cases polymers were formed. It is proposed that the modest isolated yields obtained from reactions performed on the solid phase may be due to difficulties experienced during cleavage from the resin and/or product isolation.

Experimental

Syntheses

Melting points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded using Bruker AM-300 and DRX-400 spectrometers for solutions in $CDCl_3$ unless otherwise stated. Mass spectra (ESI^+) were measured on a Bruker BioApex 47 e$^-$ FTMS (Fourier-transform mass spectrometer) with a 4.7 Tesla magnet and an Analytica electrospray source. Mass spectra (EI) were recorded on a VG TRIO-1 Quadrupole Mass Spectrometer at 70 eV with a source temperature of 200°C. Microanalyses were performed by Chemical and Microanalytical Services Pty Ltd, Melbourne. Merck Silica Gel 60 (230–400 mesh, no. 9385) was used for flash chromatography. Wang resin was used as supplied by Nova Biochem.

*Synthesis of Hex-5-enamine **4b***

A solution of hexen-5-ol (3.60 mL, 30.0 mmol) and diisopropyl azodicarboxylate (5.90 mL, 30.0 mmol) in distilled THF (20 mL) was added in a dropwise fashion to a stirred and cooled (0°C) suspension of phthalimide (4.41 g, 30.0 mmol) and triphenylphosphine (7.85 g, 30.0 mmol) in freshly distilled THF (40 mL) under an inert atmosphere. The resultant yellow solution was stirred at ambient temperature for 18 h and the solvent was then removed under reduced pressure to give a yellow oil. The oil was redissolved in methanol (50 mL) before hydrazine hydrate (1.50 mL, 35.9 mmol) was added. The mixture was heated at reflux for a further 8 h and allowed to stand overnight. Concentrated HCl (5 mL) was then added and the reaction mixture was refluxed for a further 2 h. After the mixture was cooled, the methanol was removed under reduced pressure. The resultant semi-solid was dissolved in water and extracted with dichloromethane (3 × 100 mL). The aqueous layer was concentrated to afford a white solid (3.90 g). ^{1}H NMR spectroscopy of this solid showed that it was the required hex-5-enamine hydrochloride salt. The white solid was then dissolved in the minimum amount of water, and NaOH pellets were added. The desired product **4b** was removed by pipette as a clear oil (2.75 g, 93%). ν_{max} (neat)/cm^{-1} 3377s(br), 2922s, 2856s, 1655s, 1033s, 1572m, 1501m, 1500w, 1461s, 1439s, 905s. δ_H (300 MHz) 5.91–5.78 (1H, m, H5), 4.99–4.91 (2H, m, H6), 2.69 (2H, t, *J* 6.6, H1), 2.07 (2H, q, *J* 7.0, H4), 1.48–1.41 (6H, m, H2, H3, 2 × NH). δ_C (100 MHz) 139.0 (H5), 114.7 (H6), 42.3 (H1), 33.8 and 33.4 (H2 and H4), 26.4 (H3). *m*/*z* (ESI, MeOH) 99.8 ($[M+H]^+$). Spectroscopic data were consistent with the literature.[8]

*Synthesis of 3-(But-3-en-1-yloxy)propan-1-amine **4c***

3-(But-3-en-1-yloxy)propane nitrile was synthesized by treating buten-3-ol (6.00 mL, 69.3 mmol) in acrylonitrile (5.50 mL, 83.16 mmol) with Triton B (40% in MeOH, 1.2 mL) according to literature procedure.[9] The 3-(but-3-en-1-yloxy)propane nitrile was isolated as a clear oil (4.85 g, 56%), bp 110°C/18 mmHg (lit.[9] 105–107°C/18 mmHg). The propane nitrile was then reduced with $LiAlH_4$ to give 3-(but-3-en-1-yloxy)propan-1-amine **4c** as a clear oil (4.85 g, 97%). ν_{max} (neat)/cm^{-1} 3365s, 3297s, 3077s, 2864s, 1641m, 1600m, 1467w, 1432s, 1368m, 1227w, 1112s, 995m, 913s. δ_H (300 MHz) 5.81 (1H, ddt, *J* 17.0, 10.2, 6.7, H3′), 5.13–4.98 (2H, m, H4′), 3.50 (2H, t, *J* 6.2, H3), 3.46 (2H, t, *J* 6.7, H1′), 2.78 (2H, t, *J* 6.7, H1), 2.32 (2H, qt, *J* 6.6, 1.3, H2′), 1.95 (2H, br s, 2 × NH), 1.70 (2H, quintet, *J* 6.3, H2). δ_C (100 Hz) 134.7 (C3′), 115.6 (C4′), 69.6 (C1′), 68.4 (C3), 39.1 (C1), 33.6 (C2′), 32.8 (C2). *m*/*z* (ESI, MeOH) 129.7 ($[M+H]^+$). Spectroscopic data were consistent with the literature.[10]

*Synthesis of Undec-10-enamine **4d***

Undec-10-enoyl chloride was treated with gaseous ammonia according to literature procedure[11] to give undec-10-enamide as a cream solid (5.50 g, 98%), mp 85–86°C (lit.[11] 88.5–89°C). ν_{max} (KBr)/cm^{-1} 3358s, 3078s, 2922s, 2855s, 1800s, 1638s, 1455s, 1411s, 1338w, 1127m, 989s, 961s, 911s, 722s. δ_H (300 MHz) 5.88–5.72 (2H, m, H10), 5.04–4.88 (2H, m, H11), 2.88 (2H, t, *J* 7.3, H2), 2.03 (2H, q, *J* 6.3, H9), 1.78–1.62 (2H, m, H3), 1.44–1.22 (12H, m, H4, H5, H6, H7, and H8). δ_C (100 MHz) 174.1 (C1), 139.3 (C10), 114.5 (C11), 47.3 (C2), 33.9 (C9), 29.4, 29.2, 29.1, 28.6, and 25.3 (C3, C4, C5, C6, C7, and C8). *m*/*z* (ESI, MeOH) 183.9 ($[M+H]^+$). Spectroscopic data were consistent with the literature.[11]

Undec-10-enamide (5.50 g, 30.1 mmol) was reduced with $LiAlH_4$ (2.31 g, 72.1 mmol) according to literature procedure[11] to give undec-10-enamine **4d** as a clear oil (3.00 g, 58%). ν_{max} (neat)/cm^{-1} 3334s(br), 2924s, 2853s, 1641w, 1571s, 1487s, 1466s, 1319m, 992w, 910m. δ_H (300 MHz) 5.81 (1H, ddt, *J* 16.9, 10.1, 6.6, H10), 5.04–4.89 (2H, m, H11), 2.67 (2H, t, *J* 6.8, H1), 2.08–1.98 (2H, m, H9), 1.46–1.24 (16H, m, H2, H3, H4, H5, H6, H7, H8, and 2 × NH). δ_C (100 MHz) 139.0 (C10), 114.0 (C11), 42.2 (C1), 33.7 and 33.8 (C2 and C9), 29.5, 29.4, 29.3, 29.0, 28.8, and 26.8 (C3, C4, C5, C6, C7, and C8). *m*/*z* (ESI, MeOH) 170.1 ($[M+H]^+$). Spectroscopic data were consistent with the literature.[11]

*Synthesis of Methyl 4-[(Allylamino)methyl]benzoate **8a***

Prop-2-enamine (0.24 mL, 3.33 mmol) was added to a stirred solution of *p*-carboxybenzaldehyde (500 mg, 3.33 mmol) in ethanol (20 mL). The mixture was refluxed for 2 h before sodium cyanoborohydride ($NaCNBH_3$) (251 mg, 4.00 mmol) was added. The mixture was then heated at reflux for a further 1 h. The mixture was concentrated under reduced pressure to afford a white solid. Concentrated H_2SO_4 (5 mL) followed by methanol (20 mL) were added to the white solid, and the resultant mixture was stirred for 18 h at room temperature. Upon removal of methanol under reduced pressure, the reaction mixture was basified with NaOH (4 M) and then extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated to afford a yellow oil. The crude product was purified by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 1) to afford the desired product **8a** (283 mg, 42%) as a yellow oil (Found: $[M+H]^+$ 206.1178. $C_{12}H_{15}NO_2$ requires 206.1181). ν_{max} (neat)/cm^{-1} 3450s(br), 3077m, 3000m, 2944m, 2811m, 1717s, 1611s, 1433s, 1377m, 1278s, 1183m, 1111s, 1016m, 922m, 856w, 756s. δ_H (300 MHz) 8.00 (2H, d, *J* 8.4, H2 and H6), 7.41 (2H, d, *J* 8.1, H3 and H5), 5.93 (1H, ddt, *J* 17.2, 10.3, 6.0, H2′), 5.25–5.10 (2H, m, H3′), 3.91 (3H, s, OCH_3), 3.85 (2H, s, CH_2Ph), 3.28 (2H, dt, *J* 6.0, 1.6, H1′). δ_C (100 MHz) 167.1 (CO), 144.6 (C2′), 135.7 (C4), 130.0 (C2 and C6), 129.3 (C1), 128.5 (C3 and C5), 117.4 (C3′), 52.5 (*C*H_2Ph), 52.3 (OCH_3), 51.5 (C1). *m*/*z* (ESI, MeOH) 206.1 ($[M+H]^+$).

*Synthesis of Methyl 4-[(Undec-10-enylamino)methyl]benzoate **8d***

The reaction was performed as described for the synthesis of methyl 4-[(allylamino)methyl]benzoate **8a**, but undec-10-enamine **4d** (563 mg, 3.33 mmol) was used as the starting material. After workup of the reaction mixture, a yellow oil was isolated and purified by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 1) to afford the desired product **8d** (390 mg, 33%) as a yellow oil. (Found: $[M+H]^+$ 318.2433. $C_{20}H_{31}NO_2$ requires 318.2433). ν_{max} (neat)/cm^{-1} 3450s(br), 3078s, 2922s, 2856s, 1717s, 1638s, 1611s, 1572m, 1455s, 1433s, 1411s, 1278s, 1178s, 1107s, 1010s, 905s, 856s, 755s. δ_H (300 MHz) 7.99 (2H, d, *J* 8.4, H2 and H6), 7.39 (2H, d, *J* 8.4, H3 and H5), 5.80 (1H, ddt, *J* 17.0, 10.3, 6.7, H10′), 5.04–4.89 (2H, m, H11′), 3.90 (3H, s, OCH_3), 3.84 (2H, s, CH_2Ph), 2.61 (2H, t, *J* 7.2, H1′), 2.03 (2H, q, *J* 6.7, H9′), 1.55–1.21 (14H, m, H2′, H3′, H4′, H5′, H6′, H7′, and H8′). δ_C (100 MHz) 167.2 (CO), 146.2 (C4), 139.4 (C10′), 129.9 (C2 and C6), 128.9 (C1), 128.1 (C3 and C5), 114.3 (C11′), 53.9 (*C*H_2Ph), 52.2 (OCH_3), 49.7 (C1′), 34.0 (C9′), 30.3, 29.7, 29.6, 29.3, 29.1, and 27.5 (C2′, C3′, C4′, C5′, C6′, C7′, and C8′). *m*/*z* (ESI, MeOH) 318.3 ($[M+H]^+$).

Synthesis of Methyl 4-Formylbenzoate

Methyl 4-formylbenzoate was synthesized according to literature procedure using thionyl chloride (6 mL) and *p*-carboxybenzaldehyde (5.00 g, 33.3 mmol).[12] Methyl 4-formylbenzoate was isolated as an orange-yellow solid (4.82 g, 88%), mp 60–62°C (lit.[12] 61–63°C). ν_{max} (KBr)/cm^{-1} 3022w, 2989m, 2977w, 1727s, 1685s, 1577s, 1503s, 1435m, 1392m, 1288s, 1204s, 1108s, 1013m, 958m, 852s, 810m, 757s, 687s. δ_H (300 MHz, $(CD_3)_2SO$) 10.11 (1H, s, CHO), 8.16 (2H, d, *J* 8.5,

H2 and H6), 8.05 (2H, d, *J* 8.4, H3 and H5), 3.90 (3H, s, OCH_3). δ_C (100 MHz, $(CD_3)_2SO$) 193.0 (CHO), 165.5 ($COOCH_3$), 139.1 (C1), 134.3 (C4), 129.8 and 129.7 (C2, C3, C5, and C6), 52.6 (OCH_3).

Synthesis of Methyl 4-[(Hex-5-enylamino)methyl]benzoate ***8b***

Hex-5-enamine **4b** (302 mg, 3.05 mmol) was added to a stirred solution of methyl 4-formylbenzoate (500 mg, 3.05 mmol) in ethanol (20 mL). The mixture was refluxed for 2 h before sodium cyanoborohydride ($NaCNBH_3$) (220 mg, 6.10 mmol) was added. The mixture was then heated at reflux for a further 1 h, concentrated under reduced pressure, and quenched with HCl (100 mL, 1 M). Once H_2 gas evolution had ceased, the reaction mixture was basified with NaOH (4 M) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and evaporated to afford the desired product **8b** (602 mg, 80%) as an orange oil (Found: $[M+H]^+$ 248.1642. $C_{15}H_{21}NO_2$ requires 248.1650). ν_{max} (neat)/cm^{-1} 3333s(br), 3066m, 2911s, 2855s, 1716s, 1638s, 1611s, 1577m, 1433s, 1416s, 1277s, 1172s, 989s, 911s, 727s. δ_H (300 MHz) 7.99 (2H, d, *J* 8.4, H2 and H6), 7.39 (2H, d, *J* 8.4, H3 and H5), 5.80 (1H, m, H5′), 5.04–4.90 (2H, m, H6′), 3.91 (3H, s, OCH_3), 3.84 (2H, s CH_2Ph), 2.62 (2H, t, *J* 7.1, H1′), 2.05 (2H, q, *J* 7.0, H4′), 1.58–1.36 (4H, m, H2′ and H3′). δ_C (100 MHz) 167.2 (CO), 146.2 (C4), 138.9 (C5′), 128.9 (C1), 129.9 and 128.1 (C2, C3, C5, and C6), 114.7 (C6′), 53.9 (CH_2Ph), 52.2 (OCH_3), 49.5 (C1′), 33.8 (C4′), 29.7 and 26.7 (C2′ and C3′). *m*/*z* (ESI, MeOH) 248.0 ($[M+H]^+$).

Synthesis of Methyl 4-{[(3-(But-3-en-1-yloxy)propyl)amino]methyl}-benzoate ***8c***

This reaction was carried out as described for methyl 4-[(hex-5-enylamino)methyl]benzoate **8b**, but 3-(but-3-en-1-yloxy)propan-1-amine **4c** (390 mg, 3.05 mmol) was used as the starting material. After workup of the reaction mixture, an orange oil (602 mg) was isolated. Subsequent purification of the crude product by column chromatography afforded the desired product **8c** as an orange oil (278 mg, 35%). (Found: $[M+H]^{+\bullet}$ 278.1751. $C_{16}H_{23}NO_3$ requires $[M+H]^{+\bullet}$ 278.1756). ν_{max} (neat)/cm^{-1} 3333sb, 3077m, 2944s, 2855sm 1727s, 1716s, 1644w, 1611s, 1433s, 1278s, 1106s, 1022m, 917s. δ_H (300 MHz) 7.99 (2H, d, *J* 8.4, H2 and H6), 7.40 (2H, d, *J* 8.5, H3 and H5), 5.80 (1H, m, H3″), 5.12–4.97 (2H, m, H4″), 3.91 (3H, s, OCH_3), 3.85 (2H, s, CH_2Ph), 3.51 (2H, t, *J* 6.8, H1″ or H3′), 3.46 (2H, t, *J* 6.8, H1″ or H3′), 2.73 (2H, t, *J* 6.8, H1′), 2.49 (1H, s, NH), 2.31 (2H, qt, *J* 6.7, 1.3, H2″), 1.80 (2H, quintet, *J* 6.4, H2′). δ_C (100 MHz) 167.2 (CO), 145.7 (C4), 135.4 (C3″), 128.9 (C1), 129.9 and 128.1 (C2, C3, C5, and C6), 116.6 (C4″), 70.3 and 69.7 (C3′ and C1″), 53.7 (CH_2Ph), 52.2 (OCH_3), 47.2 (C1′), 34.3 and 29.9 (C2′ and C2″). *m*/*z* (ESI, MeOH) 278.1 ($[M+H]^+$).

General Conditions for Reactions with H_2/CO

Reactions were carried out in a 100 mL Parr autoclave with a glass sleeve that contained a stirrer bead. The substrate (0.1–0.3 g, approximately 1 mmol), rhodium catalyst precursor ($[Rh(OAc)_2]_2$), and ligand (BIPHEPHOS)[7] (in a ratio of 100 : 1 : 2) were placed in the autoclave under an atmosphere of nitrogen, and deoxygenated benzene (10 mL) was then added to the autoclave.

The vessel was flushed and evacuated three times with 200 psi (1.38 Mpa) H_2/CO (1 : 1 molar mixture), and was then pressurized to 400 psi (2.76 MPa). The reaction mixtures were kept at 80°C for 20 h before the autoclave was cooled, the gases released, and the contents analyzed as reported.

Synthesis of Methyl 4-[(Pyrrolidin-1-yl)methyl]benzoate ***7a***

Method A

Wang resin (500 mg, 0.45 mmol) was pre-swollen in DMF (3 × 10 mL), and a solution of 4,4′-dimethylaminopyridine (DMAP; 27 mg, 0.23 mmol) in DMF (1 mL) was then added to the resin. In a separate vial, *p*-carboxybenzaldehyde **2** (338 mg, 0.25 mmol) was dissolved in DMF (1 mL), and was then added to a solution of DMAP (54 mg, 0.45 mmol) and 1,3-diisopropylcarbodiimide (0.35 mL, 2.25 mmol) in DMF (1 mL). This mixture was then added to the swollen resin, and was shaken overnight. The resultant orange suspension was filtered and the resin was washed with DMF (5 × 10 mL). The resin was then dried for 1.5 h before trimethyl orthoformate (TMOF; 2 mL) and prop-3-enamine **4a** (0.27 mL, 3.60 mmol) were added. The mixture was then agitated for a further 18 h. Acetic acid (0.2 mL) in methanol (0.5 mL) followed by $NaCNBH_3$ (680 mg) in THF (2 mL) were added to the resin mixture. This was left to stand for 30 min and was then manually shaken for a further 30 min. The resin mixture was subjected to the general hydroformylation conditions for 18 h using BIPHEPHOS (7.2 mg, 8.00×10^{-3} mmol) and rhodium(II) acetate dimer (2.0 mg, 0.45×10^{-2} mmol). The vessel pressure was released before the resin was filtered off and washed with benzene. After the resin was dried for 1 h, the resin-tethered amine was cleaved with TFA (10 mL, 95%). The filtrate was evaporated (using N_2) to afford an orange oil (250 mg), which was found to be the TFA salt of 4-[(pyrrolidin-1-yl)methyl]benzoic acid (Found: $[M+H]^+$ 206.1178. $C_{12}H_{15}NO_2$ requires 206.1181). δ_H (300 MHz, D_2O) 8.06 (2H, d, *J* 8.0, H2 and H6), 7.55 (2H, d, *J* 8.0, H3 and H5), 4.40 (2H, s, CH_2Ph), 3.49 (2H, m, H2′ or H5′), 3.15 (2H, m, H2′ or H5′), 2.14 (2H, m, H3′ or H4′), 1.93 (2H, m, H3′ or H4′). *m*/*z* (ESI, MeOH) 206.0 ($[(M+H) - CF_3COOH]^+$). ^{1}H NMR spectroscopic data for the title acid were consistent with the literature.[13]

Excess (trimethylsilyl)diazomethane was added dropwise to a solution of the above crude acid in methanol (10 mL), and the reaction mixture was stirred for 18 h before the methanol was evaporated. The residue was basified with saturated aqueous $NaHCO_3$ and was then extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated to afford an orange oil (112 mg). The orange oil was purified by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 3) to afford the desired product **7a** (90 mg, 91%) as a yellow oil (Found: $[M+H]^+$ 220.1340. $C_{13}H_{17}NO_2$ requires 220.1334). δ_H (300 MHz) 7.99 (2H, d, *J* 8.2, H2 and H6), 7.42 (2H, d, *J* 8.1, H3 and H5), 3.91 (3H, s, OCH_3), 3.70 (2H, s, CH_2Ph), 2.62–2.54 (4H, m, H2′ and H5′), 1.86–1.78 (4H, m, H3′ and H4′). δ_C (100 MHz) 167.2 (CO), 145.6 (C4), 129.9 (C2 and C6), 129.4 (C1), 129.2 (C3 and C5), 60.3 (CH_2Ph), 54.3 (C2′and C5′), 52.3 (OCH_3), 23.6 (C3′ and C4′). *m*/*z* (ESI, MeOH) 220.3 ($[M+H]^+$). Spectroscopic data were consistent with the literature.[14]

Method B

Methyl 4-[(allylamino)methyl]benzoate **8a** (150 mg, 0.73 mmol) was hydroformylated in the presence of BIPHEPHOS (3.2 mg) and rhodium(II) acetate dimer (11.5 mg) according to the general conditions outlined above. After 18 h, the vessel pressure was released to reveal that the glass sleeve was lined with insoluble polymeric material. The remaining solution was concentrated to afford a brown oil (70 mg). Purification by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 1) afforded the desired product **7a** (40 mg, 25%) as a yellow oil. Spectroscopic data were consistent with those described for **7a** obtained by method A.

Synthesis of Methyl 4-[(Azacyclooctan-1-yl)methyl]benzoate ***7b***

Method A

This reaction was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate **7a**, but hex-5-enamine **4b** (356 mg, 3.60 mmol) was used as the starting material. Subsequent TFA (6 mL, 95%) cleavage of the amine from the resin afforded the TFA salt of 4-[(azacyclooctan-1-yl)methyl]benzoic acid (157 mg)[15] as a clear oil (Found: $[(M+H) - CF_3COOH]^+$ 248.1648. $C_{15}H_{21}NO_2$ requires 248.1650. *m*/*z* (ESI, MeOH) 248.3 ($[(M+H) - CF_3COOH]^+$).

Esterification was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate **7a** to afford an orange oil (95 mg). Purification of the crude product by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 1) afforded the title methyl ester **7b** (66 mg, 56%) as a yellow oil (Found: $[M+H]^+$ 262.1803. $C_{16}H_{23}NO_2$ requires 262.1807). ν_{max} (neat)/cm^{-1} 2911s, 2856s, 2789s, 1722s, 1611s, 1572m, 1433s, 1411m, 1350m, 1278s, 1105s, 1017s, 967s, 850m, 756s. δ_H (300 MHz) 7.98 (2H, d, *J* 8.4, H2 and H6), 7.44 (2H, d, *J* 8.1, H3 and H5), 3.91 (3H, s, OCH_3), 3.64 (2H, s, CH_2Ph), 2.54 (4H, t, *J* 5.8, H2′ and

H8′), 1.72–1.46 (10H, m, H3′, H4′, H5′, H6′, and H7′). δ_C (100 MHz) 167.4 (CO), 147.2 (C4), 129.7 (C2 and C6), 129.1 (C3 and C5), 128.9 (C1), 63.6 (*C*H$_2$Ph), 54.6 (C2′ and C8′), 52.2 (OCH$_3$), 28.0 and 26.3 (C3′, C4′, C5′, C6′ and C7′). *m*/*z* (ESI, MeOH) 262.4 ([M + H]$^+$).

Method B

Methyl 4-[(hex-5-enylamino)methyl]benzoate **8b** (176 mg, 0.71 mmol) was hydroformylated in the presence of BIPHEPHOS (3.1 mg) and rhodium(II) acetate dimer (11.2 mg) according to the general conditions outlined above. After 18 h, the vessel pressure was released and the reaction solvent was concentrated to afford a brown oil (111 mg). Purification of the crude product by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 1) afforded the desired product **7b** (82 mg, 44%) as a yellow oil. Spectroscopic data were consistent with those described for **7b** obtained by method A.

Synthesis of Methyl 4-(1,5-Oxazanan-5-ylmethyl)benzoate ***7c***

Method A

The reaction was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate **7a**, but 3-(but-3-en-1-yloxy) propan-1-amine **4c** (461 mg, 3.60 mmol) was used as the starting material. Subsequent TFA (6 mL, 95%) cleavage of the amine from the resin afforded 4-{[(3-(butan-1-yloxy)propyl)amino]methyl}benzoic acid (196 mg) as a clear oil and only trace amounts of the title benzoate **7c**. Esterification of the crude reaction by-product was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate **7a** to afford methyl 4-{[(3-(butan-1-yloxy)propyl)amino]methyl}benzoate (87 mg, 70%) (Found: [M + H]$^+$ 280.1908. $C_{16}H_{25}NO_3$ requires 280.1913). ν_{max} (neat)/cm^{-1} 3322s(br), 2944s, 2856s, 1722s, 1611s, 1455s, 1433s, 1367m, 1277s, 1183m, 1111s, 1017s, 967m, 750s. δ_H (300 MHz) 7.97 (2H, d, *J* 8.4, H2 and H6), 7.38 (2H, d, *J* 8.5, H3 and H5), 3.90 (3H, s, OCH$_3$), 3.83 (2H, s, C*H*$_2$Ph), 3.47 (2H, t, *J* 6.2, H3′ or H1″), 3.38 (2H, t, *J* 6.6, H3′ or H1″), 2.71 (2H, t, *J* 6.8, H1′), 1.77 (2H, quintet, *J* 6.5, H2′), 1.52 (2H, quintet, *J* 7.0, H2″), 1.32 (2H, sextet, *J* 7.4, H3″), 0.89 (3H, t, *J* 7.4, H4″). δ_C (100 MHz) 167.3 (CO), 146.2 (C4), 129.9 (C2 and C6), 128.9 (C1), 128.1 (C3 and C5), 71.0 and 69.7 (*C*H$_2$Ph and C1′), 53.9 (C3′), 52.2 (OCH$_3$), 47.3 (C1″), 32.0 and 30.2 (C2′ and C2″), 19.6 (C3″), 14.1 (C4″). *m*/*z* (ESI, MeOH) 280.2 ([M + H]$^+$).

Method B

The hydroformylation reaction was performed as described in method A, but with a higher catalyst loading [BIPHEPHOS (14.4 mg, 16×10^{-3} mmol) and rhodium(II) acetate (4.0 mg, 9.0×10^{-3} mmol)]. Subsequent TFA (6 mL, 95%) cleavage of the amine from the resin afforded 4-(1,5-oxazanan-5-ylmethyl)benzoic acid (286 mg) as a clear oil. Esterification was carried out in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate **7a** to afford an orange oil (110 mg). Purification of the crude product by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 1) afforded the title compound **7c** (80 mg, 61%) as a yellow oil (Found: C 70.0, H 8.7, N 4.8, [M + H]$^+$ 292.1902. $C_{17}H_{25}NO_3$ requires C 70.0, H 8.7, N 4.8%, [M + H]$^+$ 292.1913). ν_{max} (neat)/cm^{-1} 3000s(br), 2922s, 2844s, 1722s, 1605s, 1600w, 1427s, 1272s, 1106s, 1022s, 944m, 855m, 761s. δ_H (300 MHz) 7.99 (2H, d, *J* 8.3, H2 and H6), 7.42 (2H, d, *J* 8.1, H3 and H5), 3.91 (3H, s, OCH$_3$), 3.65 (4H, t, *J* 5.3, H4′ and H6′), 3.55 (2H, s, C*H*$_2$Ph), 2.53 (2H, t, *J* 6.1, H2′ or H10′), 2.39 (2H, t, *J* 5.3, H2′ or H10′), 1.74–1.45 (8H, m, H3′, H7′, H8′, and H9′). δ_C (100 MHz) 167.4 (CO), 146.1 (C4), 129.7 (C2 and C6), 129.4 (C3 and C5), 128.9 (C1), 72.8 (*C*H$_2$Ph), 66.6 and 61.1 (C4′ and C6′), 52.2 (OCH$_3$), 55.3 and 48.7 (C2′ and C10′), 27.3 and 26.2 (H3′, H7′, H8′, and H9′). *m*/*z* (ESI, MeOH) 292.1 ([M + H]$^+$).

Method C

Methyl 4-{[(3-(but-3-en-1-yloxy)propyl)amino]methyl}benzoate **8c** (193 mg, 0.70 mmol) was hydroformylated in the presence of BIPHEPHOS (6.2 mg) and rhodium(II) acetate dimer (21.9 mg) according to the general conditions outlined above. After 18 h, the vessel pressure was released and the reaction solvent was concentrated to afford a brown oil (183 mg). The crude product was purified by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 5) to give the desired product **7c** (100 mg, 49%) as a yellow oil. Spectroscopic data were consistent with those described for **7c** obtained by method B.

Synthesis of Methyl 4-[(Azacyclotridecan-1-yl)methyl]benzoate ***7d***

Method A

The reaction was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate **7a**, but undec-10-enamine **4d** (608 mg, 3.6 mmol) was used as the starting material. Subsequent TFA (6 mL, 95%) cleavage of the amine from the resin afforded the TFA salt of 4-[(azacyclotridecan-1-yl)methyl]benzoic acid (247 mg) as a clear oil (*m*/*z* 306.3 [M + H]$^+$). Esterification was carried out in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate **7a** to afford an orange oil (150 mg). The crude product was purified by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 5) to afford the title compound **7d** (74 mg, 50%) as a yellow solid, mp 98–102°C (Found: [M + H]$^+$ 332.2587. $C_{21}H_{33}NO_2$ requires 332.2589). ν_{max} (neat)/cm^{-1} 3411s(br), 2966m, 2911s, 2844s, 2777m, 1716s, 1611m, 1561s, 1461s, 1433s, 1272s, 1100s. δ_H (300 MHz) 7.97 (2H, d, *J* 8.2, H2 and H6), 7.40 (2H, d, *J* 8.1, H3 and H5), 3.90 (3H, s, OCH$_3$), 3.56 (2H, s, C*H*$_2$Ph), 2.42–2.28 (4H, m, H2′ and H13′), 1.50–1.18 (20H, m, H3′, H4′, H5′, H6′, H7′, H8′, H9′, H10′, H11′, and H12′). δ_C (100 MHz) 167.2 (CO), 138.9 (C4), 129.4 (C2 and C6), 129.1 (C1), 128.7 (C3 and C5), 59.2 (*C*H$_2$Ph), 55.8 and 53.8 (C2′ and C13′), 52.7 (OCH$_3$), 29.5, 29.3, 27.1, and 27.0 (C3′, C4′, C5′, C6′, C7′, C8′, C9′, C10′, C11′, and C12′). *m*/*z* (ESI, MeOH) 332.3 ([M + H]$^+$).

Method B

Methyl 4-[(undec-10-enylamino)methyl]benzoate **8d** (341 mg, 1.07 mmol) was hydroformylated in the presence of BIPHEPHOS (34 mg, 4.3×10^{-2} mmol) and rhodium(II) acetate dimer (9.5 mg, 2.15×10^{-2} mmol) according to the general procedure described above. After 18 h, the vessel pressure was released to reveal that the glass sleeve was lined with insoluble polymeric material. The remaining solution was concentrated to afford a brown oil (356 mg). The crude product was purified by column chromatography (SiO_2; ethyl acetate/hexane, 1 : 5) to afford the title compound **7d** (50 mg, 14%) as a yellow oil. Spectroscopic data were consistent with those described for **7d** obtained by method A.

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References

[1] E. Teoh, E. M. Campi, W. R. Jackson, A. J. Robinson, *Chem. Commun.* **2002**, 978. doi:10.1039/B200374K

[2] M. P. Doyle, A. V. Kalinin, D. G. Ene, *J. Am. Chem. Soc.* **1996**, *118*, 8837. doi:10.1021/JA961682M

[3] D. Bergmann, E. M. Campi, W. R. Jackson, A. F. Patti, D. Saylik, *Aust. J. Chem.* **2000**, *53*, 835. doi:10.1071/CH00112

[4] P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, et al., *Chem. Rev.* **1999**, *99*, 3329. doi:10.1021/CR970413R

[5] T. Takahashi, S. Ebata, D. Takayuki, *Tetrahedron Lett.* **1998**, *39*, 1369. doi:10.1016/S0040-4039(97)10847-4

[6] G. Dessole, M. Marchetti, M. Taddei, *J. Comb. Chem.* **2003**, *5*, 198. doi:10.1021/CC020055S

[7] G. D. Cuny, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 2066.
[8] M. R. Gagné, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992**, *114*, 275.
[9] B. Simonot, G. Rousseau, *Synth. Commun.* **1993**, *23*, 549.
[10] M. Dufour, J. C. Gramian, H. P. Husson, M. E. Sinibaldi, Y. Troin, *Tetrahedron Lett.* **1989**, *30*, 3429. doi:10.1016/S0040-4039(00)99263-3
[11] Y. Dobashi, S. Hara, *J. Org. Chem.* **1987**, *52*, 2490.
[12] S. K. Sharma, M. Tandon, J. W. Lown, *Eur. J. Org. Chem.* **2000**, *11*, 2095. doi:10.1002/1099-0690(200006)2000:11<2095::AID-EJOC2095>3.0.CO;2-J
[13] G. K. Jahangiri, J. Reymond, *J. Am. Chem. Soc.* **1994**, *116*, 11264.
[14] M. Bogenstaetter, C. Wenying, A. K. Kwok, *Int. Patent WO 0212224* **2002**.
[15] J. G. Lombardino, *U.S. Patent 4 623 486* **1986**.