Gold-catalyzed synthesis of enantioenriched furfurylamines from amino acids.

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Abstract

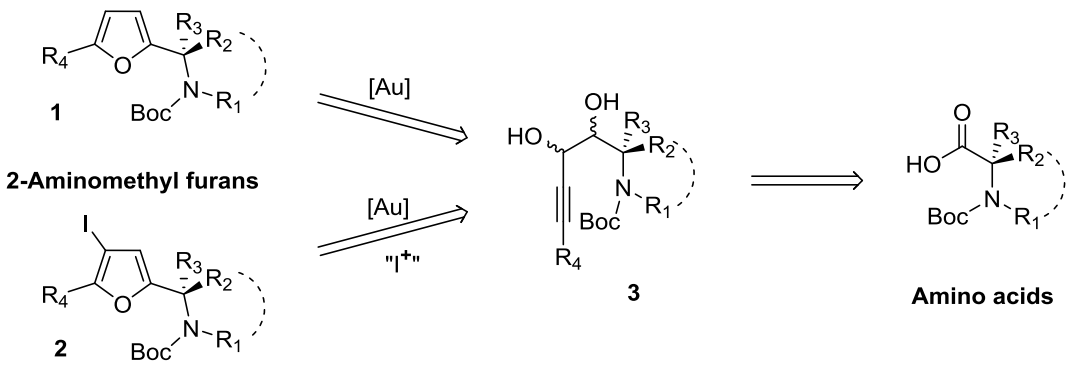
A convenient gold-catalyzed asymmetric synthesis of polysubstituted furfurylamines starting from amino acids has been achieved. The cyclization proceeded under mild conditions and generally provided the furan or iodofuran derivatives in good to excellent yields and high enantiomeric excess. Iodofurans were validated as good intermediates for classical organometallic coupling reactions.

1. Introduction

Polysubstituted furans are key structural units found in many natural products[1] and pharmaceuticals.[2] Thus, several methods for their synthesis have been developed in the past few years,[3] including transition-metal-mediated cyclizations and cycloisomerizations.[4]

Optically active 2-aminomethyl-furans have important applications as chiral ligands or organocatalysts,[5] and as building blocks for various biologically active molecules[6] and provide access to many nitrogen containing compounds such as piperidines or aza-sugars -by the aza-Achmanowicz rearrangement-[7] or amino acids by oxidative cleavage.[8] However, few stereoselective syntheses of chiral furfurylamines have been described and most of them involve the modification of substituted furans, such as the asymmetric aminohydroxylation of vinylfuran or the enantioselective reduction of furanyl ketones.[9] Thus, the search for efficient, convenient and highly stereoselective alternative synthetic routes is of great interest.

We have previously reported diverse gold-catalyzed approaches to nitrogen containing 5- or 6- membered heterocycles from amino acids.[10] We herein report an efficient synthetic route to some chiral di- and tri-substituted α–aminomethylfuran derivatives from α-aminoalkynyl-1,2-diols prepared from commercially available amino-acids. Our synthetic approach is outlined in scheme 1.



Scheme 1. Retrosynthetic strategy.

The structural diversity of commercially available enantiopure amino acids and the opportunity for late-stage diversification at intermediate diol **3** should allow rapid generation of enantioenriched 2-amino furan libraries by this strategy. One major advantage of gold catalyzed cyclization is minimal racemization under the very mild conditions.

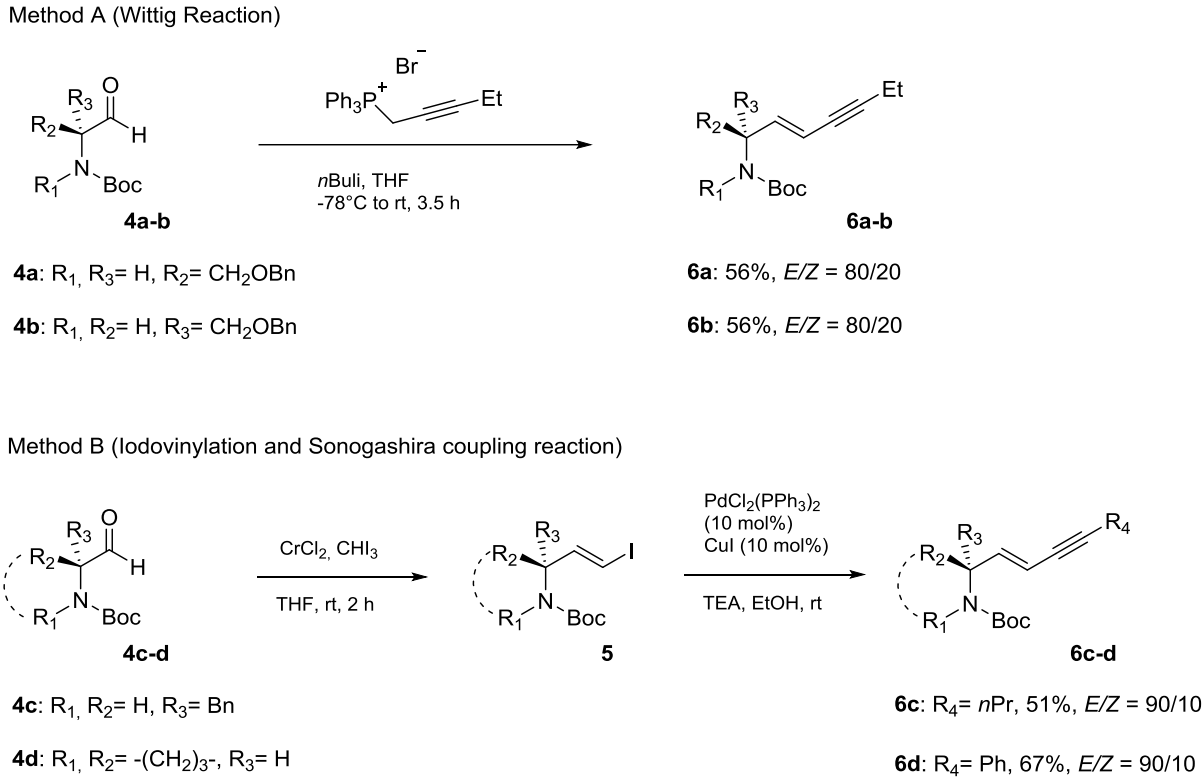
2. Results and discussion

Our initial efforts focused on the synthesis of the key intermediates acetylenic diols **3**, precursors of chiral 2-aminomethylfurans **1** or **2** by gold-catalyzed dehydrative cyclization. We first prepared aldehydes **4a-d** on a gram scale in two steps from commercially available *N*-Boc protected amino acids. Amino acids were converted to their corresponding Weinreb amides using TBTU, DIEA and *N,O*-dimethylhydroxylamine hydrochloride in DMF, then reduced without any racemization using lithium aluminium hydride in diethylether at -15°C according to a published procedure.[11] The observed optical rotation of these derivatives **4** were in agreement with the literature.[12]

Intermediates enynes **6** were obtained from aldehydes **4** by one step (Wittig reaction, Method A) or two steps (Takai iodovinylation[13] then Sonogashira coupling reaction, Method B) routes (Scheme 2).

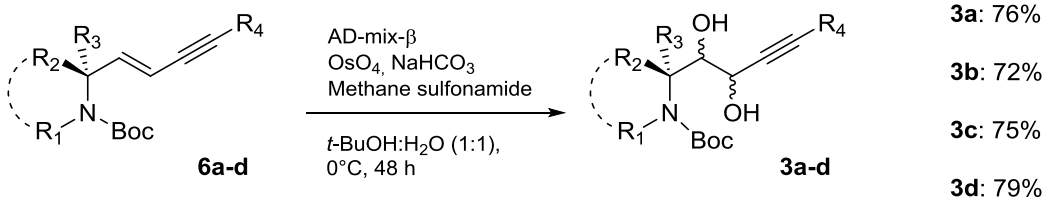
Wittig reaction of **4a-b** with 2-pentynyltriphenylphosphonium bromide and *n*-BuLi in THF afforded amino enynes **6a-b** in moderate yield as a mixture of diastereoisomers (*E/Z*: 80/20).[14] Method B is a more general strategy due to the wide variety of commercially available terminal alkynes. *Trans* vinyl iodides **5** were obtained by treatment of aldehydes **4** with iodoform in the presence of $CrCl_2$,[15] and Sonogashira coupling[16] of 1-pentyne or phenylacetylene in the presence of $PdCl_2(PPh_3)_2$ yielded enynes **6c-d** (51-67 % yield over two

steps). The *trans* geometry of the vinyl iodides **5** was confirmed by the coupling constant of the two vinylic protons (J = 14.5 Hz).



Scheme 2. Synthesis of enyne intermediates **6**.

We next focused on the dihydroxylation[17] of alkenes **6a-d** to obtain dihydroxy alkynes **3** (Scheme 3). Osmium tetroxide and *N*-methylmorpholine *N*-oxide failed to deliver the expected diols **3**, but modified Sharpless asymmetric dihydroxylation conditions with additional methane sulfonamide[18] allowed the isolation of the diols **3a-d** in a range of 72-79 % yield. The use of AD-mix-β –easier to manipulate– and methane sulfonamide in *t*-BuOH:H_2O (1:1) gave best yields.



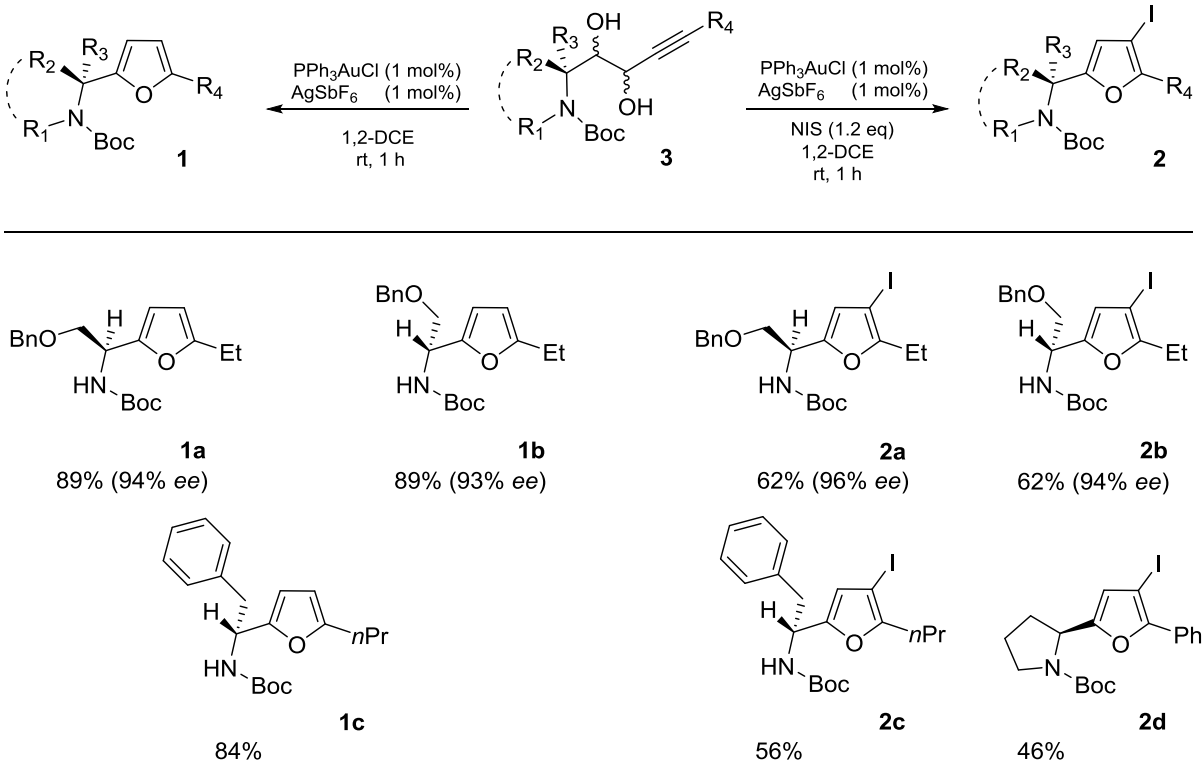
Scheme 3. Dihydroxylation of intermediates **6**.

With these diols **3** in hands, we next turned our attention to their gold-catalyzed dehydrative cyclization into di-substituted furans **1** and 4-iodofurans **2** using reaction conditions that were successful in our previous work (Scheme 4).[10]

In order to validate this cyclization, diol **3a** was treated with PPh_3AuCl (1 mol%) and $AgSbF_6$ (1 mol%) in 1,2-dichloroethane (1,2-DCE) at room temperature to afford furan **1a** in 89% yield in 1 h. As expected, no reaction was observed when $AgSbF_6$ or PPh_3AuCl catalysts were used separately.

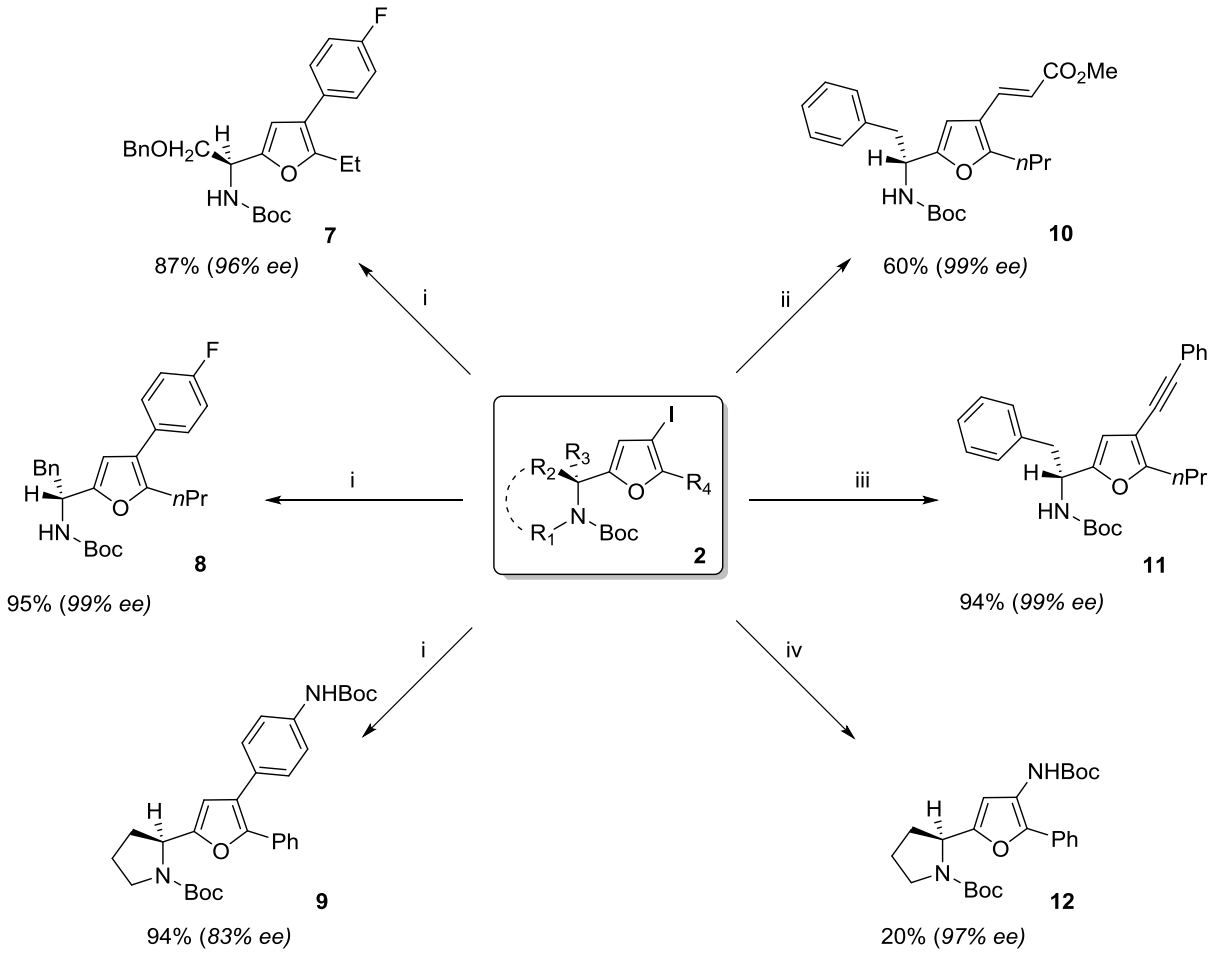
Iodocyclization was next investigated. The reaction of **3a** with NIS or I_2 as electrophilic halogen sources in the absence of a catalyst returned either starting **3a** or complex mixtures with only traces **2a**. Catalytic iodocyclization under conditions previously developed in our laboratory[19] revealed that the use of PPh_3AuCl (1 mol%) in the presence of $AgSbF_6$ (1 mol%), with NIS (1.2 eq) as electrophile, in 1,2-DCE at room temperature, afforded furan **2a** in 62% yield in 1 h (Scheme 3). Similar treatment of enantiomeric **3b** allowed purity measurement of **1a-b** and **2a-b** (93-96% *ee*) by chiral HPLC, which indicated minimal *ee* erosion during the sequence.

Various α,β-dihydroxyalkynes **3** were submitted to our reaction conditions to generate series of disubstituted furans **1** and iodofurans **2** in moderate to excellent yields (Scheme 4).



Scheme 4. Gold-catalyzed cyclization of substrates **3** to furans **1** and **2**.

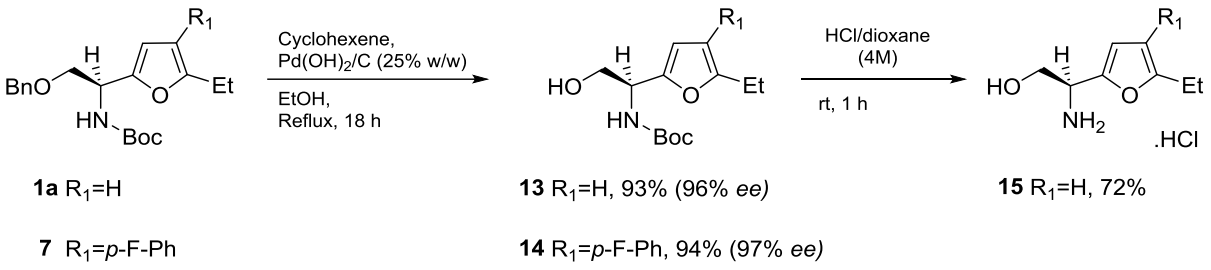
The value of iodo-furans **2** as chiral building blocks was demonstrated by further manipulation using Suzuki-Miyaura,[20] Heck,[21] Sonogashira[22] and Buchwald-Hartwig[23] couplings (Scheme 5). Compounds **7**-**9** were obtained in excellent isolated yields (87-94%) by Suzuki-Miyaura cross-coupling reaction of **2** with arylboronic acids. Heck and Sonogashira reactions of **2c** with ethyl acrylate or phenylacetylene respectively provided adducts **10** and **11** in 60% and 94% isolated yields. Finally, Buchwald-Hartwig amination of **2d** with *tert*-butylcarbamate gave the corresponding aminofuran **12**, albeit in low yield.



Scheme 5. Reagents and conditions: Suzuki-Miyaura coupling reaction (i) Ar-$B(OH)_2$, K_3PO_4, S-Phos (10 mol%), $Pd(OAc)_2$ (5 mol%), toluene, 80°C, 3 h; Heck coupling reaction (ii) Methyl acrylate, TEA, $Pd(PPh_3)_4$ (10 mol%), DMF, 80°C, 2 h; Sonogashira coupling reaction (iii) Phenylacetylene, $PdCl_2(PPh_3)_2$ (1 mol%), CuI (2 mol%), TEA, rt, 4 h; Buchwald-Hartwig coupling reaction (iv) *tert*-Butyl carbamate, Cs_2CO_3, CuI (20 mol%), N,N‘-DMEDA (40 mol%), toluene, 90°C, 18 h.

Access to fully deprotected β-amino alcohol derivatives by our strategy was then investigated. Efficient hydrogenolysis of the benzyl groups in **1a** and **7** was accomplished

with cyclohexene in the presence of Pearlman's catalyst to give **13** and **14** with an excellent enantiomeric excess (Scheme 6).



Scheme 6. Removal of protecting groups and access to amino-alcohol derivatives

Finally, *N*-Boc deprotection of **13** with 4M HCl in dioxane proceeded smoothly to give β-amino alcohol **15** in 72% yield.

3. Conclusion

In conclusion, we have reported a convenient gold-catalyzed approach for the synthesis of polysubstituted aminomethyl-furan derivatives from chiral acetylenic diol intermediates. The reaction proceeds under mild conditions, generally providing furan products in good to excellent yields and enantiopurity. Such compounds may have applications as chiral ligands, organocatalysts and pharmaceuticals.

4. Experimental

4.1 General

All reagents of high quality were purchased from commercial suppliers, and used without further purification. All reactions requiring anhydrous conditions were performed under an argon atmosphere using oven dried glassware. DMF and THF were distilled from CaH_2 and Na/benzophenone, respectively. ^{1}H and ^{13}C NMR were recorded at 300 and 75 MHz respectively on a Bruker AM 300 spectrometer, using $CDCl_3$ (and TMS as internal standard). δ values are given in parts per million (ppm), coupling constants (*J* values) are given in Hertz

(Hz), and multiplicity of signals are reported as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; bs, broad singlet. Thin layer chromatography was performed using precoated silica gel plate (0.2 mm thickness). Infrared spectra were recorded using an Universal Attenuated Total Reflectance Accessory (UATR). All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature.

4.2 Typical procedure for the preparation of vinyl iodides 5

Chromium(II) chloride (2.22 g, 18.0 mmol) was suspended in dry THF (25 mL) at room temperature under argon. A solution of aldehyde **4c** or **4d** (4.0 mmol) and iodoform (2.37 g, 6.0 mmol) in THF (25 mL) was added dropwise. After stirring in the dark at room temperature for 2 h, the reaction mixture was hydrolysed with a satured solution of NH_4Cl (50 mL) and extracted with diethylether (3 × 40 mL). The combined organic layers were washed with brine, then dried over magnesium sulfate, concentrated and purified by silica gel chromatography (2% ethyl acetate in dichloromethane) to afford the products **5c** and **5d** as a mixture of isomers E/Z, ratio: 90/10.

4.2.1 *tert*-Butyl (*R,E)*-(4-iodo-1-phenylbut-3-en-2-yl)carbamate 5c

970 mg (65%). Data of the separated major isomer E: white solid, mp = 108-109 °C; $[\alpha]_D^{22}$= + 23.8 (*c* 1.04, CH_2Cl_2); IR (UATR): 3351, 1687, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.21 (m, 3H), 7.17-7.14 (m, 2H), 6.47 (dd, *J* = 14.5 Hz, *J* = 5.9 Hz, 1H), 6.19 (dd, *J* = 14.5 Hz, *J* = 1.2 Hz, 1H), 4.47 (bs, 1H), 4.39 (bs, 1H), 2.82 (bd, *J* = 6.6 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.0, 145.5, 136.7, 129.6, 128.7, 126.9, 80.0, 77.5, 55.9, 41.2, 28.4; HRMS (ESI, m/z): Calcd. for $C_{15}H_{20}NO_2INa$: 396.0437, found $[M+Na]^+$: 396.0437.

4.2.2 (*S,E/Z)*-2-(2-Iodovinyl)pyrrolidine-1-carboxylic acid *tert*-Butyl ester 5d

870 mg (67%), pale yellow oil. Data of the mixture of isomers: IR (UATR): 1687, 1607 cm^{-1}; spectroscopic data for the unseparated major isomer E: ^1H NMR (300 MHz, $CDCl_3$, 50 °C): δ 6.42 (dd, *J* = 14.4 Hz, *J* = 6.5 Hz, 1H), 6.14 (d, *J* = 14.4 Hz, 1H), 4.24 (bs, 1H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.05-1.90 (m, 1H), 1.89-1.69 (m, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz,

$CDCl_3$, 50 °C): δ 154.5, 146.5, 79.7, 76.1, 61.3, 46.4, 31.4, 28.7, 23.3; HRMS (ESI, m/z): Calcd. for $C_{11}H_{18}NO_2INa$: 346.0280, found $[M+Na]^+$: 346.0283.

4.3 Typical procedure for the preparation of enynes 6

4.3.1 From aldehydes 4 (Method A)

To a stirred suspension of 2-pentynyltriphenylphosphonium bromide[14] (1.43 g, 3.5 mmol) in 18 mL of dry THF at -78 °C under argon atmosphere was added dropwise 1.7 mL (3.5 mmol) of a 2.1 M solution of n-butyllithium in hexane. After stirring at -78 °C for 1 h, a solution of *N*-Boc-L-serinal **4a** or *N*-Boc-D-serinal **4b** (0.98 g, 3.5 mmol) in 15 mL of dry THF was added. After stirring at -78 °C for 30 min, the mixture was allowed to warm to room temperature over 2 h. Then 40 mL H_2O was added and the mixture was extracted with diethylether (3 × 40mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel, eluting with 2% diethylether in dichloromethane gave **6a** or **6b**.

4.3.1.1 *tert*-Butyl (*S,E)*-(1-(benzyloxy)oct-3-en-5-yn-2-yl)carbamate 6a

650 mg (56%), pale yellow oil, as a mixture of *E/Z* isomers, ratio: 80/20. Data of the separated major *E* isomer: $[\alpha]_D^{22}$= -29.0 (*c* 1.05, $CHCl_3$); IR (HATR): 3337, 2216, 1698, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 6.03 (dd, *J* = 15.9 Hz, *J* = 6.1 Hz, 1H), 5.68 (dm, *J* = 15.9 Hz, 1H), 4.88 (bs, 1H), 4.52 (s, 2H), 4.34 (bs, 1H), 3.54 (dd, *J* = 9.5 Hz, *J* = 4.4 Hz, 1H), 3.47 (dd, *J* = 9.5 Hz, *J* = 4.5 Hz, 1H), 2.30 (qd, *J* = 7.5 Hz, *J* = 2.1 Hz, 1H), 1.44 (s, 9H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 139.7, 137.9, 128.6, 127.9, 127.8, 111.8, 92.7, 79.8, 77.8, 73.4, 72.0, 52.1, 28.5, 14.0, 13.2; HRMS (ESI, m/z): Calcd. for $C_{20}H_{27}NO_3Na$: 352.1888, found $[M+Na]^+$: 352.1884.

4.3.1.2 *tert*-Butyl (*R,E)*-(1-(benzyloxy)oct-3-en-5-yn-2-yl)carbamate 6b

650 mg (56%), pale yellow oil. Data of the separated major *E* isomer: $[\alpha]_D^{22}$= +27.1 (*c* 0.93, $CHCl_3$); spectral data and HRMS are identical with those reportated for **6a**.

4.3.2 From vinyl iodides 5 (Method B)

To a degassed solution of vinyl iodide **5c** or **5d** (2.5 mmol) and triethylamine (0.7 mL, 5 mmol) in 25 mL EtOH were added successively under argon atmoshere, $PdCl_2(PPh_3)_2$ (17.5 mg, 0.025mmol, 1 mol%), CuI (23.8 mg, 0.125 mmol, 5 mol%) and the appropriate alkyne (2.75 mmol). The mixture was stirred 72 h for **6c** and 24 h for **6d** at room temperature. After the reaction was completed (^{1}H NMR analysis), 50 mL H_2O was added and the mixture was extracted with diethylether (3 × 40mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel, eluting with 20% cyclohexane in dichloromethane gave **6c-d** as a mixture of *E/Z* isomers, ratio:90/10.

4.3.2.1 *tert*-Butyl (*R,E)*-(1-phenylnon-3-en-5-yn-2-yl)carbamate 6c

780 mg (78%). Data of the separated major *E* isomer: brown solid, mp = 84-85 °C; IR (UATR): 3354, 2219, 1687, 1603 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.16 (m, 5H), 5.96 (dd, *J* = 15.9 Hz, *J* = 5.5 Hz, 1H), 5.56 (dm, *J* = 15.9 Hz, 1H), 4.44 (bs, 2H), 2.82 (bd, *J* = 5.9 Hz, 2H), 2.25 (td, *J* = 7.0 Hz, *J* = 2.1 Hz, 2H), 1.53 (sext, *J* = 7.2 Hz, 2H), 1.39 (s, 9H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 141.3, 137.2, 129.6, 128.6, 126.7, 111.0, 91.2, 79.7, 78.5, 53.0, 41.6, 28.5, 22.3, 21.5, 13.7; HRMS (ESI, m/z): Calcd. for $C_{20}H_{27}NO_2Na$: 336.1939, found $[M+Na]^+$: 336.1938.

4.3.2.2 (*S,E)*-2-Hept-1-en-3-yn-1-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester 6d

740 mg (100%), orange solid, mp = 86-87 °C. Data of the mixture of isomers: IR (UATR): 1688, 1594 cm^{-1}; spectroscopic data for the unseparated major *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C): δ 7.42-7.40 (m, 2H), 7.30-7.25 (m, 3H), 6.10 (dd, *J* = 15.7 Hz, *J* = 6.2 Hz, 1H), 5.74 (d, *J* = 15.9 Hz, 1H), 4.36 (bs, 1H), 3.49-3.32 (m, 2H), 2.08-2.01 (m, 1H), 1.92-1.79 (m, 2H), 1.77-1.72 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 50 °C): δ 154.6, 144.1, 131.7, 128.4, 128.2, 123.8, 109.8, 89.9, 87.8, 79.6, 58.8, 46.5, 32.2, 28.7, 23.4; HRMS (ESI, m/z): Calcd. for $C_{19}H_{23}NO_2Na$: 320.1626, found $[M+Na]^+$: 320.1622.

4.4 Typical procedure for the preparation of diols 3

To a solution of enynes **6a-d** (2.0 m mol) in *t*-BuOH/H_2O (1:1, 26 mL) were added successively at 0°C AD-mix-β (2.8 g, 1.4 g/mmol of substrate) , a solution of 0.05% (w/v) OsO_4 in *t*-BuOH (6 mL, 0.012 mmol), $NaHCO_3$ (0.5 g, 6.0 mmol) and methanesulfonamide (0.38 g, 4 mmol). The mixture was stirred vigorously at 0°C 48 h for **3a-c** and 24 h for **3d**. The reaction was quenched with $Na_2S_2O_3$ (3 g) maintaining vigorous agitation for 30 min at 0°C. Diethylether (20 mL) was added and the mixture was warmed to room temperature under constant agitation. The organic layer was separated and the aqueous layer was extacted with diethylether (3 × 40 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (20% ethyl acetate in dichloromethane for **3a**, **3b** and **3d**, 30% ethyl acetate in dichlorometane for **3c**) afforded the dihydroxylated derivatives **3a-d** as a mixture of diastereomers used in the next step without separation.

4.4.1 *tert*-Butyl ((2*S*)-(1-(benzyloxy)-3,4-dihydroxyoct-5-yn-2-yl)carbamate 3a

550 mg (76%), pale yellow oil. Data of the separated major dihydroxylated product: $[\alpha]_D^{22}$= + 31.6 (*c* 1.01, CH_2Cl_2); IR (HATR): 3389, 2289, 2232, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 5.15 (bd, *J* = 8.7 Hz, 1H), 4.54 (s, 2H), 4.34 (bd, *J* = 7.5 Hz, 1H), 4.12-4.01 (m, 1H), 3.84 (bd, *J* = 6.2 Hz, 1H), 3.74-3.56 (m, 2H), 3.51(bs, 1H), 2.94(bs, 1H), 2.22 (qd, *J* = 7.5 Hz, *J* = 1.8 Hz, 2H), 1.44 (s, 9H), 1.13 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 137.7, 128.6, 128.0, 127,8, 89.1, 80.0, 76.9, 75.1, 73.5, 71.2, 64.0, 50.7, 28.5, 13.8, 12.6; HRMS (ESI, m/z): Calcd. for $C_{20}H_{29}NO_5Na$: 386.1943, found $[M+Na]^+$: 386.1945.

4.4.2 *tert*-Butyl ((2*R*)-(1-(benzyloxy)-3,4-dihydroxyoct-5-yn-2-yl)carbamate 3b

520 mg (72%), pale yellow oil. Data of the separated major dihydroxylated product: $[\alpha]_D^{22}$= + 3.4 (*c* 1.35, $CHCl_3$); IR (HATR): 3400, 2287, 2233, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40-7.28 (m, 5H), 5.29 (bd, *J* = 7.4 Hz, 1H), 4.57 (AB System, J_{AB} = 11.7 Hz, 1H), 4.51 (AB System, J_{AB} = 11.7 Hz, 1H), 4.48-4.43 (m, 1H), 3.95 (d, *J* = 9.5 Hz, 1H), 3.73-3.61 (m, 3H), 3.02 (bs, 2H), 2.24 (qd, *J* = 7.5 Hz, *J* = 2.0 Hz, 2H), 1.44 (s, 9H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 137.8, 128.6, 128.0, 127,8, 88.2, 80.7,

74.1, 73.7, 69.2, 62.9, 51.6, 28.4, 13.8, 12.6; HRMS (ESI, m/z): Calcd. for $C_{20}H_{29}NO_5Na$: 386.1943, found $[M+Na]^+$: 386.1945.

4.4.3 *tert*-Butyl ((2*R*)-3,4-dihydroxy-1-phenylnon-5-yn-2-yl)carbamate 3c

520 mg (75%). Data of the separated major dihydroxylated product: cream solid, mp = 108-109 °C; $[\alpha]_D^{22}$= + 23.9 (*c* 0.78, CH_2Cl_2); IR (UATR): 3566, 3348, 2227, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 4.60 (bd, *J* = 8.6 Hz, 1H), 4.46-4.42 (m, 1H), 3.96-3.82 (m, 1H), 3.82 (bd, *J* = 4.4 Hz, 1H), 3.47-3.38 (m, 1H), 3.09 (dd, *J* = 14.0 Hz, *J* = 4.1 Hz, 1H), 2.97-2.90 (m, 1H), 2.91 (bd, *J* = 6.0 Hz, 1H), 2.22 (td, *J* = 7.1 Hz, *J* = 2.0 Hz, 2H), 1.55 (sext, *J* = 7.3 Hz, 2H), 1.37 (s, 9H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 137.4, 129.6, 128.8, 126.8, 87.1, 80.7, 78.0, 76.0, 63.1, 52.6, 36.5, 28.4, 22.1, 20.9, 13.7; HRMS (ESI, m/z): Calcd. for $C_{20}H_{29}NO_4Na$:370.1994, found $[M+Na]^+$: 370.1991.

4.4.4 (2*R*)-2-(1,2-Dihydroxyhept-3-yn-1-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester 3d

520 mg (79%), pale yellow oil. Data of the separated major dihydroxylated product: $[\alpha]_D^{22}$= -100.2 (*c* 1.31, CH_2Cl_2); IR (UATR): 3381, 2243, 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.47-7.43 (m, 2H), 7.32-7.27 (m, 3H), 5.21 (bs, 1H), 4.62-4.53 (m, 1H), 4.13 (td, *J* = 7.6 Hz, *J* = 3.6 Hz, 1H), 3.73-3.67 (m, 2H), 3.57-3.49 (m, 1H), 3.38-3.30 (m, 1H), 2.12-1.80 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 132.0, 128.5, 128.3, 122.7, 88.2, 85.3, 81.2, 78.2, 64.5, 59.6, 47.7, 29.2, 28.5, 24.3; HRMS (ESI, m/z): Calcd. for $C_{19}H_{25}NO_4Na$: 354.1681, found $[M+Na]^+$: 354.1681.

4.5 Typical procedure for the synthesis of furans 1

To a degassed solution of dihydroxylated derivatives **3a-c** (0.6 mmol) in 1,2-dichloroethane (4 mL) was added under argon atmosphere 0.4 mL of a freshly prepared solution of PPh_3AuCl (14.8 mg, 0.03 mmol) and $AgSbF_6$ (10.3 mg, 0.03mmol) in 2 mL degassed 1,2- dichloroethane. After stirring for 1 h at room temperature, the reaction mixture was concentrated and purified by silica gel chromatography eluting with dichloromethane to afford the 2,5-disubstitued furans **1a-c.**

4.5.1 *tert*-Butyl (*S*)-(2-(benzyloxy)-1-(5-ethylfuran-2-yl)ethyl)carbamate 1a

184 mg (89%), colorless oil. $[\alpha]_D^{22}$= -35.1 (*c* 1.00, CH_2Cl_2), 94% *ee*; IR (UATR): 3336, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38-7.24 (m, 5H), 6.11 (d, *J* = 3.1 Hz, 1H), 5.89 (dt, *J* = 3.1 Hz, *J* = 0.9 Hz, 1H), 5.08 (bs, 1H), 4.93 (bs, 1H), 4.55 (AB System, J_{AB} = 12.1 Hz, 1H), 4.49 (AB System, J_{AB} = 12.1 Hz, 1H), 3.76 (dd, *J* = 9.7 Hz, *J* = 4.9 Hz, 1H), 3.70 (dd, *J* = 9.7 Hz, *J* = 5.0 Hz, 1H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.44 (s, 9H), 1.20 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 155.4, 151.1, 138.1, 128.5, 127.8, 127.7, 107.2, 104.7, 79.8, 73.2, 71.0, 48.9, 28.5, 21.5, 12.2; HRMS (ESI, m/z): Calcd. for $C_{20}H_{27}NO_4Na$: 368.1832, found $[M+Na]^+$: 368.1833; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 95/5, flow rate = 1 mL/min, wavelength = 230 nm): Rt =7.42 (major) and 8.22 (minor).

4.5.2 *tert*-Butyl (*R*)-(2-(benzyloxy)-1-(5-ethylfuran-2-yl)ethyl)carbamate 1b

184 mg (89%), colorless oil. $[\alpha]_D^{22}$= +33.4 (*c* 0.99, CH_2Cl_2), 93% *ee*; spectral data and HRMS are identical with those reportated for **1a**; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 95/5, flow rate = 1 ml/min, wavelength = 230 nm): Rt = 7.40 (minor) and 8.19 (major).

4.5.3 *tert*-Butyl (*R*)-(2-phenyl-1-(5-propylfuran-2-yl)ethyl)carbamate 1c

166 mg (84%), colorless oil. $[\alpha]_D^{22}$= +43.4 (*c* 1.07, CH_2Cl_2), ≥ 99% *ee*; IR (UATR): 3343, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.25-7.17 (m, 3H), 7.06-7.03 (m, 2H), 5.88 (d, *J* = 3.0 Hz, 1H), 5.84 (d, *J* = 3.0 Hz, 1H), 4.93 (bs, 1H), 4.82 (bs, 1H), 3.09 (bd, *J* = 6.6 Hz, 2H), 2.57 (t, *J* = 7.4 Hz, 2H), 1.65 (sext, *J* = 7.4 Hz, 2H), 1.40 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 155.1, 151.9, 137.5, 129.6, 128.3, 126.5, 107.0, 105.5, 79.7, 50.3, 40.8, 30.2, 28.5, 21.6, 13.8; HRMS (ESI, m/z): Calcd. for $C_{20}H_{27}NO_3Na$: 352.1889, found $[M+Na]^+$: 352.1887; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 99/1, flow rate = 1 mL/min, wavelength = 220 nm): Rt =10.08.

4.6 Typical procedure for the synthesis of iodofurans 2

To a degassed solution of dihydroxylated derivatives **3a-d** (0.6 mmol) in 1,2-dichloroethane (4 mL) were added successively under argon atmosphere NIS (0.16 g, 0.72 mmol) and 0.4 mL of a freshly prepared solution of PPh_3AuCl (14.8 mg, 0.03 mmol) and $AgSbF_6$ (10.3 mg, 0.03 mmol) in 2 mL degassed 1,2- dichloroethane. After stirring for 1 h at room temperature, 20% $Na_2S_2O_3$ (5 mL) was added and the mixture was extracted with diethylether (3 × 10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel eluting with dichloromethane afforded the 2,5-disubstituted 3-iodofurans **2a-d**.

4.6.1 *tert*-Butyl (*S*)-(2-(benzyloxy)-1-(5-ethyl-4-iodofuran-2-yl)ethyl)carbamate 2a

175 mg (62%), pale yellow oil. $[\alpha]_D^{22}$= -36.5 (*c* 1.02, CH_2Cl_2), 96% *ee*; IR (UATR): 3332, 1704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37-7.24 (m, 5H), 6.20 (s, 1H), 511 (bs, 1H), 4.91 (bs, 1H), 4.55 (AB System, J_{AB} = 12.1 Hz, 1H), 4.48 (AB System, J_{AB} = 12.1 Hz, 1H), 3.75 (dd, *J* = 9.6 Hz, *J* = 4.4 Hz, 1H), 3.68 (dd, *J* = 9.6 Hz, *J* = 4.7 Hz, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.45 (s, 9H), 1.17 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 155.3, 152.8, 137.9, 128.6, 127.9, 127.8, 114.1, 80.1, 73.3, 70.6, 61.7, 48.8, 28.5, 21.1, 12.6; HRMS (ESI, m/z): Calcd. for $C_{20}H_{26}NO_4INa$: 494.0804, found $[M+Na]^+$: 494.0806; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 97/3, flow rate = 1 ml/min, wavelength = 230 nm): Rt = 9.06 (major) and 9.89 (minor).

4.6.2 *tert*-Butyl (*R*)-(2-(benzyloxy)-1-(5-ethyl-4-iodofuran-2-yl)ethyl)carbamate 2b

175 mg (62%), pale yellow oil. $[\alpha]_D^{22}$= +36.3 (*c* 1.03, CH_2Cl_2), 94% *ee*; spectral data and HRMS are identical with those reportated for **2a**; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 97/3, flow rate = 1 ml/min, wavelength = 230 nm): Rt = 9.09 (minor) and 9.91 (major).

4.6.3 *tert*-Butyl (*R*)-(1-(4-iodo-5-propylfuran-2-yl)-2-phenylethyl)carbamate 2c

153 mg (56%), white solid, mp =79-80 °C; $[\alpha]_D^{22}$= +38.3 (*c* 1.08, CH_2Cl_2); IR (UATR): 3316, 1685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28-7.17 (m, 3H), 7.06-7.03 (m, 2H), 6.02 (s, 1H), 4.95 (bs, 1H), 4.76 (bs, 1H), 3.07 (bd, *J* = 6.5 Hz, 2H), 2.62 (t, *J* = 7.4 Hz, 2H), 1.65

(sext, J = 7.4 Hz, 2H), 1.40 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 155.0, 153.7, 136.9, 129.5, 128.5, 126.8, 113.9, 80.0, 62.7, 49.9, 40.4, 29.4, 28.4, 21.8, 13.7; HRMS (ESI, m/z): Calcd. for $C_{20}H_{26}NO_3INa$: 478.0855, found $[M+Na]^+$: 478.0854.

4.6.4 (*S*)-2 -(4-Iodo-5-phenylfuran-2-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester 2d

121 mg (46%), yellow solid, mp = 71-72 °C; $[\alpha]_D^{22}$= -101.0 (*c* 1.04, CH_2Cl_2); IR (UATR): 1690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 55 °C): δ 7.92 (d, J = 7.3 Hz, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 6.29 (s, 1H), 4.90 (bs, 1H), 3.59-3.41 (m, 2H), 2.23-2.13 (m, 1H), 2.12-2.00 (m, 2H), 1.96-1.88 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): δ 157.1, 154.5, 150.8, 130.6, 128.5, 128.1, 126.3, 116.5, 79.9, 61.2, 54.8, 46.5, 32.4, 28.6, 23.9; HRMS (ESI, m/z): Calcd. for $C_{19}H_{22}NO_3INa$: 462.0542, found $[M+Na]^+$: 462.0540.

4.7 Typical procedure for the Suzuki-Miyaura coupling of iodofurans 2 with 4-substituted phenylboronic acid

To a degassed solution of iodofurans **2a, 2c** or **2d** (0.25 mmol) and the appropriate aryl boronic acid (0.375 mmol) in toluene (2.5mL) were added successively under argon atmosphere K_3PO_4 (106.0 mg, 0.50 mmol), S-Phos (10.3 mg, 0.025 mmol, 10 mol%) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 5 mol%). The resulting mixture was heated to 80°C for 3 h. After cooling, the mixture was diluted with diethylether, filtered over a Celite® plug, wich was washed with diethylether. After removal of solvents in vaccuo, the crude product was purified by silica gel chromatography eluting with 20% diethylether in petoleum ether for **7**, **8** and 25% ethyl acetate in cyclohexane for **9**.

4.7.1 *tert*-Butyl (*S*)-(2-(benzyloxy)-1-(5-ethyl-4-(4-fluorophenyl)furan-2-yl)ethyl)carbamate 7

96 mg (87%), colorless oil; $[\alpha]_D^{22}$= -36.4 (*c* 0.99, CH_2Cl_2), 96% *ee*; IR (UATR): 3336, 1711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.24 (m, 7H), 7.10-7.02 (m, 2H), 6.28 (s, 1H), 5.14 (bs, 1H), 4.97 (bs, 1H), 4.58 (AB System, J_{AB} = 12.2 Hz, 1H), 4.52 (AB System, J_{AB} = 12.2 Hz, 1H), 3.81 (dd, J = 9.7 Hz, J = 4.6 Hz, 1H), 3.75 (dd, J = 9.7 Hz, J = 4.8 Hz, 1H), 272 (q, J = 7.5 Hz, 2H), 1.46 (s, 9H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 161.7 (J^1_{CF} = 245.3 Hz), 155.4, 152.1, 151.0, 138.1, 130.4 (J^4_{CF} = 3.3 Hz), 129.3 (J^3_{CF} = 7.9 Hz), 128.5, 127.8, 127.7, 120.2, 115.5 (J^2_{CF} = 21.4 Hz), 108.3, 80.0, 73.3, 70.9, 48.9, 28.5, 20.4, 13.1; HRMS (ESI, m/z): Calcd. for $C_{26}H_{30}NO_4FNa$: 462.2057, found $[M+Na]^+$: 462.2059; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 95/5, flow rate = 1 mL/min, wavelength = 220 nm): Rt =10.01 (minor) and 10.70 (major).

4.7.2 *tert*-Butyl (*R*)-(1-(4-(4-fluorophenyl)-5-propylfuran-2-yl)-2-phenylethyl)carbamate 8

103 mg (95%), colorless oil; $[\alpha]_D^{22}$= +36.6 (*c* 1.00, CH_2Cl_2), ≥ 99% *ee*; IR (UATR): 3345, 1700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.16 (m, 5H), 7.10-7.01 (m, 4H), 6.07 (s, 1H), 4.99 (bs, 1H), 4.85 (bs, 1H), 3.13 (bd, *J* = 6.5 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 1.71 (sext, *J* = 7.4 Hz, 2H), 1.41(s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7 (J^1_{CF} = 245.5 Hz), 155.1, 151.8, 151.0, 137.3, 130.4 (J^4_{CF} = 3.2 Hz), 129.6, 129.3 (J^3_{CF} = 7.9 Hz), 128.4, 126.7, 120.7, 115.5 (J^2_{CF} = 21.4 Hz), 108.1, 79.9, 50.1, 40.7, 28.9, 28.5, 22.1, 14.0; HRMS (ESI, m/z): Calcd. for $C_{26}H_{30}NO_3FNa$: 446.2107, found $[M+Na]^+$: 446.2107; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 98/2, flow rate = 1 mL/min, wavelength = 220 nm): Rt =10.65.

4.7.3 (*S*)-2-(4-(4-((tert-Butoxycarbonyl)amino)phenyl)-5-phenylfuran-2-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester 9

119 mg (94%), white solid, mp = 220-221 °C; $[\alpha]_D^{22}$= -86.3 (*c* 0.91, CH_2Cl_2), 83% *ee*; IR (UATR): 3247, 1726, 1672 cm^{-1}; ^{1}H NMR (300 MHz, DMSO, 80 °C): δ 9.13 (bs, 1H), 7.48-7.43 (m, 4H), 7.35-7.30 (m, 2H), 7.27-7.22 (m, 3H), 6.32 (s, 1H), 4.88 (dd, *J* = 7.7 Hz, *J* = 2.5 Hz, 1H), 3.52-3.36 (m, 2H), 2.29-2.16 (m, 1H), 2.11-1.86 (m, 3H), 1.50 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ 155.1, 153.1, 152.4, 145.5, 138.4, 130.6, 128.1, 128.0, 127.1, 127.0, 125.1, 122.2, 118.2, 109.1, 78.8, 78.2, 53.9, 45.7, 31.1, 27.8, 27.7, 23.0; HRMS (ESI, m/z): Calcd. for $C_{30}H_{36}N_2O_5Na$: 527.2522, found $[M+Na]^+$: 527.2519; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 90/10, flow rate = 1 mL/min, wavelength = 250 nm): Rt = 7.51 (minor) and 10.27 (major).

4.8 (*R*,*E*)-3-(5-(1-((*tert*-butoxycarbonyl)amino)-2-phenylethyl)-2-propylfuran-3-yl)acrylic acid methyl ester 10

To a degassed solution of iodofuran **2c** (114 mg, 0.25 mmol) in dry DMF (2 mL) were added successively under argon atmosphere methyl acrylate (45 μl , 0.5 mmol), triethylamine (70 μl, 0.5 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol, 10 mol%). The mixture was heated to 80 °C for 2 h. After cooling, H_2O (3 mL) was added and the mixture was extracted with diethylether (3×5 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel eluting with 2% diethylether in dichloromethane afforded the pure product **10** as a yellow solid: 62 mg (60%), mp = 104-105 °C; $[\alpha]_D^{22}$= +31.7 (*c* 0.94, CH_2Cl_2), 99% *ee;* IR (UATR): 3343, 1714, 1688, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, *J* = 15.7 Hz, 1H), 7.27-7.17 (m, 3H), 7.06-7.04 (m, 2H), 6.12 (s, 1H), 5.95 (d, *J* = 15.7 Hz, 1H), 4.97 (bs, 1H), 4.80 (bs, 1H), 3.76 (s, 3H), 3.09 (bd, *J* = 6.6 Hz, 2H), 2.69 (t, *J* = 7.4 Hz, 2H), 1.68 (sext, *J* = 7.4 Hz, 2H), 1.41 (s, 9H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 158.0, 155.0, 153.6, 136.9, 135.4, 129.5, 128.5, 126.8, 118.1, 115.8, 104.4, 80.1, 51.6, 50.0, 40.4, 28.5, 28.3, 22.1, 13.8; HRMS (ESI, m/z): Calcd. for $C_{24}H_{31}NO_5Na$: 436.2100, found $[M+Na]^+$: 436.2101; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 98/2, flow rate = 1 mL/min, wavelength = 290 nm): Rt =20.29 (major), 27.17 (minor).

4.9 (*R*)-(2-Phenyl-1-(4-(phenylethynyl)-5-propylfuran-2-yl)ethyl)carbamic acid *tert*-butyl ester 11

To a degassed solution of iodofuran **2c** (114 mg, 0.25 mmol) in triethylamine (2 mL) were added under argon atmoshere $PdCl_2(PPh_3)_2$ (1.8 mg, 0.0025 mmol, 1 mol%) and CuI (1.0 mg, 0.005 mmol, 2 mol%). The reaction mixture was stirred for 15 min at room temperature. Then a solution of phenylacetylene (69 μl, 0.63 mmol) in triethylamine (0.4 mL) was added dropwise and the mixture was stirred for 4 h at room temperature. Subsequently, the mixture was diluted with diethylether (10 mL) and washed with brine. The organic extract was separated, dried over magnesium sulfate and concentated. Chromatography on silica gel eluting with 20% diethylether in petroleum ether afforded the pure product **11** as a pale yellow solid: 101 mg (94%), mp = 96-97 °C; $[\alpha]_D^{22}$= +34.2 (*c* 1.04, CH_2Cl_2), ≥ 99% *ee*; IR (UATR): 3389, 2223, 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.43 (m, 2H), 7.35-7.17 (m, 10H), 7.08-7.05 (m, 2H), 6.06 (s, 1H), 4.96 (bs, 1H), 4.79 (bs, 1H), 3.10 (bd, *J* = 6.7 Hz, 2H), 2.74 (t, *J* = 7.4 Hz, 2H), 1.74 (sext, *J* = 7.4 Hz, 2H), 1.41 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 155.0, 152.1, 137.0, 131.4, 129.5, 128.5, 128.4, 128.0, 126.7, 123.8, 109.4, 103.7, 91.8, 81.9, 80.0, 50.0, 40.5, 29.3, 28.5, 21.6, 13.9; HRMS

(ESI, m/z): Calcd. for $C_{28}H_{31}NO_3Na$: 452.2202, found $[M+Na]^+$: 452.2205; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 98/2, flow rate = 1 mL/min, wavelength = 280 nm): Rt =10.63.

4.10 (*S*)-2-(4-((*tert*-butoxycarbonyl)amino)-5-phenylfuran-2-yl)pyrrolidine-1-carboxylic acid *tert*-butyl ester 12

To a degassed mixture of iodofuran **2d** (110 mg, 0.25 mmol), *tert*-butyl carbamate (35 mg, 0.3 mmol), cesium carbonate (122 mg, 0.37 mmol) and CuI (9.5 mg, 0.05 mmol, 20 mol%) in dry toluene (2.5 mL), was added under argon atmosphere N,N'-DMEDA (11 μl, 0.1 mmol, 40 mol%). The mixture was heated to 90 °C for 18 h. After cooling, the mixture was diluted with dichloromethane, filtered over a Celite plug, which was washed with dichloromethane. After removal of solvents in vaccuo, the crude product was purified by silica gel chromatography eluting with 5% ethyl acetate in dichloromethane to afford the pure product **12** as a colorless oil: 22 mg (20%); $[\alpha]_D^{22}$= -89.0 (*c* 1.23, CH_2Cl_2), 97% *ee*; IR (UATR): 3291, 1720, 1679 cm^{-1}; ^1H NMR (300 MHz, DMSO, 80 °C): δ 8.38 (bs, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 6.28 (s, 1H), 4.83 (dd, *J* = 7.8 Hz, *J* = 2.3 Hz, 1H), 3.49-3.35 (m, 2H), 2.26-2.13 (m, 1H), 2.06-1.88 (m, 3H), 1.43 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, DMSO, 80 °C): δ 153.6, 153.4, 153.1, 141.4, 130.0, 128.0, 126.3, 123.8, 121.0, 107.2, 78.6, 78.3, 54.0, 45.7, 31.0, 27.7, 22.9; HRMS (ESI, m/z): Calcd. for $C_{24}H_{32}N_2O_5Na$: 451.2209, found $[M+Na]^+$: 451.2207; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 95/5, flow rate = 1 mL/min, wavelength = 291 nm): Rt = 10.55 (major) and 17.67 (minor).

4.11 Typical procedure for *O*-debenzylation

To a solution of furans **1a** or **7** (0.2 mmol) in ethanol (2.4 mL) and cyclohexene (1.2 mL) was added 20% palladium hydroxyde on carbon (25% catalyst / substrate by weight). The suspension was stirred under reflux for 18 h. After cooling, the catalyst was filtered over a Celite plug, washed with dichloromethane and the volatiles were removed by evaporation in vacuo. The residue was purified by silica gel chromatography eluting with a mixture of cyclohexane / ethyl acetate / methanol (75 / 25 /1).

4.11.1 (*S*)-(1-(5-ethylfuran-2-yl)-2-hydroxyethyl)carbamic acid *tert*-butyl ester 13

47 mg (93%), colorless oil; $[\alpha]_D^{22}$= -51.1 (*c* 1.00, CH_2Cl_2), 96% *ee*; IR (UATR): 3396, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.13 (d, *J* = 3.1 Hz, 1H), 5.91 (d, *J* = 3.1 Hz, 1H), 5.16 (bs, 1H), 4.82 (bs, 1H), 3.90 (dd, *J* = 11.2 Hz, *J* = 5.4 Hz, 1H), 3.83 (dd, *J* = 11.2 Hz, *J* = 4.7 Hz, 1H), 2.61 (q, *J* = 7.5 Hz, 2H), 1.45 (s, 9H), 1.21 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 156.0, 150.3, 107.7, 104.7, 80.2, 64.9, 51.1, 28.5, 21.5, 12.1; HRMS (ESI, m/z): Calcd. for $C_{13}H_{21}NO_4Na$: 278.1363, found $[M+Na]^+$: 278.1363; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 97/3, flow rate = 1 mL/min, wavelength = 220 nm): Rt =21.60 (minor) and 23.26 (major).

4.11.2 (*S*)-(1-(5-ethyl-4-(4-fluorophenyl)furan-2-yl)-2-hydroxyethyl)carbamic acid *tert*-butyl ester 14

66 mg (94%), colorless oil; $[\alpha]_D^{22}$= -49.4 (*c* 0.50, CH_2Cl_2), 97% *ee*; IR (UATR): 3410, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H), 7.11-7.03 (m, 2H), 6.32 (s, 1H), 5.18 (bs, 1H), 4.88 (bs, 1H), 4.00-3.85 (m, 2H), 2.74 (q, *J* = 7.5 Hz, 2H), 2.14 (bs, 1H), 1.47 (s, 9H), 1.25 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8 (J^1_{CF} = 245.5 Hz), 155.9, 152.5, 150.2, 130.0, (J^4_{CF} = 3.3 Hz), 129.3 (J^3_{CF} = 7.8 Hz), 120.3, 115.6 (J^2_{CF} = 21.4 Hz), 108.7, 80.3, 64.8, 51.1, 28.5, 20.4, 13.0; HRMS (ESI, m/z): Calcd. for $C_{19}H_{24}NO_4FNa$: 372.1587, found $[M+Na]^+$: 372.1585; HPLC analysis (Chiralpak IA column, heptane/2-propanol = 95/5, flow rate = 1 mL/min, wavelength = 220 nm): Rt =15.26 (minor) and 17.42 (major).

4.12 (*S*)-2-Amino-2-(5-ethylfuran-2-yl)ethan-1-ol, hydrochloride 15

To the product **13** (47 mg, 0.18 mmol) was added 4M HCl in dioxane (0.5 mL) and let stir for 1 h. The reaction mixture was concentrated in vacuo, taken up with a mixture of diethylether / ethyl acetate (4 / 1). The solid part was separated by filtration, washed with diethylether and dried in vacuum dessicator. Yield: 25 mg (72 %), beige solid, mp = 101-102°C; $[\alpha]_D^{22}$= -16.2 (*c* 0.50, MeOH); IR (UATR): 3550-2400 (broad), 2034 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 6.43 (d, *J* = 3.2 Hz, 1H), 6.07 (d, *J* = 3.2 Hz, 1H), 4.41 (ABX System, J_{AX} = 8.2 Hz, J_{BX} = 4.9 Hz, 1H), 3.94 (ABX System, J_{AB} = 11.6 Hz, J_{BX} = 4.9 Hz, 1H), 3.88 (ABX System, J_{AB} = 11.6 Hz, J_{AX} = 8.3 Hz, 1H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.5 Hz,

3H); ^{13}C NMR (75 MHz, CD_3OD): δ 160.4, 146.9, 111.4, 106.3, 61.9, 51.9, 22.1, 12.5; HRMS (ESI, m/z): Calcd. for $C_8H_{11}O_2$: 139.0759, found $[M\text{-}NH3+H]^+$: 139.0760.

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References

1. (a) *Natural products chemistry*; Nakanishi, K., Ed.; Kodansha scientific books; Kodansha ; Academic Press: Tokyo : New York, 1974; (b) Look, S. A.; Burch, M. T.; Fenical, W.; Zheng, Q.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741-5746.
2. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795-819.
3. (a) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955-2020; (b) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076-2080.
4. (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084; (b) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395-3442; (c) Hoffmann, M.; Miaskiewicz, S.; Weibel, J.-M.; Pale, P.; Blanc, A. *Beilstein J. Org. Chem.* **2013**, *9*, 1774-1780; (d) Dudnick, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645-7655; (e) Wang, E.; Fu, X.; Xie, X.; Chen, J.; Gao, H.; Liu, Y. *Tetrahedron Lett.* **2011**, *52*, 1968-1972; (f) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624-4627; (g) Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839-1845; (h) Blanc, A. ; Tenbrink, K. ; Weibel, J.-M. ; Pale, P. *J. Org. Chem.* **2009**, *74*, 5342-5348; (i) Kotikalapudi, R.; Swamy, K. C. K. *Tetrahedron Lett.* **2012**, *53*, 3831-3834; (j) Wang, T.; Shi, S.; Rudolph, M.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2014**, *356*, 2337-2342; (k) Wang, T.; Shi, S.; Hansmann, M. A.; Rettenmeier, E.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2014**, *53*, 3715-3719; (l) Hashmi, A. S. K.;

Schwarz, L. *Chem. Ber./Recueil* **1997**, *130*, 1449-1456; (m) Hashmi, A. S. K.; Ruppert, T. L.; Knöfel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295-7304.

5. Paolucci, C.; Rosini, G. *Tetrahedron : Asym* **2008**, *18*, 2923-2946.
6. (a) Zhou, W.-S.; Lu, Z.-H.; Xu, Y.-M.; Liao, L.-X.; Wang, Z.-M. *Tetrahedron* **1999**, *55*, 11959-11983; (b) Ciufolini, M.; Hermann, C. Y. W.; Dong, Q. ; Shimizu, T.; Swaminathan, S.; Yi, N. *Synlett* **1998**, 105-114; (c) Chen, W. P. ; Roberts, S. M. *J. Chem. Soc. Perkin Trans. 1* **1999**, 103-105.
7. (a) Yi, N. ; Ciufolini, M. A. *Tetrahedron Lett.* **1995**, *36*, 6595-6598; (b) Yana, C. F.; Xu, Y. M.; Liao, L. X.; Zhou, W. S. *Tetrahedron Lett.* **1998**, *39*, 9227-9228; (c) Achmatowicz, O. ; Bukowski, P. ; Szechnev, B. ; Zwierzchowska, Z. ; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973-1996.
8. (a) Shono, T.; Matsumura, Y.; Tsubata, J. *Chem. Lett.* **1981**, 1121-1124; (b) Ben-Ishai, D.; Satati, I.; Bernstein, Z. *Tetrahedron Lett.* **1976**, *32*, 1571-1573; (c) Kasai, M.; Ziffer, H. *J. Org. Chem.* **1983**, *48*, 2346-2349.
9. (a) Demir, A. S.; Sesenoglu, O.; Uelkue, D.; Arıcı, C. *Helv. Chim. Acta* **2003**, *86*, 91-105; (b) Bushey, M. L.; Hankaas, M. H.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2984-2985; (c) Alvaro, G. ; Martelli, G. ; Savoia, D. ; Zuffoli, A. *Synthesis* **1998**, 1773-1777; (d) Irako, N.; Hamada, Y. ; Shioiri, T. *Tetrahedron* **1995**, *51*, 12731-12744; (e) Zhou, W. S.; Lu, Z. H.; Wang, Z. M. *Tetrahedron Lett.* **1991**, *32*, 1467-1470. For the synthesis of the next higher homologous by enzyme catalysis see: Hashmi, A. S. K.; Ata, F.; Haufe, P.; Rominger, F. *Tetrahedron* **2009**, *65*, 1919-1927.
10. (a) Gouault, N.; Le Roch, M.; Cornée, C. ; David, M. ; Uriac, P. *J. Org. Chem.* **2009**, *74*, 5614-5617; (b) Gouault, N.; Le Roch, M. ; Cheignon, A. ; Uriac, P.; David, M. *Org. Lett.* **2011**, *13*, 4371-4373; (c) Trinh, T. T. H. ; Nguyen, K. H. ; de Aguiar Amaral, P. ; Gouault, N. *Beilstein J. Org. Chem.* **2013**, *9*, 2042-2047.

11. Campbell, A.; Raynham, T.; Taylor, K. *Synthesis* **1998**, *12*, 1707-1709.

12. (a) Alfaro, R.; Yuste, F.; Ortiz, B.; Sanchez-Obregon, R.; Garcıa Ruano, J. L. *Tetrahedron* **2009**, *65*, 357-363; (b) Xu, G. G.; Etzkorn, F. A. *Org. Lett*. **2010**, *12*, 696-699; (c) Song, X.-N.; Yao, Z.-J. *Tetrahedron* **2010**, *66*, 2589-2593.

13. Takai, K.; Nitta, K.; Utimoto, K. D. *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.

14. (a) Fu, Y.; Bieschke, J.; Kelly, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 15366-15367; (b) Kaltenbronn, J. Hudspeth, J. P.; Lunney, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenburg, A. D. *J. Med. Chem.* **1990**, *33*, 838-845.

15. D'Aniello, F.; Mann, A.; Schoenfelder, A.; Taddei, M. *Tetrahedron* **1997**, *53*, 1447-1456.

16. (a) El Sohly, A. M.; Wespe, D. A.; Poore, T. J.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 5789-5794; (b) Pawluc, P.; Franczyk, A.; Walkowiak, J.; Hreczycho, G.; Kubicki, M.; Marciniec, B. *Tetrahedron* **2012**, *68*, 3545-3551.

17. (a) Reddy, J. S.; Rao, B. V. *J. Org. Chem.* **2007**, *72*, 2224-2227; (b) Aoki, S.; Matsui, K.; Tanaka, K.; Satari, R.; Kobayashi, M. *Tetrahedron* **2000**, *56*, 9945-9948.

18. Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, 605-606.

19. Nguyen, K. H.; Tomasi, S.; Le Roch, M.; Toupet, L.; Renault, J.; Uriac, P.; Gouault, N. *J. Org. Chem.* **2013**, *78*, 7809-7815.

20. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168.

21. Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518-5526.

22. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467-4470.

23. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1348-1350; (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609-3612.