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Synthesis of Quinuclidines by Intramolecular Silver-Catalysed Amine Additions to Alkynes

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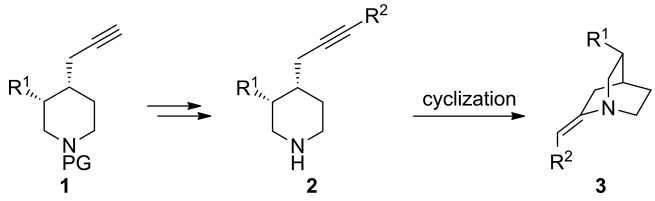
A new method has been developed for the synthesis of 2-alkylidenequinuclidines based on a silver triflate catalysed intramolecular hydroamination of 4-(prop-2-ynyl)piperidines. Monosubstituted piperidines reacted less efficiently than *cis*-disubstituted piperidines, and the reaction was selective for an alkyne moiety, even in the presence of a vinyl group at the 3-position. The hydroamination occurred readily with a terminal alkyne, as well as with an internal alkyne bearing an aliphatic or aromatic group at the terminal carbon atom. Using this silver-catalysed cyclization, a short procedure was developed for the relay synthesis of the cinchona alkaloids dihydroquinidine and dihydroquinine.

Introduction

2-Alkylidenequinuclidines **3** are valuable for the development of pharmaceutical compounds.[1–6] They are usually prepared in good yields under basic conditions by an aldol condensation between 3-quinuclidinone hydrochloride and an aldehyde.[7] The α,β-unsaturated system can be further functionalized by means of 1,2-addition,[1] 1,4-addition,[2] hydrogenation,[3] or deoxygenation reactions.[4] Chirality can be introduced through tautomerization using chiral acids[5] or by asymmetric carbonyl reduction.[6] However, with this approach, it is difficult to introduce functional groups at positions other than the α,β-unsaturated system. The only known procedure for functionalization at other sites in these α,β-unsaturated quinuclidines is hydroxylation with enzymes.[8] Alternative methods to prepare quinuclidines involve cyclizations of 4-substituted piperidines using the ring nitrogen atom as a nucleophile.[9] This strategy has been used for the total synthesis of cinchona alkaloids[9a–9d] and their derivatives.[9e,9f]

In conjunction with our work on the use of cinchona alkaloids and their derivatives as organocatalysts, we became interested in new methods for the synthesis of enantiomerically pure quinuclidines and other small chiral bicyclic bridgehead nitrogen compounds. We envisioned that the intramolecular addition of secondary amines to alkynes as shown in Scheme 1 could be a valuable strategy for the synthesis of enantiomerically pure substituted 2-alkylidenequinuclidines **3**.



Scheme 1. Strategy for the synthesis of substituted 2-alkylidenequinuclidines **3**.

The intramolecular addition of amines to alkynes,[10] allenes,[11] and alkenes[12] is a powerful strategy for the construction of monocyclic nitrogen-containing heterocycles. This reaction has been intensively studied, and it may be catalysed by a variety of different types of species, including metals,[13] acids,[14] and even bases.[15] Late-transition-metal complexes with palladium,[16] platinum,[17] silver,[18] and gold[19] are widely used, because they have a higher functional-group tolerance than complexes of early transition metals. Only a few studies are known in which a late-transition-metal-catalysed hydroamination process has led to nitrogen-containing bicyclic compounds. Recently, Sperger and Fiksdahl reported the synthesis of bicyclic bridgehead nitrogen compounds by an intramolecular gold-catalysed addition of a secondary amine to an internal alkyne (Scheme 2).[20] Treatment of pyrrolidine **4** with a catalytic gold complex in the presence of $AgSbF_6$ gave a mixture of 5-*exo-dig* and 6-*endo-dig* cyclization products **5** and **6**, respectively. With triethylphoshine as ligand, a 1:2 ratio was obtained, while with bulky phosphine ligand **7**, 6-*endo* product **6** was formed almost exclusively.

A similar cyclization process to form a nitrogen-bridgehead compound was used in the total synthesis of commu-

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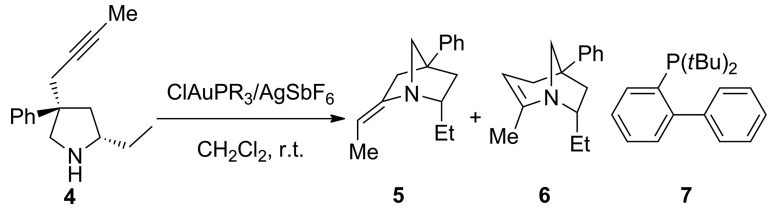
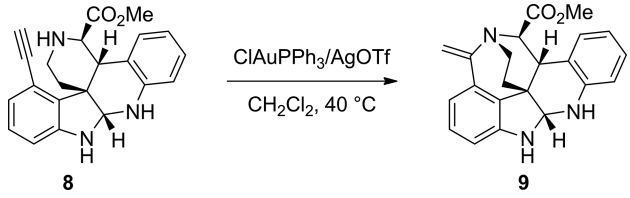


Scheme 2. Formation of bicyclic amines by a gold-catalysed hydroamination (ref.[20]).

nesin B reported by Crawley and Funk.[21] There, a gold-catalysed 7-*exo*-*dig* cyclization of **8** produced hexacyclic compound **9** in 89% yield (Scheme 3).



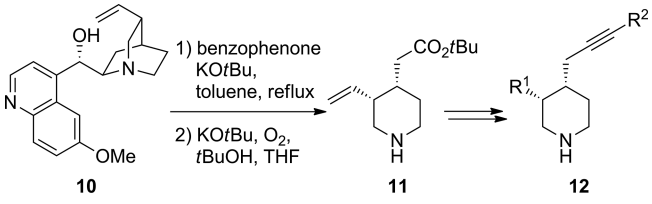
Scheme 3. Gold-catalysed hydroamination as a key step in the total synthesis of communesin B (ref.[21]).

Based on these findings, we imagined that the intramolecular hydroamination of 4-(prop-2-ynyl)piperidines catalysed by gold complexes could lead to substituted 2-alkylidenequinuclidines. In addition, late-transition-metal complexes such as silver complexes could be suitable catalysts for this hydroamination, as they have activation modes similar to those of related gold complexes.[18] Such a method could be useful for the preparation of pharmaceutical compounds, cinchona alkaloids and their analogues, or other compounds containing a quinuclidine ring system.

Results and Discussion

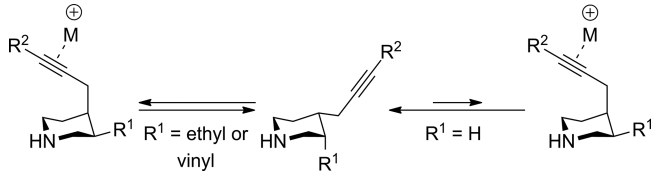
Substrate Synthesis

It has been reported that the cinchona alkaloid quinidine (**10**) may easily be transformed into enantiomerically pure 3,4-*cis*-substituted piperidine **11** (Scheme 4).[22]



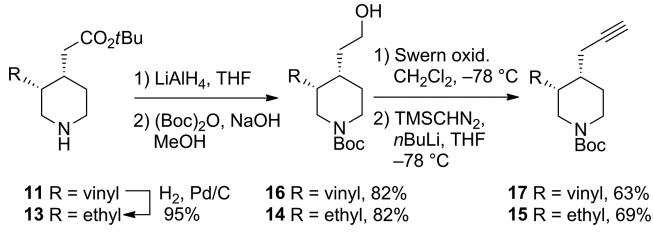
Scheme 4. Oxidation of quinidine to a 3,4-*cis*-disubstituted piperidine (cf. ref.[22]).

From **11**, the 4-(prop-2-ynyl)piperidines **12** required for the hydroamination reaction can be prepared by Sonogashira coupling[23] and alkylation reactions.[24] Apart from the fact that compounds **12** are enantiopure, the *cis* orientation of the two substituents should also facilitate the cyclization, consistent with the expectation that for a successful hydroamination the propynyl group should be in the axial position (see Scheme 5).



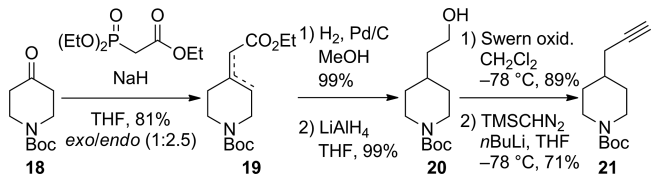
Scheme 5. Reactivity difference between mono- and disubstituted piperidines in hydroamination with formation of quinuclidines.

The syntheses of the disubstituted piperidines started with the hydrogenation of the vinyl group in the known enantiopure piperidine **11**[22] to give **13** (Scheme 6). Alkynes **15** and **17** were obtained in a four-step procedure by starting from **13** and **11**, respectively. First, the *tert*-butyl esters were reduced with $LiAlH_4$ to their corresponding alcohols, and subsequent Boc (*tert*-butoxycarbonyl) protection of the amine group gave **14** and **16** in good yields. Swern oxidation of the alcohols gave the required aldehydes, which were converted into alkynes **15** and **17** by a Seyferth–Gilbert homologation[25] with trimethylsilyldiazomethane and *n*-butyllithium in THF.



Scheme 6. Synthesis of *cis*-disubstituted 4-(prop-2-yn-1-yl)piperidines **15** and **17** (TMS = trimethylsilyl).

4-Propynylpiperidine **21** was prepared in order to compare the reactivity of monosubstituted species with *cis*-disubstituted piperidines (Scheme 7).



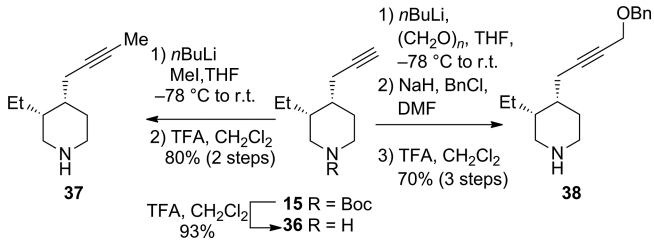
Scheme 7. Synthesis of Boc-protected 4-(prop-2-yn-1-yl)piperidine **21**.

N-Boc-protected piperidone **18** was subjected to a Horner–Wadsworth–Emmons olefination reaction with triethyl phosphonoacetate and sodium hydride, leading to a 1:2.5 mixture of *exo*/*endo* isomers **19** in 81% yield.[26] Next,

the mixture of isomers was hydrogenated to give the saturated ester, which was reduced to alcohol **20** with $LiAlH_4$ in THF. Swern oxidation to the aldehyde was followed by a Seyferth–Gilbert homologation to give alkyne **21** in 71% yield.

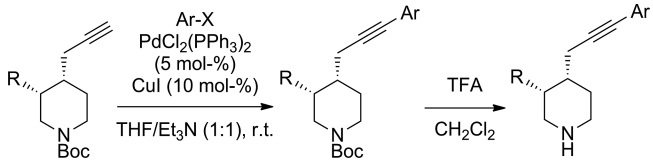
Aryl-substituted alkynes **22**–**28** were obtained in yields of 72–95% (Table 1) by the slightly modified Sonogashira coupling developed by Hoffmann for the coupling of aryl halides onto 10,11-didehydrocinchona alkaloids.[27] To obtain the free amine, the Boc group was cleaved off with a 1:10 mixture of TFA (trifluoroacetic acid)/dichloromethane to give **29**–**35** in good to excellent yields.

The Boc group of alkyne **15** was also removed in excellent yield with a 1:10 mixture of TFA/dichloromethane to give **36**, as shown in Scheme 8. Methylation of **15** with *n*-butyllithium and methyl iodide in THF followed by Boc removal gave alkyne **37**. Alkyne **15** also served as the starting material for the preparation of benzyl ether **38** in an overall yield of 70% (Scheme 8).



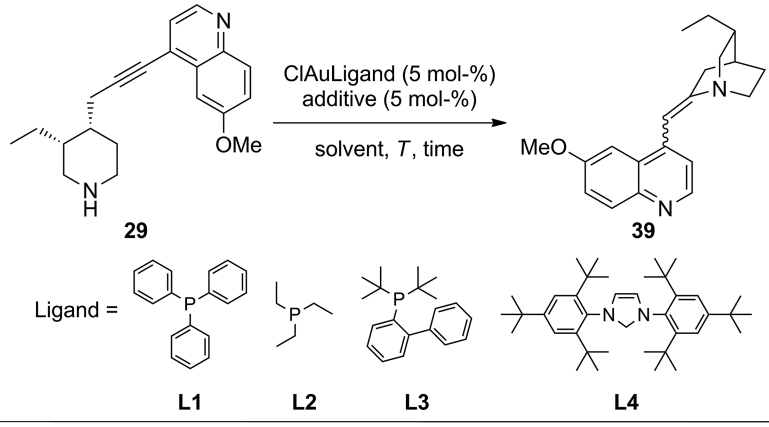
Scheme 8. Synthesis of piperidines **36**–**38**.

Table 1. Formation of substituted piperidines by Sonogashira coupling and Boc removal.



Entry	Starting material	R	Ar–X	Product of Sonogashira coupling (yield [%])	Product of Boc removal (yield [%])
1	**15**	ethyl	4-bromo-6-methoxyquinoline	**22** (91)	**29** (88)
2	**15**	ethyl	4-bromopyridine	**23** (72)	**30** (78)
3	**15**	ethyl	iodobenzene	**24** (80)	**31** (97)
4	**15**	ethyl	1-iodonaphthalene	**25** (88)	**32** (95)
5	**17**	vinyl	iodobenzene	**26** (92)	**33** (91)
6	**21**	H	4-bromo-6-methoxyquinoline	**27** (95)	**34** (75)
7	**21**	H	iodobenzene	**28** (74)	**35** (99)

Table 2. Catalyst screening for the hydroamination.



Entry[a]	Ligand	Additive	Solvent	Temperature [°C]	Time [h]	Conversion [%][b]
1[c]	**L1**	$AgSbF_6$	CH_2Cl_2	room temp.	16	<10
2[c]	**L1**	AgOTf	CH_2Cl_2	room temp.	16	<10
3[c]	**L2**	AgOTf	CH_2Cl_2	room temp.	16	<10
4[c]	**L3**	AgOTf	CH_2Cl_2	room temp.	16	<10
5	**L4**	AgOTf	CH_2Cl_2	room temp.	16	0
6	**L1**	AgOTf	toluene	100	6	100
7[d]	–	AgOTf	toluene	100	2	100

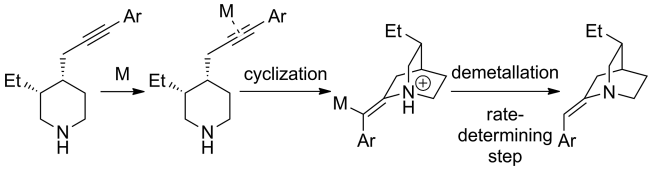
[a] The reaction was carried out with a substrate concentration of 0.3 M. [b] Conversion determined by ^1H NMR spectroscopy. [c] Longer reaction times gave no more conversion. [d] The reaction was carried out in the absence of any gold complex.

Catalyst Screening

We started our screening for the best catalyst for the intramolecular hydroamination of alkyne **29** with $ClAuPPh_3$, with $AgSbF_6$ as the additive (Table 2, Entry 1), in dichloromethane at room temperature. Unfortunately, after 16 h, only a small amount of the product was formed.

It has been reported that sulfonate counterions can be crucial for a good conversion in transition-metal-catalysed hydroamination reactions.[28] Thus, we changed the additive to silver triflate, but no improvement in conversion was observed (Table 2, Entry 2). Recently, Xu's group reported that the reaction rate of gold-catalysed hydroamination reactions with alkynes can be accelerated by the presence of relatively electron-rich ligands on the gold atom, such as **L2**–**L4** in Table 2 (Table 2, Entries 3–5).[29] Triethylphosphine (**L2**) (Table 2, Entry 3) led to a fast degradation of the catalyst, and only a small amount of product was observed. With the more bulky ligand **L3**, a poor conversion was also observed (Table 2, Entry 4). NHC ligand **L4**, which is considered to be strongly electron-donating,[30] gave no conversion at all (Table 2, Entry 5). Subsequently, the reaction with the gold complex containing **L1** was carried out at elevated temperature in toluene. Fortunately, at 100 °C, the complex with **L1** gave full conversion after 6 h (Table 2, Entry 6). As a control experiment, silver triflate was tested in the absence of any gold complex (Table 2, Entry 7). To our surprise, full conversion was now observed after only 2 h at 100 °C.

A likely mechanism of the hydroamination process is shown in Scheme 9. Activation of the alkyne occurs by complexation with the metal atom, and this is followed by attack of the secondary amine onto the alkyne. The resulting intermediate undergoes demetallation through proton transfer from the protonated quinuclidine to the double bond to give the (*Z*) isomer. Xu reported that demetallation is the rate-determining step in the hydroamination of alkynes catalysed by gold complexes.[29]



Scheme 9. Mechanism of the late-transition-metal-catalysed hydroamination of alkynes.

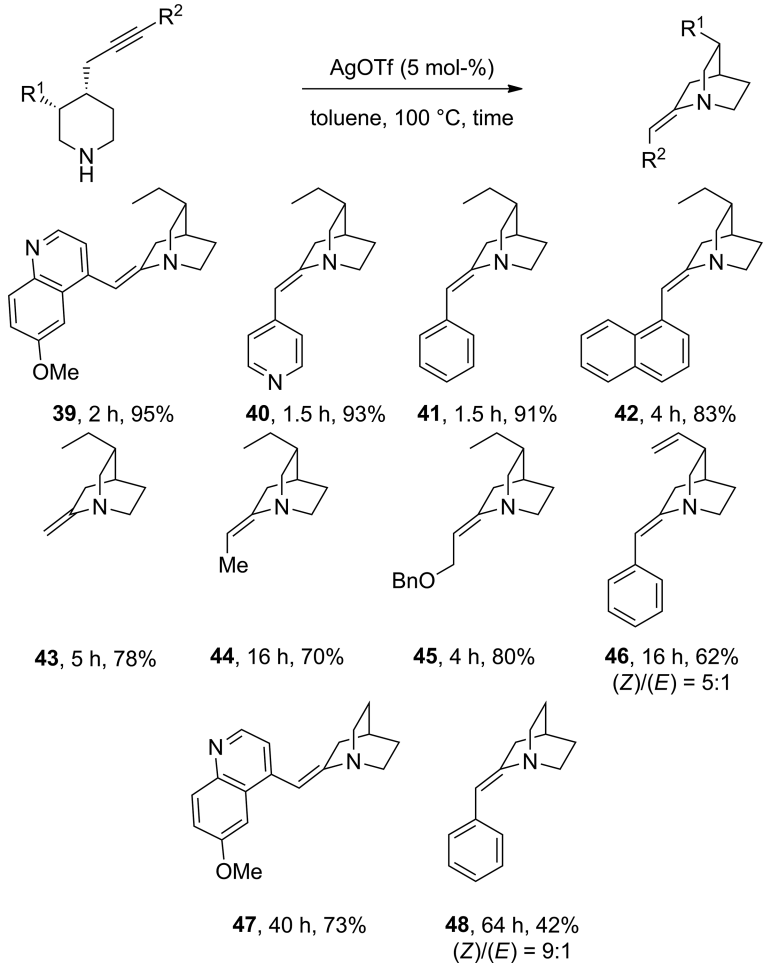
Because gold and silver are not very different chemically, it can be presumed that the demetallation step is also rate-determining for silver complexes. Possible differences in the reactivity of gold and silver complexes may be attributed to the fact that gold is more electronegative than silver (Au = 2.4 vs. Ag = 1.9).[31] This results in a stronger interaction of the alkyne moiety with the gold atom than with the silver atom. As a result, cleavage of a carbon–gold bond in the cyclized product (Scheme 9) is likely to be more difficult than that of a carbon–silver bond. Overall, this may cause silver triflate to be a more effective catalyst in the hydroamination reaction than the gold complexes shown in Table 2.

Reaction Scope

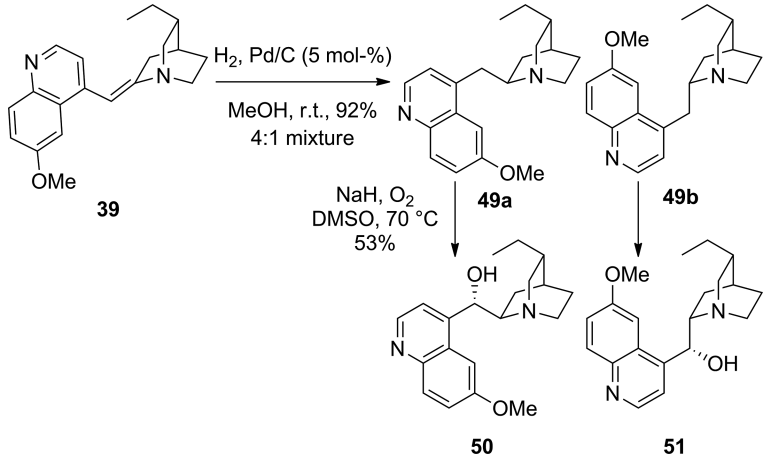
Using the optimized conditions, the reaction scope was investigated (Scheme 10). The product (i.e., **39**) of the cyclization of **29** in Table 2 was obtained in 95% isolated yield. To our surprise, **39** was isolated exclusively as the (*E*) isomer. So apparently, after cyclization, the initially formed (*Z*) isomer isomerizes to the more stable (*E*) isomer. The pyridine, benzene, and naphthalene analogues (i.e., **40**–**42**) could also be isolated in high yield as pure (*Z*) isomers. If the conditions of Table 2, Entry 6 were used, i.e., with the addition of the gold complex with **L1**, the yield of **41** was only 40% after 40 h. Terminal alkyne **36** (Scheme 8) gave the corresponding product (i.e., **43**) in good yield (78%). Aliphatic internal alkynes **37** and **38** cyclized to give the corresponding methyl- and benzyloxy-substituted products (i.e., **44** and **45**) in 70 and 80% yields, respectively. The cyclization to give **45** was slow at room temperature, with only 8% conversion observed after 8 h, while at 50 °C the conversion was >90% after 8 h. Vinyl-substituted piperidine **33** cyclized cleanly to give product **46**, and reaction at the vinyl group was observed. Nevertheless, 50 mol-% of AgOTf was needed to obtain full conversion. Product **46** was obtained as a 5:1 mixture of (*Z*)/(*E*) isomers. Unsubstituted piperidines **34** and **35** cyclized much more slowly than the corresponding ethyl- or vinyl-substituted substrates. For the cyclization to **47**, an extra 5 mol-% of AgOTf was added after 24 h to reach full conversion, and the product was isolated in 73% yield as the (*E*) isomer. For the cyclization of **35**, 20 mol-% of catalyst was used, and after stirring for 60 h, only 50% conversion was observed. The addition of more AgOTf did not improve the conversion, but **48** could be isolated in 42% yield as a 9:1 mixture of (*Z*)/(*E*) isomers. The longer reaction times for the cyclizations of monosubstituted piperidines indicate that there is a stronger preference for equatorial orientation of the alkyne moiety in these substrates compared to 3,4-*cis*-disubstituted piperidines (see Scheme 5).

Starting from **29**, dihydroquinidine (**50**), and dihydroquinine (**51**) could be obtained in two steps after the initial silver-catalysed cyclization (Scheme 11).[32]

The double bond of **39** was hydrogenated in the presence of Pd/C in methanol to give a 4:1 inseparable mixture of diastereoisomers **49a/49b**. Oxidation of the diastereoisomers by molecular oxygen in DMSO gave a 10:2.5:3:0.5 mixture of dihydroquinidine (**50**), dihydroquinine (**51**), *epi*-dihydroquinidine, and *epi*-dihydroquinine, respectively.[32] After separation, a mixture of dihydroquinidine (**50**) and dihydroquinine (**51**) was obtained in a yield of 53%.[33]



Scheme 10. Scope of the silver-catalysed hydroamination reaction.



Scheme 11. Synthesis of dihydroquinidine (**50**) and dihydroquinine (**51**).

Conclusions

A new approach to substituted 2-alkylidenequinuclidines has been developed. The key step is a silver triflate catalysed intramolecular hydroamination reaction of 4-(prop-2-yn-1-yl)piperidines. These piperidines were easily prepared by a Seyferth–Gilbert homologation followed by Sonogashira coupling or alkylation reactions. 2-Alkylidenequinuclidines were obtained in moderate to excellent yields, and in most examples as the (*Z*) isomers. If the alkyne was substituted with a quinoline, complete isomerization to the (*E*) isomer occurred. *cis*-Disubstituted piperidines reacted much more quickly than monosubstituted piperidines, consistent with the expectation that the propynyl group prefers the axial

position in these compounds. After the cyclization, the cinchona alkaloids dihydroquinidine and dihydroquinine could be obtained in a two-step procedure.

Experimental Section

General: Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Toluene and dichloromethane were freshly distilled from calcium hydride. Tetrahydrofuran and diethyl ether were freshly distilled from sodium with benzophenone as indicator. Thin layer chromatography (TLC) was performed with aluminum sheets, silica gel 60 F254. Column chromatographic separations were performed by using silica gel 60 Å, 0.032–0.063 mm. Infrared spectra were obtained from a neat thin film. Nuclear magnetic resonance (NMR) spectra were obtained with either a 400 or a 500 MHz instrument and are reported in ppm on the δ scale, relative to chloroform (δ = 7.26 ppm for ^{1}H NMR and δ = 77.0 ppm for ^{13}C NMR). Spin multiplicity is described by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, and br. = broad. Coupling constants (J) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded with proton decoupling as APT (attached proton test) spectra. Accurate mass data were obtained by fast atom bombardment (FAB) or electron-spray ionization (ESI) high resolution mass spectrometry.

***tert*-Butyl 2-[(3*R*,4*S*)-3-Ethylpiperidin-4-yl]acetate (13):** Piperidine **11** (8.4 g, 37.3 mmol)[22] was dissolved in methanol (200 mL). Pd/C (10 wt.-%; 1.98 g, 1.86 mmol) was added, and the mixture was stirred under hydrogen at room temperature overnight. The resulting mixture was filtered through Celite, and the solvent was evaporated under reduced pressure to give **13** (8.1 g, 35.6 mmol, 95%) as a yellowish oil. $[\alpha]_D$ = +0.71 (c = 0.57, MeOH). IR (neat): $\tilde{\nu}$ = 2963, 2930, 2874, 1725, 1392, 1255, 1149 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.89–2.92 (m, 1 H), 2.84–2.70 (m, 3 H), 2.20 (br., 3 H), 1.50–1.48 (m, 4 H), 1.45 (s, 9 H), 1.39–1.23 (m, 2 H), 0.91 (t, J = 7.36 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 79.8, 47.8, 44.5, 39.5, 36.9, 35.0, 29.0, 27.9, 19.4, 11.8 ppm. HRMS (FAB): calcd. for $C_{13}H_{26}NO_2$ [M + H]$^+$ 228.1964; found 228.1967.

***tert*-Butyl (3*R*,4*S*)-3-Ethyl-4-(2-hydroxyethyl)piperidine-1-carboxylate (14):** A solution of **13** (8.1 g, 35.6 mmol) in THF (50 mL) was added dropwise to $LiAlH_4$ (1.6 g, 42.8 mmol) in THF (200 mL) at 0 °C. The resulting mixture was warmed up to room temperature and stirred for 1 h. Then THF (250 mL) was added, followed by a careful quench with water (2.1 mL; 1.3 g/g $LiAlH_4$), NaOH (15% aq.; 2.1 mL; 1.3 g/g $LiAlH_4$), and water (5.2 mL; 3.25 g/g $LiAlH_4$). The resulting mixture was stirred vigorously for 15 min. Next, the mixture was filtered, and the filtrate was extracted three times with diethyl ether. The solvent was removed from the combined organic extracts under reduced pressure.

The residue was dissolved in methanol (120 mL), and $(Boc)_2O$ (9.3 g, 42.7 mmol) and NaOH (1.7 g, 42.7 mmol) were added. The resulting mixture was stirred overnight. The crude material was concentrated. The residue was dissolved in EtOAc, and water was added. After separation of the layers, the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, and dried with $MgSO_4$. The crude product was concentrated under reduced pressure, and the product was purified by flash column chromatography (petroleum ether/EtOAc, 2:1) to give **14** (7.5 g, 29.2 mmol, 82%) as a yellowish oil. $[\alpha]_D$ = +17.1 (c = 0.44, MeOH). IR (neat): $\tilde{\nu}$ = 3428, 2966, 2931, 2873, 1693, 1669, 1430, 1391, 1245, 1167 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.02–3.94 (br., 2 H), 3.69 (br., 2 H), 2.98 (br., 1 H), 2.89–2.86 (m, 1 H), 1.80 (m, 1 H), 1.62–1.52 (m, 2 H), 1.47 (s, 9 H), 1.44 (m, 3 H), 1.27–1.16 (m, 2 H), 0.97 (t, J = 7.3 Hz, 3 H), (OH is missing) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 79.1, 60.2, 46.3, 43.1, 39.9, 35.5, 34.9, 28.3, 27.2, 16.8, 12.2 ppm. HRMS (FAB): calcd. for $C_{14}H_{28}NO_3$ [M + H]$^+$ 258.2069; found 258.2064.

***tert*-Butyl (3*R*,4*S*)-3-Ethyl-4-(2-oxoethyl)piperidine-1-carboxylate:** Oxalyl chloride (4.1 mL, 48.3 mmol) was dissolved in CH_2Cl_2 (250 mL), and the solution was cooled to –78 °C. DMSO (7.5 mL, 105 mmol) was added dropwise, and the resulting mixture was stirred for 30 min. Next, a solution of **14** (5.4 g, 21.0 mmol) in CH_2Cl_2 (35 mL) was added dropwise. Stirring was continued for 1 h. Et_3N (15 mL, 109 mmol) was added, and the resulting mixture was warmed up to room temperature. Next, water was added, and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ and brine. The solution was dried with $MgSO_4$, and the solvent was evaporated. The product was purified by flash column chromatography (petroleum ether/EtOAc, 4:1) to give the title aldehyde (5.2 g, 20.4 mmol, 97%) as a colourless oil. $[\alpha]_D$ = +18.3 (c = 0.57, MeOH). IR (neat): $\tilde{\nu}$ = 2964, 2931, 2874, 1692, 1670, 1429, 1391, 1365, 1244, 1140, 1124 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (d, J = 1.68 Hz, 1 H), 3.92–2.84 (br., 1 H), 3.59 (br., 1 H), 3.13 (br., 1 H), 2.97–2.94 (m, 1 H), 3.40 (t, J = 8.8 Hz, 2 H), 2.32 (br., 1 H), 1.51–1.38 (br. m, 12 H), 1.28–1.57 (m, 2 H), 0.94 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 154.5, 78.2, 47.2, 45.8, 42.2, 39.4, 33.0, 27.9, 26.9, 17.2, 11.7 ppm. HRMS (FAB): calcd. for $C_{14}H_{26}NO_3$ [M + H]$^+$ 256.1913; found 256.1910.

***tert*-Butyl (3*R*,4*R*)-3-Ethyl-4-(prop-2-yn-1-yl)piperidine-1-carboxylate (15):** Trimethylsilyldiazomethane (2 M in hexane; 15 mL, 30.5 mmol) was dissolved in THF (100 mL), and the solution was cooled to –78 °C. Next, *n*-butyllithium (1.6 M in hexane; 18 mL, 28.4 mmol) was added, and the mixture was stirred for 30 min. A solution of the above aldehyde *tert*-butyl (3*R*,4*S*)-3-ethyl-4-(2-oxoethyl)piperidine-1-carboxylate (5.2 g, 20.3 mmol) in THF (20 mL) was added, and stirring was continued at –78 °C for 30 min. The mixture was warmed up to room temperature, and then it was quenched with saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, and dried with $MgSO_4$, and the solvent was evaporated in vacuo. The product was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give alkyne **15** (3.6 g, 14.3 mmol, 71%) as a white solid. m.p. 55–56 °C. $[\alpha]_D$ = +30.0 (c = 0.38, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2967, 2931, 2872, 1686, 1391, 1242, 1164, 1137, 629 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.02–3.94 (br., 1 H), 3.79–3.65 (br., 1 H), 3.01 (br., 1 H), 2.87–2.75 (m, 1 H), 2.14 (d, J = 7.6 Hz, 2 H), 1.97 (t, J = 2.6 Hz, 1 H), 1.86 (m, 1 H), 1.60 (m, 1 H), 1.51 (m, 1 H), 1.45 (s, 9 H), 1.40 (m, 1 H), 1.23–1.13 (m, 2 H), 0.97 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 81.8, 78.2, 69.1, 45.5 42.3, 38.6, 38.3, 27.7, 26.4, 21.3, 16.0, 11.6 ppm. HRMS (FAB): calcd. for $C_{15}H_{26}NO_2$ [M + H]$^+$ 252.1964; found 252.1964.

***tert*-Butyl (3*R*,4*S*)-4-(2-Hydroxyethyl)-3-vinylpiperidine-1-carboxylate (16):** A solution of **11** (3.45 g, 20 mmol)[22] in THF (25 mL) was added dropwise to $LiAlH_4$ (0.91 g, 24.0 mmol) in THF (100 mL) at 0 °C. The resulting mixture was warmed up to room temperature and stirred for 1 h. It was then diluted with THF (100 mL) and carefully quenched with water (1.2 mL; 1.3 g/g $LiAlH_4$), NaOH (15% aq.; 1.2 mL; 1.3 g/g $LiAlH_4$), and water (3.0 mL; 3.25 g/g $LiAlH_4$). The resulting mixture was stirred vigorously for 15 min. Next, the mixture was filtered, and the filtrate was extracted three

times with diethyl ether. The solvent was removed from the combined organic extracts under reduced pressure.

The residue was dissolved in methanol (70 mL). Then $(Boc)_2O$ (5.2 g, 24 mmol) and NaOH (0.96 g, 24 mmol) were added, and the resulting mixture was stirred overnight. The mixture was concentrated in vacuo, the residue was dissolved in EtOAc, and then water was added. After separation of the layers, the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, and dried with $MgSO_4$. The solvent was removed in vacuo, and the product was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give alcohol **16** (4.2 g, 16.4 mmol, 82%) as a sticky, colourless oil. $[\alpha]_D$ = +58.0 (c = 0.51, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3428, 2975, 2929, 2862, 1693, 1670, 1430, 1392, 1246, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.82 (m, 1 H), 5.15 (s, 1 H), 5.12 (d, J = 4.2 Hz, 1 H), 4.15 (br., 1 H), 3.98 (d, J = 12.6 Hz, 1 H), 3.71 (d, J = 2.8 Hz, 2 H), 3.02 (dd, J = 13.2, 2.9 Hz, 1 H), 2.93–2.78 (br., 1 H), 2.30 (br., 1 H), 1.83 (m, 1 H), 1.63–1.52 (m, 3 H), 1.47 (s, 9 H), 1.39 (m, 1 H) ppm; OH signal missing. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 135.7, 116.6, 79.2, 59.7, 43.2, 43.0, 39.8, 35.7, 34.9, 28.2, 27.3 ppm. HRMS (FAB): calcd. for $C_{14}H_{26}NO_3$ $[M + H]^+$ 256.1907; found 256.1895.

***tert*-Butyl (3*R*,4*S*)-4-(2-Oxoethyl)-3-vinylpiperidine-1-carboxylate:** Oxalyl chloride (2.2 mL, 25.2 mmol) was dissolved in CH_2Cl_2 (150 mL), and the solution was cooled to –78 °C. DMSO (3.9 mL, 55.0 mmol) was added dropwise, and the resulting mixture was stirred for 30 min. Next, a solution of **16** (2.8 g, 11.0 mmol) in CH_2Cl_2 (25 mL) was added dropwise, and stirring was continued for 1 h. Et_3N (8.0 mL, 57.2 mmol) was added, and the resulting mixture was warmed up to room temperature. Water was added, and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ and brine. The solution was dried with $MgSO_4$, and the solvent was evaporated. The product was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give the title aldehyde (2.6 g, 10.4 mmol, 95%) as a colourless oil. $[\alpha]_D$ = +50.1 (c = 1.05, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2975, 2929, 2861, 1723, 1688, 1424, 1365, 1244, 1169, 1146 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.79 (d, J = 5.1 Hz, 1 H), 5.80 (m, 1 H), 5.16 (d, J = 10.4 Hz, 1 H), 5.09 (d, J = 18.0 Hz, 1 H), 4.12 (br., 1 H), 3.93 (dd, J = 13.2, 1.4 Hz, 1 H), 3.09 (dd, J = 13.2, 2.8 Hz, 1 H), 2.98–2.81 (br., 1 H), 2.49 (m, 1 H), 2.31 (m, 3 H), 1.53–1.40 (m, 11 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 154.3, 134.9, 117.0, 78.8, 48.3, 46.8, 42.2, 41.9, 32.7, 27.9, 27.0 ppm. HRMS (ESI): calcd. for $C_{14}H_{23}NO_3Na$ $[M + Na]^+$ 276.1570; found 276.1561.

***tert*-Butyl (3*R*,4*R*)-4-(Prop-2-yn-1-yl)-3-vinylpiperidine-1-carboxylate (17):** Trimethylsilyldiazomethane (2 M in hexane; 1.0 mL, 2.0 mmol) was dissolved in THF (10 mL), and the solution was cooled to –78 °C. *n*-Butyllithium (1.6 M in hexane; 1.25 mL, 2.0 mmol) was added, and the mixture was stirred for 30 min. A solution of the above aldehyde *tert*-butyl (3*R*,4*S*)-4-(2-oxoethyl)-3-vinylpiperidine-1-carboxylate (506 mg, 2.0 mmol) in THF (3 mL) was added, and stirring was continued at –78 °C for 30 min. The mixture was warmed up to room temperature, and then quenched with saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, and dried with $MgSO_4$, and the solvent was evaporated. The product was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give alkyne **17** (330 mg, 1.3 mmol, 66%) as a colourless oil. $[\alpha]_D$ = +36.9 (c = 0.57, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2975, 2928, 2861, 2042, 1689, 1423, 1392, 1244, 1166, 1142 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.77 (dt, J = 17.2, 9.9 Hz, 1 H), 5.22 (dd, J = 16.0, 2.0 Hz, 1 H), 5.16 (dd, J = 10.4, 1.8 Hz, 1 H), 4.18 (br., 1 H), 4.02 (d, J = 12.8 Hz, 1 H), 3.00 (dd, J = 13.3, 3.0 Hz, 1 H), 2.81 (br., 1 H), 2.50 (br., 1 H), 2.17 (dd, J = 7.8, 2.6 Hz, 2 H), 2.00 (t, J = 2.6 Hz, 1 H), 1.90–1.81 (m, 1 H), 1.64 (m, 1 H), 1.47 (s, 9 H), 1.42 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7, 134.4, 117.3, 82.4, 79.0, 69.4, 43.0, 41.7, 38.5, 28.1, 26.9, 22.4 ppm; signal of 1 C atom next to NBoc not observed. HRMS (ESI): calcd. for $C_{15}H_{23}NO_2Na$ $[M + Na]^+$ 272.1621; found 272.1616.

***tert*-Butyl 4-(2-Ethoxy-2-oxoethylidene)piperidine-1-carboxylate (19a) and *tert*-Butyl 4-(2-Ethoxy-2-oxoethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (19b):** A solution of triethyl phosphonoacetate (9.13 mL, 46 mmol) and NaH (60 wt.-%; 2.9 g, 73.6 mmol) in THF (75 mL) was stirred at room temperature under nitrogen. After 1 h, **18** (6.50 g, 32.84 mmol) was added, and the resulting mixture was stirred at room temperature until the reaction was complete (2 h). NH_4Cl was then added to the flask to quench the reaction. The aqueous layer was extracted with CH_2Cl_2, and the resulting organic layers were combined, washed with brine, and dried with $MgSO_4$. Concentration under reduced pressure gave the crude product, which was purified by flash chromatography. The mixture of *endo*- and *exo*-alkenes was separated by flash chromatography (EtOAc/petroleum ether, 1:6) to give the alkenes (7.15 g, 26.2 mmol, 81%) in a 1:2.5 *exo*/*endo* ratio, *exo* isomer **19a** as a white solid, *endo* isomer **19b** as a colourless oil.

Data for 19a: M.p. 68–71 °C. IR (neat): $\tilde{\nu}$ = 2978, 1696, 1652, 1477, 1394, 1253, 1164, 1140, 1115, 1038, 997 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.73 (s, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 3.58–3.41 (m, 4 H), 2.95 (t, J = 5.5 Hz, 2 H), 2.35–2.25 (m, 2 H), 1.49 (s, 9 H), 1.30 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 157.6, 154.4, 115.1, 79.6, 59.5, 36.2, 29.3, 28.2, 14.1 ppm.

Data for 19b: IR (neat): $\tilde{\nu}$ = 2977, 1734, 1693, 1413, 1365, 1284, 1239, 1170, 1149, 1108, 1031 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.49 (s, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.86 (d, J = 1.2 Hz, 2 H), 3.47 (t, J = 5.7 Hz, 2 H), 2.98 (s, 2 H), 2.10 (d, J = 1.1 Hz, 2 H), 1.42 (s, 9 H), 1.22 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 154.6, 129.8, 122.2, 79.3, 60.4, 43.0, 42.5, 28.2, 28.1, 14.0 ppm; signal of 1 C atom next to NBoc not observed. HRMS (FAB): calcd. for $C_{14}H_{24}NO_4$ $[M + H]^+$ 269.1627; found 269.1621.

***tert*-Butyl 4-(2-Ethoxy-2-oxoethyl)piperidine-1-carboxylate:** The above mixture of **19** (7.02 g, 25.89 mmol) was dissolved in ethanol (50 mL). Pd/C (5 mol-%; 1.33 g, 1.29 mmol) was added, and the reaction mixture was stirred under hydrogen until the reaction was complete. The reaction mixture was filtered through a pad of Celite, and the solvent was evaporated under reduced pressure to give the title compound (6.28 g, 23.18 mmol, 90%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 2977, 2930, 1732, 1688, 1419, 1365, 1286, 1237, 1154, 1119, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.15 (q, J = 7.1 Hz, 2 H), 4.09 (d, J = 13.3 Hz, 2 H), 2.73 (dt, J = 13.3, 2.5 Hz, 2 H), 2.24 (d, J = 7.1 Hz, 2 H), 2.05–1.84 (m, 1 H), 1.70 (d, J = 12.7 Hz, 2 H), 1.47 (s, 9 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.17 (m, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.3, 154.6, 79.2, 60.1, 41.0, 32.9, 31.6, 29.5, 28.3, 14.1 ppm. HRMS (FAB): calcd. for $C_{14}H_{26}NO_4$ $[M + H]^+$ 271.1784; found 271.1783.

***tert*-Butyl 4-(2-Hydroxyethyl)piperidine-1-carboxylate (20):** The above ester *tert*-butyl 4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (6.28 g, 23.18 mmol) was dissolved in THF (150 mL), and the solution was cooled to 0 °C. A solution of $LiAlH_4$ in THF (1.0 M; 23.28 mL) was added. The reaction mixture was warmed up to room temperature over 1 h, then it was cooled again to 0 °C and carefully quenched by the sequential addition of water (50 mL), NaOH (3 M aq.; 50 mL), and water (100 mL). The mixture was stirred at the same temperature for 30 min, then it was filtered

through a pad of Celite to remove solids. The layers were separated, and the aqueous layer was washed with EtOAc three times. The combined organic layers were washed with brine, dried, and filtered, and the solvent was evaporated to give alcohol **20** (5.45 g, 23.81 mmol, 100%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3419, 2924, 2853, 1691, 1666, 1421, 1365, 1276, 1245, 1161, 1057, 975, 867, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.08 (br., 2 H), 3.70 (dt, J = 10.8, 5.5 Hz, 2 H), 2.69 (t, J = 11.4 Hz, 2 H), 1.74 (br., 1 H), 1.67 (d, J = 13.3 Hz, 2 H), 1.64–1.56 (m, 1 H), 1.52 (dd, J = 13.1, 6.5 Hz, 2 H), 1.45 (s, 9 H), 1.12 (m, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 154.6, 79.1, 60.0, 39.1, 32.4, 31.9, 28.3 ppm; signals of C atoms next to NBoc not observed. HRMS (FAB): calcd. for $C_{12}H_{24}NO_3$ $[M + H]^+$ 229.1678; found 229.1680.

***tert*-Butyl 4-(2-Oxoethyl)piperidine-1-carboxylate:** Dimethyl sulfoxide (8.4 mL, 119 mmol) was added dropwise to a solution of oxalyl chloride (4.6 mL, 54.7 mmol) in CH_2Cl_2 (275 mL) at –78 °C. After 30 min, a solution of alcohol **20** (5.45 g, 23.81 mmol) in CH_2Cl_2 (40 mL) was slowly added. After 1 h, Et_3N (17 mL, 123 mmol) was added, and the mixture was warmed up to room temperature. Then water was added, and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by flash chromatography (EtOAc/petroleum ether, 1:2) to give the title compound (4.79 g, 21.1 mmol, 89%) as an orange solid. M.p. 37–38 °C. IR (neat): $\tilde{\nu}$ = 2975, 2925, 2852, 2719, 1723, 1688, 1421, 1365, 1280, 1245, 1167, 1135 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.79 (t, J = 1.7 Hz, 1 H), 4.10 (br., 2 H), 2.76 (t, J = 11.9 Hz, 2 H), 2.40 (dd, J = 6.7, 1.7 Hz, 2 H), 2.20–1.94 (m, 1 H), 1.70 (d, J = 13.7 Hz, 2 H), 1.46 (s, 9 H), 1.19 (m, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 201.3, 154.6, 79.3, 50.2, 43.5, 31.7, 30.5, 28.3 ppm. HRMS (FAB): calcd. for $C_{12}H_{22}NO_3$ $[M + H]^+$ 227.1521; found 227.1526.

***tert*-Butyl 4-(Prop-2-yn-1-yl)piperidine-1-carboxylate (21):** *n*-Butyllithium (1.6 M in hexane; 8.9 mL, 14.3 mmol) was added to a solution of trimethylsilyldiazomethane (2 M in hexane; 8.25 mL, 16.5 mmol) in THF (50 mL) at –78 °C. The reaction mixture was stirred for 45 min. Then a solution of the above aldehyde *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (2.5 g, 11.0 mmol) in THF (10 mL) was added, and stirring was continued at –78 °C for 1 h. Then the reaction mixture was warmed up to room temperature, and it was quenched with a saturated solution of NH_4Cl. The layers were separated, and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried with $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 6:1) gave alkyne **21** (1.75 g, 7.82 mmol, 71%) as a yellowish oil. IR (neat): $\tilde{\nu}$ = 3304, 3250, 2976, 2929, 2853, 1687, 1419, 1365, 1279, 1243, 1164, 1124, 632 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.12 (d, J = 13.4 Hz, 2 H), 2.70 (dt, J = 13.2, 2.6 Hz, 2 H), 2.16 (dd, J = 6.7, 2.7 Hz, 2 H), 2.00 (t, J = 2.7 Hz, 1 H), 1.77 (d, J = 15.3 Hz, 2 H), 1.64 (m, 1 H), 1.47 (s, 9 H), 1.21 (m, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 154.7, 82.2, 79.2, 69.5, 43.6, 35.3, 31.2, 28.3, 25.3 ppm. HRMS (FAB): calcd. for $C_{13}H_{22}NO_2$ $[M + H]^+$ 223.1572; found 223.1564.

General Procedure for Sonogashira Coupling: A mixture of THF and Et_3N (1:1, v/v) was prepared, and argon was bubbled through the mixture for 15 min. $PdCl_2(PPh_3)_2$ (5 mol-%) and CuI (10 mol-%) were added, and the bubbling of argon was continued for a further 15 min. Next, the aryl halide (1.5 equiv.) was added, followed by the alkyne (0.1 M). The resulting mixture was stirred at room temperature overnight, and then it was quenched with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, dried with $MgSO_4$, and concentrated under reduced pressure. The product was purified by flash chromatography.

General Procedure for Boc Deprotection: The Boc-protected piperidine (0.1 M) was dissolved in CH_2Cl_2, and the solution was cooled to 0 °C. TFA (as a solution of 10%, v/v, of TFA in CH_2Cl_2) was added dropwise, the mixture was warmed up to room temperature, and stirred overnight. It was then diluted with diethyl ether, and carefully treated with saturated aqueous K_2CO_3. The organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried with Na_2SO_4, and concentrated in vacuo to give the free amine.

4-{3-[(3*R*,4*R*)-3-Ethylpiperidin-4-yl]prop-1-yn-1-yl}-6-methoxyquinoline (29): According to the general procedure for Sonogashira coupling, alkyne **15** (252 mg, 1.0 mmol) was treated with 4-bromo-6-methoxyquinoline (355 mg, 1.5 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), and CuI (19 mg, 0.10 mmol) in THF/Et_3N (10 mL). The product was purified by flash chromatography (petroleum ether/EtOAc, 3:1) to give **22** (371 mg, 0.91 mmol, 91%) as a sticky, orange oil. $[\alpha]_D$ = +18.2 (c = 0.67, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2966, 2931, 2874, 1690, 1618, 1503, 1428, 1242, 1228, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, J = 4.4 Hz, 1 H), 8.01 (d, J = 12.8 Hz, 1 H), 7.50 (d, J = 2.8 Hz, 1 H), 7.44–7.38 (m, 2 H), 4.15–4.00 (br., 1 H), 3.97 (s, 3 H), 3.87–3.79 (br., 1 H), 3.10 (br., 1 H), 2.97–2.93 (m, 1 H), 2.59 (d, J = 7.8 Hz, 2 H), 2.10 (br., 1 H), 1.79–1.59 (br., 3 H), 1.49 (s, 9 H), 1.40–1.27 (m, 2 H), 1.04 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 154.9, 147.0, 144.0, 131.1, 129.1, 128.7, 123.8, 122.3, 103.4, 98.3, 79.2, 78.0, 55.4, 46.1, 42.8, 39.3, 39.1, 28.3, 27.2, 22.9, 16.9, 12.2 ppm.

According to the general procedure for Boc deprotection, **22** (332 mg, 0.81 mmol) was dissolved in CH_2Cl_2 (8 mL), and TFA (0.8 mL) was added. After workup, **29** (220 mg, 0.71 mmol, 88%) was obtained as an orange oil. $[\alpha]_D$ = +8.2 (c = 0.38, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3286, 2956, 2924, 2872, 2222, 1689, 1501, 1471, 1428, 1225, 910, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, J = 4.4 Hz, 1 H), 7.97 (d, J = 9.2 Hz, 1 H), 7.49 (d, J = 2.6 Hz, 1 H), 7.40–7.35 (m, 2 H), 3.95 (s, 3 H), 3.03 (d, J = 12.0 Hz, 1 H), 2.93 (d, J = 11.9 Hz, 1 H), 2.73 (d, J = 12.2 Hz, 2 H), 2.57 (d, J = 7.2 Hz, 2 H), 2.11 (m, 2 H), 1.71 (br., 3 H), 1.48–1.25 (m, 2 H), 0.98 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 146.7, 143.8, 130.8, 128.8, 128.5, 123.4, 122.0, 103.1, 98.7, 77.5, 55.0, 47.6, 44.6, 39.4, 37.8, 28.6, 21.3, 18.6, 11.7 ppm. HRMS (ESI): calcd. for $C_{20}H_{25}N_2O$ $[M + H]^+$ 309.1961; found 309.1970.

4-{3-[(3*R*,4*R*)-3-Ethylpiperidin-4-yl]prop-1-yn-1-yl}pyridine (30): According to the general procedure for Sonogashira coupling, alkyne **15** (500 mg, 1.98 mmol) was treated with 4-bromopyridine (469 mg, 2.97 mmol), $PdCl_2(PPh_3)_2$ (69 mg, 0.1 mmol), and CuI (38 mg, 0.2 mmol) in THF/Et_3N (20 mL). The product was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give **23** (470 mg, 1.43 mmol, 72%) as a sticky, orange oil. $[\alpha]_D$ = +25.4 (c = 0.26, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2968, 2930, 2873, 1686, 1592, 1391, 1343, 1242, 1164, 821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.57 (br., 2 H), 7.26 (d, J = 3.3 Hz, 2 H), 4.06–3.99 (m, 1 H), 3.76 (br., 1 H), 3.07 (br., 1 H), 2.92–2.83 (m, 1 H), 2.41 (d, J = 7.8 Hz, 2 H), 1.99 (br., 1 H), 1.64–1.53 (m, 3 H), 1.48 (s, 9 H), 1.33–1.20 (m, 2 H), 1.02 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 149.4, 131.8, 93.8, 79.4, 79.0, 46.0, 42.7, 39.2, 38.7, 28.8, 27.0, 23.1, 22.5, 16.6, 12.0 ppm.

According to the general procedure for Boc deprotection, **23** (460 mg, 1.4 mmol) was dissolved in CH_2Cl_2 (15 mL), and TFA (1.5 mL) was added. After workup, **30** (245 mg, 1.07 mmol, 78%) was obtained as an orange oil. $[\alpha]_D$ = +7.6 (c = 0.51, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3301, 2958, 2926, 2873, 2223, 1678, 1488, 1463,

821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, J = 4.4 Hz, 2 H), 7.25 (d, J = 4.4 Hz, 2 H), 3.02–2.97 (m, 1 H), 2.91 (dd, J = 12.6, 5.4 Hz, 1 H), 2.73–2.69 (m, 2 H), 2.42 (dd, J = 8.5, 2.5 Hz, 2 H), 2.05–2.00 (m, 1 H), 1.80 (br., 1 H), 1.67–1.59 (m, 3 H), 1.46–1.41 (m, 1 H), 1.39–1.28 (m, 1 H), 0.96 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 131.8, 125.4, 94.3, 79.1, 47.6, 44.5, 39.3, 37.4, 28.5, 21.0, 18.7, 11.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{21}N_2$ $[M + H]^+$ 229.1699; found 229.1710.

(3*R*,4*R*)-3-Ethyl-4-(3-phenylprop-2-yn-1-yl)piperidine (31): According to the general procedure for Sonogashira coupling, alkyne **15** (500 mg, 1.98 mmol) was treated with iodobenzene (0.33 mL, 2.97 mmol), $PdCl_2(PPh_3)_2$ (69 mg, 0.1 mmol), and CuI (38 mg, 0.2 mmol) in THF/Et_3N (20 mL). The product was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give **24** (520 mg, 1.58 mmol, 80%) as an orange oil. $[a]_D$ = +24.6 (c = 0.39, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2968, 2930, 2873, 1689, 1426, 1365, 1242, 1137, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (m, 2 H), 7.33–7.21 (m, 3 H), 4.06–3.99 (m, 1 H), 3.76 (br., 1 H), 3.08 (br., 1 H), 2.90 (m, 1 H), 2.39 (d, J = 7.5 Hz, 2 H), 1.98 (br., 1 H), 1.71 (br., 1 H), 1.61–1.54 (br., 2 H), 1.48 (s, 9 H), 1.32–1.20 (m, 2 H), 1.02 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 131.4, 128.5, 127.5, 123.7, 88.3, 81.7, 79.1, 46.2, 42.9, 39.3, 39.1, 28.3, 27.1, 23.1, 16.7, 12.2 ppm. HRMS (FAB): calcd. for $C_{21}H_{30}NO_2$ $[M + H]^+$ 328.2277; found 328.2273.

According to the general procedure for Boc deprotection, **24** (484 mg, 1.48 mmol) was dissolved in CH_2Cl_2 (15 mL), and TFA (1.5 mL) was added. After workup, **31** (326 mg, 1.43 mmol, 97%) was obtained as an orange oil. $[a]_D$ = +11.3 (c = 0.56, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3279, 2957, 2922, 2872, 2227, 1571, 1490, 1462, 1263, 755, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 2 H), 7.33–7.28 (m, 3 H), 3.00 (dd, J = 12.1, 4.0 Hz, 1 H), 2.94 (dd, J = 12.1, 4.2 Hz, 1 H), 2.71 (dd, J = 12.3, 3.2 Hz, 2 H), 2.40 (dd, J = 8.5, 3.0 Hz, 2 H), 2.02 (m, 1 H), 1.69–1.61 (m, 4 H), 1.46–1.35 (m, 2 H), 0.96 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.3, 128.0, 127.3, 123.8, 88.8, 81.4, 47.8, 44.7, 39.6, 37.8, 23.3, 21.1, 18.8, 11.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}N$ $[M + H]^+$ 228.1752; found 228.1750.

(3*R*,4*R*)-3-Ethyl-4-[3-(1-naphthyl)prop-2-yn-1-yl]piperidine (32): According to the general procedure for Sonogashira coupling, alkyne **15** (500 mg, 1.98 mmol) was treated with 1-iodonaphthalene (0.43 mL, 2.97 mmol), $Pd(Cl)_2(PPh_3)_2$ (69 mg, 0.1 mmol), and CuI (38 mg, 0.2 mmol) in THF/Et_3N (20 mL). The product was purified by flash column chromatography (petroleum ether/EtOAc, 20:1) to give **25** (654 mg, 1.73 mmol, 88%) as a viscous, orange oil. $[a]_D$ = +25.6 (c = 0.41, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2969, 2930, 2872, 1688, 1426, 1325, 1166, 829, 799 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (dd, J = 8.1, 0.7 Hz, 1 H), 7.86 (d, J = 7.3 Hz, 1 H), 7.81 (d, J = 8.2 Hz, 1 H), 7.62 (dd, J = 7.1, 1.0 Hz, 1 H), 7.58 (m, 1 H), 7.54 (m, 1 H), 7.43 (dd, J = 8.2, 7.2 Hz, 1 H), 4.15–4.04 (m, 1 H), 3.86 (br., 1 H), 3.12 (br., 1 H), 3.01–2.87 (m, 1 H), 2.56 (d, J = 7.9 Hz, 2 H), 2.08 (m, 1 H), 1.81 (m, 1 H), 1.66–1.55 (m, 2 H), 1.49 (s, 9 H), 1.47–1.40 (m, 1 H), 1.33–1.26 (m, 1 H), 1.06 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 133.2, 132.9, 129.9, 128.0, 127.8, 127.4, 126.0, 125.9, 125.0, 121.3, 93.2, 79.6, 78.9, 53.6, 46.0, 42.9, 39.2, 28.2, 27.1, 22.9, 16.5, 12.1 ppm. HRMS (FAB): calcd. for $C_{25}H_{32}NO_2$ $[M + H]^+$ 378.244; found 378.2433.

According to the general procedure for Boc deprotection, **25** (130 mg, 0.34 mmol) was dissolved in CH_2Cl_2 (3 mL), and TFA (0.3 mL) was added. After workup, free amine **32** (90 mg, 0.32 mmol, 95%) was obtained as an orange oil. $[a]_D$ = +9.1 (c = 0.33, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3057, 2957, 2924, 2871, 1688, 1460, 1439, 1200, 1175, 1135, 799, 774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, J = 8.8 Hz, 1 H), 7.85 (d, J = 8.4 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 1 H), 7.63 (dd, J = 7.1, 1.0 Hz, 1 H), 7.59–7.50 (m, 2 H), 7.42 (dd, J = 8.2, 7.2 Hz, 1 H), 3.10–3.05 (m, 1 H), 2.98 (dd, J = 12.8, 5.6 Hz, 1 H), 2.82–2.76 (m, 2 H), 2.59 (dd, J = 10.8, 2.0 Hz, 2 H), 2.15 (m, 1 H), 1.80–1.70 (m, 3 H), 1.53–1.42 (m, 3 H), 1.00 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.3, 133.0, 128.3, 127.1, 126.4, 125.1, 124.2, 121.5, 93.8, 79.5, 47.7, 44.7, 39.4, 37.9, 30.2, 28.7, 23.8, 21.4, 18.8, 11.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{24}N$ $[M + H]^+$ 278.1903; found 278.1924.

(3*R*,4*R*)-3-Ethenyl-4-(3-phenylprop-2-yn-1-yl)piperidine (33): According to the general procedure for Sonogashira coupling, alkyne **17** (328 mg, 1.32 mmol) was treated with iodobenzene (0.22 mL, 1.98 mmol), $Pd(Cl)_2(PPh_3)_2$ (46 mg, 0.067 mmol), and CuI (25 mg, 0.13 mmol) in THF/Et_3N (13 mL). The product was purified by flash column chromatography (petroleum ether/EtOAc, 20:1) to give **26** (394 mg, 1.21 mmol, 92%) as an orange oil. $[a]_D$ = +81.7 (c = 0.43, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2975, 2926, 2858, 2231, 1688, 1422, 1391, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 2 H), 7.31 (m, 3 H), 5.82 (m, 1 H), 5.25 (dd, J = 17.2, 1.2 Hz, 1 H), 5.19 (dd, J = 10.4, 1.2 Hz, 1 H), 4.12 (br., 1 H), 4.05 (d, J = 12.2 Hz, 1 H), 3.02 (dd, J = 13.2, 2.9 Hz, 1 H), 2.83 (br., 1 H), 2.56 (br., 1 H), 2.23 (d, J = 7.6 Hz, 2 H), 1.95 (m, 1 H), 1.63 (m, 1 H), 1.50 (s, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 134.7, 131.4, 128.1, 127.5, 123.7, 117.5, 88.3, 81.8, 79.3, 42.9, 42.0, 39.4, 39.0, 28.3, 27.2, 23.5 ppm.

According to the general procedure for Boc deprotection, **26** (240 mg, 0.74 mmol) was dissolved in CH_2Cl_2 (7 mL), and TFA (0.7 mL) was added. After workup, free amine **33** (152 mg, 0.67 mmol, 91%) was obtained as an orange oil. $[a]_D$ = +80.5 (c = 0.76, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3293, 2920, 2225, 1689, 1490, 1441, 756, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (m, 2 H), 7.30 (m, 3 H), 6.11 (ddd, J = 19.5, 17.1, 9.2 Hz, 1 H), 5.20 (m, 2 H), 3.15 (dt, J = 12.4, 5.0 Hz, 1 H), 3.06 (dd, J = 12.4, 3.2 Hz, 1 H), 2.92 (dd, J = 12.4, 3.2 Hz, 1 H), 2.85 (br., 1 H), 2.75 (m, 1 H), 2.54 (m, 1 H), 2.32 (d, J = 8.0 Hz, 2 H), 1.97 (m, 1 H), 1.72 (m, 1 H), 1.53 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 131.3, 128.0, 127.4, 123.7, 117.0, 88.5, 81.6, 50.9, 45.8, 42.2, 38.4, 28.2, 23.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{20}N$ $[M + H]^+$ 226.1590; found 226.1600.

4-[3-(Piperidin-4-yl)prop-1-yn-1-yl]-6-methoxyquinoline (34): According to the general procedure for Sonogashira coupling, alkyne **21** (283 mg, 1.27 mmol) was treated with 4-bromo-6-methoxyquinoline (450 mg, 1.91 mmol), $Pd(Cl)_2(PPh_3)_2$ (35 mg, 0.064 mmol), and CuI (25 mg, 0.13 mmol) in THF/Et_3N (13 mL). The product was purified by flash column chromatography (petroleum ether/EtOAc, 4:1) to give **27** (0.45 g, 1.2 mmol, 95%) as an orange oil. IR (neat): $\tilde{\nu}$ = 2974, 2928, 2851, 2223, 1688, 1618, 1580, 1423, 1365, 1243, 1226, 1164, 848 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, J = 4.0 Hz, 1 H), 8.01 (d, J = 9.2 Hz, 1 H), 7.51 (d, J = 2.8 Hz, 1 H), 7.42–7.38 (m, 2 H), 4.17 (br., 2 H), 3.97 (s, 3 H), 2.77 (t, J = 11.6 Hz, 2 H), 2.59 (d, J = 6.4 Hz, 2 H), 1.92 (d, J = 11.5 Hz, 2 H), 1.85 (m, 1 H), 1.48 (s, 9 H), 1.44–1.31 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 154.7, 146.9, 144.0, 131.1, 129.1, 128.6, 123.7, 122.3, 103.4, 97.7, 79.3, 78.3, 55.3, 35.6, 31.4, 28.3, 26.6 (carbons next to NBoc were not observed) ppm. HRMS (FAB): calcd. for $C_{23}H_{29}N_2O_3$ $[M + H]^+$ 381.2178; found 381.2175.

According to the general procedure for Boc deprotection, **27** (166 mg, 0.44 mmol) was dissolved in CH_2Cl_2 (4 mL), and TFA (0.4 mL) was added. After workup, free amine **34** (93 mg, 0.33 mmol, 75%) was obtained as an orange oil. IR (neat): $\tilde{\nu}$ = 3314, 2924, 2580, 2237, 1618, 1581, 1503, 1472, 1446, 1268, 1254, 1228, 848 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, J =

4.4 Hz, 1 H), 7.97 (d, J = 9.2 Hz, 1 H), 7.51 (d, J = 2.8 Hz, 1 H), 7.39–7.35 (m, 2 H), 3.95 (s, 3 H), 3.12 (d, J = 12.0 Hz, 2 H), 2.65 (dd, J = 12.0, 10.8 Hz, 2 H), 2.53 (d, J = 6.8 Hz, 2 H), 2.22 (br., 1 H), 1.92 (d, J = 12.8 Hz, 2 H), 1.78 (m, 1 H), 1.43–1.32 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 147.3, 144.1, 131.1, 129.1, 123.6, 122.3, 103.5, 98.3, 78.1, 55.3, 46.3, 35.9, 32.8, 29.5, 27.7 ppm. HRMS: calcd. for $C_{18}H_{21}N_2O$ $[M + H]^+$ 281.1654; found 281.1650.

4-(3-Phenylprop-2-yn-1-yl)piperidine (35): According to the general procedure for Sonogashira coupling, alkyne **21** (236 mg, 1.06 mmol) was treated with iodobenzene (0.18 mL, 1.59 mmol), $Pd(Cl)_2(PPh_3)_2$ (37 mg, 0.05 mmol), and CuI (20 mg, 0.11 mmol) in THF/Et_3N (10 mL). The product was purified by flash column chromatography (petroleum ether/EtOAc, 30:1) to give **28** (220 mg, 0.74 mmol, 74%) as an orange oil. IR (neat): $\tilde{\nu}$ = 2975, 2929, 2851, 1690, 1469, 1421, 1130, 1166, 756, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 2 H), 7.30 (m, 3 H), 4.15 (br., 2 H), 2.74 (t, J = 11.8 Hz, 2 H), 2.39 (d, J = 6.6 Hz, 2 H), 1.83 (d, J = 13.2 Hz, 2 H), 1.75 (m, 1 H), 1.48 (s, 9 H), 1.33–1.27 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7, 131.4, 128.0, 127.5, 123.6, 87.8, 81.9, 79.2, 35.7, 31.4, 28.3, 26.2 ppm; signals of C atoms next to NBoc not observed.

According to the general procedure for Boc deprotection, **28** (220 mg, 0.73 mmol) was dissolved in CH_2Cl_2 (7 mL), and TFA (0.7 mL) was added. After workup, free amine **35** (144 mg, 0.73 mmol, 99%) was obtained as an orange oil. IR (neat): $\tilde{\nu}$ = 3309, 2922, 2848, 1688, 1546, 1489, 1263, 1133, 756, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 2 H), 7.30 (m, 3 H), 3.18 (d, J = 12.3 Hz, 2 H), 2.84 (br., 1 H), 2.69 (t, J = 12.3 Hz, 2 H), 2.38 (d, J = 6.7 Hz, 2 H), 1.89 (d, J = 13.4 Hz, 2 H), 1.76–1.69 (m, 1 H), 1.40–1.28 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.4, 128.0, 127.4, 123.7, 88.0, 81.8, 45.8, 35.5, 32.0, 26.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}N$ $[M + H]^+$ 200.1434; found 200.1441.

(3*R*,4*R*)-3-Ethyl-4-(prop-2-yn-1-yl)piperidine (36): According to the general procedure for Boc deprotection, **15** (252 mg, 1 mmol) was dissolved in CH_2Cl_2 (10 mL), and TFA (1 mL) was added. After workup, free amine **36** (142 g, 0.93 mmol, 93%) was obtained as a colourless oil. $[\alpha]_D$ = +21.1 (c = 1.06, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3309, 2961, 2928, 2874, 1677, 1463, 1441, 909, 732, 641 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.00–2.95 (m, 1 H), 2.89 (dd, J = 12.6, 5.5 Hz, 1 H), 2.74–2.68 (m, 2 H), 2.28 (br., 1 H), 2.20 (m, 2 H), 1.98 (t, J = 2.5 Hz, 1 H), 1.93 (m, 1 H), 1.65–1.56 (m, 3 H), 1.41–1.36 (m, 1 H), 1.36–1.24 (m, 1 H), 0.95 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.9, 68.9, 47.5, 44.5, 39.2, 37.4, 28.3, 19.9, 18.5, 11.6 ppm. HRMS (ESI): calcd. for $C_{10}H_{18}N$ $[M + H]^+$ 152.1434; found 152.1439.

(3*R*,4*R*)-3-Ethyl-4-(but-2-yn-1-yl)piperidine (37): Alkyne **15** (252 mg, 1 mmol) was dissolved in THF (3 mL), and the solution was cooled to –78 °C. *n*BuLi (1.6 M in hexane; 0.69 mL, 1.1 mmol) was added dropwise, and the mixture was stirred for 30 min. Next, methyl iodide (0.16 mL, 2.5 mmol) was added, and the resulting mixture was warmed up to room temperature and stirred overnight. Saturated aqueous NH_4Cl was added, and the layers were separated. The aqueous layer was extracted twice with EtOAc. The organic layers were combined, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 20:1) to give the product (212 mg, 0.80 mmol, 80%) as a colourless oil (10% of starting alkyne **15** could not be removed). $[\alpha]_D$ = +29.3 (c = 0.42, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2967, 2922, 2863, 1689, 1424, 1391, 1241, 1165, 1135 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.00 (br., 1 H), 3.71 (br., 1 H), 3.04 (br., 1 H), 2.89–2.79 (m, 1 H), 2.10 (d, J = 7.6 Hz, 2 H), 1.80 (m, 4 H), 1.55–1.48 (m, 12 H), 1.31–1.13 (m, 2 H), 0.99 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 78.9, 76.4, 69.3, 46.2, 42.8, 39.3, 39.1, 28.3, 26.9, 22.4, 16.7, 12.1, 3.3 ppm.

According to the general procedure for Boc deprotection, the preceding product (118 mg, 0.44 mmol) was dissolved in CH_2Cl_2 (5 mL), and TFA (0.5 mL) was added. After workup, free amine **37** (72 mg, 0.43 mmol, 99%) was obtained as an orange oil (10% of the non-methylated alkyne remained in the product). $[\alpha]_D$ = +18.3 (c = 0.71, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3308, 2958, 2919, 2872, 1463, 1420, 1201, 808 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.96 (m, 1 H), 2.88 (dd, J = 12.6, 5.4 Hz, 1 H), 2.73–2.66 (m, 2 H), 2.11 (m, 2 H), 2.07 (m, 1 H), 1.86 (m, 1 H), 1.80 (t, J = 2.5 Hz, 3 H), 1.62–1.53 (m, 3 H), 1.38–1.32 (m, 1 H), 1.32–1.26 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.7, 76.1, 47.8, 44.7, 39.5, 37.9, 28.6, 20.3, 18.8, 11.8, 3.3 ppm. HRMS (ESI): calcd. for $C_{11}H_{20}N$ $[M + H]^+$ 166.1590; found 166.1596.

(3*R*,4*R*)-3-Ethyl-4-(4-benzyloxybut-2-yn-1-yl)piperidine (38): Alkyne **15** (340 mg, 1.34 mmol) was dissolved in THF (2 mL), and the solution was cooled to –78 °C. *n*BuLi (1.6 M in hexane; 0.92 mL, 1.47 mmol) was added dropwise, and the mixture was stirred for 30 min. Next, a solution of paraformaldehyde (101 mg, 3.37 mmol) in THF (2 mL) was added, and the resulting mixture was warmed up to room temperature and stirred overnight. Saturated aqueous NH_4Cl was added, and the layers were separated. The aqueous layer was extracted twice with EtOAc. The organic layers were combined, dried with $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (petroleum ether/EtOAc, 4:1) to give the alcohol (305 mg, 1.08 mmol, 81%) as a colourless oil. $[\alpha]_D$ = +23.6 (c = 0.33, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3243, 2968, 2930, 2868, 1689, 1668, 1428, 1343, 1244, 1165 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28 (dt, J = 6.0, 2.1 Hz, 2 H), 4.00 (br., 1 H), 3.73 (br., 1 H), 3.03 (br., 1 H), 2.89 (m, 1 H), 2.20 (d, J = 7.9 Hz, 2 H), 1.87 (m, 1 H), 1.62–1.50 (m, 4 H), 1.47 (s, 9 H), 1.25–1.15 (m, 2 H), 0.98 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 83.7, 79.7, 79.2, 50.7, 46.2, 42.8, 39.2, 38.8, 28.2, 26.8, 22.3, 16.7, 12.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{27}NO_3Na$ $[M + Na]^+$ 304.1883; found 304.1869.

This alcohol (290 mg, 1.03 mmol) was dissolved in DMF (4 mL), and the solution was cooled to 0 °C. Sodium hydride (60% in mineral oil; 62 mg, 1.54 mmol) was added in portions. The resulting mixture was warmed up to room temperature, and stirred for 2 h. Next, benzyl chloride (0.13 mL, 1.43 mmol) was added, and the mixture was stirred overnight. The reaction was quenched with NH_4Cl. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed with brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The product was purified by flash column chromatography (petroleum ether/EtOAc, 10:1) to give the benzyl ether (337 mg, 0.91 mmol, 88%) as a colourless oil. $[\alpha]_D$ = +18.9 (c = 1.71, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2969, 2930, 2861, 1688, 1426, 1364, 1280, 1166, 1091, 1072 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5 H), 4.06 (s, 2 H), 4.18 (t, J = 2.0 Hz, 2 H), 4.00 (br., 1 H), 3.73 (br., 1 H), 3.05 (br., 1 H), 2.90–2.83 (m, 1 H), 2.23 (d, J = 7.6 Hz, 2 H), 1.89 (m, 1 H), 1.62 (m, 3 H), 1.47 (m, 9 H), 1.31–1.16 (m, 2 H), 0.99 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 137.5, 128.3, 127.9, 127.7, 85.2, 79.1, 77.0, 71.3, 57.6, 46.2, 42.8, 39.3, 38.9, 28.3, 27.0, 21.9, 16.6, 12.2 ppm. HRMS (ESI): calcd. for $C_{23}H_{33}NO_3Na$ $[M + Na]^+$ 394.2353; found 394.2333.

According to the general procedure for Boc deprotection, the preceding benzyl ether (330 mg, 0.89 mmol) was dissolved in CH_2Cl_2 (9 mL), and TFA (0.9 mL) was added. After workup, free amine

38 (240 mg, 0.88 mmol, 99%) was obtained as a colourless oil. $[\alpha]_D$ = +10.6 (*c* = 0.6, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3263, 2923, 2856, 1689, 1454, 1354, 1087, 1070, 737, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H), 4.61 (s, 2 H), 4.18 (t, *J* = 2.1 Hz, 2 H), 2.97 (dt, *J* = 12.4, 5.3 Hz, 1 H), 2.89 (dd, *J* = 12.6, 5.5 Hz, 1 H), 2.74–2.67 (m, 2 H), 2.24 (m, 2 H), 1.93 (m, 2 H), 1.63–1.55 (m, 3 H), 1.40–1.35 (m, 1 H), 1.33–1.27 (m, 1 H), 0.94 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 128.1, 127.8, 127.5, 85.6, 76.7, 71.1, 57.5, 47.7, 44.6, 39.4, 37.6, 28.6, 20.4, 18.7, 11.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}NO$ $[M + H]^+$ 272.2009; found 272.2002.

General Procedure for Silver-Catalysed Hydroamination of Alkynes: The free amine (0.3 M) was dissolved in toluene under argon. Silver triflate (5 mol-%) was added, and the resulting mixture was stirred at 100 °C until TLC showed that all the starting material had disappeared. The solution was cooled to room temperature and directly purified by flash column chromatography to give the quinuclidine.

(1*S*,4*S*,5*R*,*E*)-5-Ethyl-2-[(6-methoxyquinolin-4-yl)methylene]-quinuclidine (39): According to the general procedure, amine **29** (92 mg, 0.3 mmol) in toluene (1 mL) was treated with silver triflate (4 mg, 0.015 mmol). The mixture was stirred at 100 °C for 2 h. Purification by flash column chromatography (EtOAc) gave bicyclic quinuclidine **39** (87 mg, 0.29 mmol, 95%) as an orange oil. $[\alpha]_D$ = +8.3 (*c* = 0.57, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2939, 2870, 1620, 1590, 1560, 1508, 1265, 1229, 1036, 859, 819 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 4.4 Hz, 1 H), 8.00 (d, *J* = 9.2 Hz, 1 H), 7.36 (dd, *J* = 9.2, 2.4 Hz, 1 H), 7.30–7.25 (m, 2 H), 6.88 (s, 1 H), 3.91 (s, 3 H), 3.40 (dd, *J* = 13.6, 10 Hz, 1 H), 3.13 (t, *J* = 7.2 Hz, 2 H), 2.66–2.56 (m, 2 H), 2.28 (d, *J* = 18 Hz, 1 H), 1.90 (d, *J* = 2.4 Hz, 1 H), 1.66–1.56 (m, 3 H), 1.34 (quint, *J* = 7.6 Hz, 2 H), 0.87 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 155.0, 147.3, 144.5, 140.5, 131.4, 127.8, 121.7, 120.4, 115.7, 101.9, 56.9, 55.4, 49.4, 37.4, 28.5, 27.9, 27.6, 26.6, 11.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{25}N_2O$ $[M + H]^+$ 309.1961; found 309.1969.

(1*S*,4*S*,5*R*,*Z*)-5-Ethyl-2-(pyridin-4-ylmethylene)quinuclidine (40): According to the general procedure, amine **30** (68 mg, 0.3 mmol) in toluene (1 mL) was treated with silver triflate (4 mg, 0.015 mmol). The mixture was stirred at 100 °C for 1.5 h. Purification by flash column chromatography (EtOAc) gave quinuclidine **40** (63 mg, 0.28 mmol, 93%) as a colourless oil. $[\alpha]_D$ = +12.2 (*c* = 0.69, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3049, 2928, 2864, 1653, 1592, 1460, 1450, 1414, 873, 668, 637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 6.0 Hz, 2 H), 7.65 (d, *J* = 6.0 Hz, 2 H), 5.79 (s, 1 H), 3.27 (dd, *J* = 13.6, 9.5 Hz, 1 H), 3.06–2.94 (m, 1 H), 2.94–2.88 (m, 1 H), 2.57 (dd, *J* = 17.6, 2.2 Hz, 1 H), 2.43 (ddd, *J* = 13.6, 6.3, 2.2 Hz, 1 H), 2.24 (d, *J* = 17.6 Hz, 1 H), 1.92 (m, 1 H), 1.66–1.56 (m, 3 H), 1.38–1.22 (m, 2 H), 0.88 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 149.7, 144.0, 123.2, 117.4, 55.0, 47.3, 37.2, 30.3, 27.8, 27.5, 26.4, 11.9 ppm. HRMS (ESI): calcd. for $C_{15}H_{21}N_2$ $[M + H]^+$ 229.1699; found 229.1710.

(1*S*,4*S*,5*R*,*Z*)-2-Benzylidene-5-ethylquinuclidine (41): According to the general procedure, amine **31** (68 mg, 0.3 mmol) in toluene (1 mL) was treated with silver triflate (4 mg, 0.015 mmol). The mixture was stirred at 100 °C for 1.5 h. Purification by flash column chromatography (petroleum ether/EtOAc, 20:1) gave quinuclidine **41** (62 mg, 0.27 mmol, 91%) as an orange oil. $[\alpha]_D$ = +40.4 (*c* = 0.24, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3062, 2954, 2929, 2862, 1693, 1598, 1573, 892, 755, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.2 Hz, 2 H), 7.30–7.27 (m, 2 H), 7.15 (t, *J* = 7.4 Hz, 1 H), 5.83 (t, *J* = 1.8 Hz, 1 H), 3.26 (dd, *J* = 13.5, 9.4 Hz, 1 H), 3.0–2.95 (m, 2 H), 2.57 (dd, *J* = 17.1, 2.4 Hz, 1 H), 2.48 (ddd, *J* = 13.5, 8.3, 6.2 Hz, 1 H), 2.23 (d, *J* = 16.8 Hz, 1 H), 1.88 (q, *J* = 2.9 Hz, 1 H), 1.66 (m, 1 H), 1.55 (m, 2 H), 1.42–1.36 (m, 2 H), 0.89 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 136.8, 128.7, 127.9, 125.8, 119.0, 55.2, 47.3, 37.4, 30.0, 28.0, 27.7, 26.4, 11.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}N$ $[M + H]^+$ 228.1752; found 228.1748.

(1*S*,4*S*,5*R*,*Z*)-5-Ethyl-2-(naphthalen-1-ylmethylene)quinuclidine (42): According to the general procedure, amine **32** (83 mg, 0.3 mmol) in toluene (1 mL) was treated with silver triflate (4 mg, 0.015 mmol). The mixture was stirred at 100 °C for 4 h. Purification by flash column chromatography (petroleum ether/EtOAc, 15:1) gave quinuclidine **42** (69 mg, 0.25 mmol, 83%) as an orange oil. $[\alpha]_D$ = +29.4 (*c* = 0.32, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3055, 2925, 2680, 1692, 1650, 1460, 1449, 893, 793, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.4 Hz, 1 H), 7.86 (d, *J* = 7.3 Hz, 1 H), 7.83 (d, *J* = 7.3 Hz, 1 H), 7.43 (d, *J* = 8.2 Hz, 1 H), 7.53–7.45 (m, 3 H), 6.52 (s, 1 H), 3.27 (dd, *J* = 13.4, 9.3 Hz, 1 H), 3.02–2.97 (m, 2 H), 2.74 (dd, *J* = 17.1, 2.4 Hz, 1 H), 2.52 (ddd, *J* = 13.4, 7.4, 1.4 Hz, 1 H), 2.41 (d, *J* = 17.1 Hz, 1 H), 1.96 (q, *J* = 2.9 Hz, 1 H), 1.79–1.71 (m, 1 H), 1.64–1.51 (m, 2 H), 1.50–1.32 (m, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 133.6, 133.2, 131.7, 128.4, 127.0, 126.5, 125.7, 125.3, 125.1, 124.3, 116.4, 55.9, 48.0, 37.5, 29.9, 28.1, 27.7, 26.6, 12.0 ppm. HRMS (ESI): calcd. for $C_{20}H_{24}N$ $[M + H]^+$ 278.1903; found 278.1916.

(1*S*,4*S*,5*R*)-5-Ethyl-2-methylenequinuclidine (43): According to the general procedure, amine **36** (46 mg, 0.3 mmol) in toluene (1 mL) was treated with silver triflate (4 mg, 0.015 mmol). The mixture was stirred at 100 °C for 5 h. Purification by flash column chromatography (EtOAc/MeOH, 100:4) gave quinuclidine **43** (36 mg, 0.23 mmol, 78%) as an orange oil. $[\alpha]_D$ = +22.2 (*c* = 0.65, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2955, 2928, 2870, 1656, 1461, 1433, 1260, 1031, 877 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.91 (t, *J* = 2.1 Hz, 1 H), 4.57 (t, *J* = 2.1 Hz, 1 H), 3.27 (dd, *J* = 13.4, 9.6 Hz, 1 H), 3.01–2.94 (m, 2 H), 2.50–2.44 (ddd, *J* = 13.7, 8.4, 2.2 Hz, 2 H), 2.16 (dd, *J* = 17.1, 1.2 Hz, 1 H), 1.84 (q, *J* = 2.8 Hz, 1 H), 1.65–1.58 (m, 1 H), 1.55–1.49 (m, 2 H), 1.39–1.35 (m, 2 H), 0.89 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 104.4, 56.4, 49.0, 37.1, 28.1, 27.8 27.7, 26.5, 11.9 ppm. HRMS (ESI): calcd. for $C_{10}H_{18}N$ $[M + H]^+$ 152.1434; found 152.1441.

(1*S*,4*S*,5*R*,*Z*)-5-Ethyl-2-ethylidenequinuclidine (44): According to the general procedure, amine **37** (50 mg, 0.3 mmol) in toluene (1 mL) was treated with silver triflate (4 mg, 0.015 mmol). The mixture was stirred at 100 °C for 16 h. Purification by flash column chromatography (EtOAc) gave quinuclidine **44** (35 mg, 0.21 mmol, 70%) as an orange oil. $[\alpha]_D$ = +33.0 (*c* = 0.33, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2962, 1283, 1238, 1244, 1158, 1029, 638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.34 (q, *J* = 7.2 Hz, 1 H), 3.77 (dd, *J* = 12.6, 10.4 Hz, 1 H), 3.50 (m, 1 H), 3.24 (m, 1 H), 2.74 (ddd, *J* = 12.9, 9.0, 2.2 Hz, 1 H), 2.62 (dt, *J* = 19.0, 2.0 Hz, 1 H), 2.35 (d, *J* = 16.4 Hz, 1 H), 2.07 (q, *J* = 2.7 Hz, 1 H), 1.89–1.82 (m, 6 H), 1.45 (quintet, *J* = 7.4 Hz, 2 H), 0.93 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2, 115.8, 55.7, 48.6, 36.5, 28.0, 27.1, 26.7, 26.2, 11.7, 11.5 ppm. HRMS (ESI): calcd. for $C_{11}H_{20}N$ $[M + H]^+$ 166.1590; found 166.1598.

(1*S*,4*S*,5*R*,*Z*)-2-[2-(Benzyloxy)ethylidene]-5-ethylquinuclidine (45): According to the general procedure, amine **38** (81 mg, 0.3 mmol) in toluene (1 mL) was treated with silver triflate (4 mg, 0.015 mmol). The mixture was stirred at 100 °C for 4 h. Purification by flash column chromatography (petroleum ether/EtOAc, 4:1) gave quinuclidine **45** (65 mg, 0.24 mmol, 80%) as an orange oil. $[\alpha]_D$ = +53.9 (*c* = 0.36, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2928, 2861, 1678,

1496, 1096, 1065, 734, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 5 H), 5.18 (t, J = 6.6 Hz, 1 H), 4.51 (s, 2 H), 4.23 (d, J = 6.6 Hz, 2 H), 3.20 (dd, J = 13.6, 9.6 Hz, 1 H), 2.93 (m, 1 H), 2.84 (m, 1 H), 2.44 (d, J = 16.9 Hz, 1 H), 2.36 (ddd, J = 13.4, 8.4, 2.1 Hz, 1 H), 2.12 (d, J = 16.9 Hz, 1 H), 1.82 (q, J = 2.5 Hz, 1 H), 1.62 (m, 1 H), 1.54–1.48 (m, 2 H), 1.38–1.33 (m, 2 H), 0.88 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4, 138.7, 128.2, 127.7, 127.3, 116.5, 72.0, 65.3, 55.8, 48.3, 37.4, 28.5, 27.9, 27.5, 26.4, 11.9 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}NO$ [M + H]$^+$ 272.2009; found 272.2020.

(1*S*,4*S*,5*R*,*Z*)-2-Benzylidene-5-vinylquinuclidine (46): According to the general procedure, amine **33** (67 mg, 0.3 mmol) in toluene (1 mL) was treated with silver triflate (38 mg, 0.15 mmol). The mixture was stirred at 100 °C for 16 h. Purification by flash column chromatography (petroleum ether/EtOAc, 20:1) gave bicyclic quinuclidine **46** (42 mg, 0.19 mmol, 63%) as a 5:1 mixture of (*Z*)/(*E*) isomers, as an orange oil. IR (neat): $\tilde{\nu}$ = 2927, 2863, 1657, 1492, 912, 893, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 7.6 Hz, 2 H), 7.33 (m, 2 H), 7.18 (t, J = 7.4 Hz, 1 H), 5.92–5.85 (m, 2 H), 5.10–5.04 (m, 2 H), 3.31 (m, 1 H), 3.07 (m, 2 H), 2.77 (dd, J = 13.7, 6.4 Hz, 0.8 H), 2.65 (dd, J = 18.6, 1.5 Hz, 0.8 H), 2.59 (dd, J = 17.2 2.3 Hz, 0.2 H), 2.52 (ddd, J = 13.5, 6.2, 1.9 Hz, 0.2 H), 2.41 (q, J = 7.8 Hz, 0.8 H), 2.30–2.23 (m, 1 H), 1.96 (m, 0.8 H), 1.90 (m, 0.2 H), 1.71–1.64 (m, 2 H), 1.57 (m, 0.2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 141.2, 136.7, 128.8, 28.0, 126.0, 125.9, 125.3, 119.5, 119.1, 114.4, 55.2, 53.5, 47.4, 47.4, 39.9, 37.5, 30.3, 30.1, 29.8, 28.1, 27.7, 27.3, 26.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{20}N$ [M + H]$^+$ 226.1590; found 226.1602.

(*E*)-2-[(6-Methoxyquinolin-4-yl)methylene]quinuclidine (47): According to the general procedure, amine **34** (67 mg, 0.24 mmol) in toluene (0.8 mL) was treated with silver triflate (3.1 mg, 0.012 mmol). The mixture was stirred at 100 °C for 40 h [after 24 h, additional silver triflate (5 mol-%) was added to reach full conversion]. Purification by flash column chromatography (EtOAc/MeOH, 97:3) gave quinuclidine **47** (49 mg, 0.18 mmol, 73%) as an orange oil. IR (neat): $\tilde{\nu}$ = 2937, 2868, 1619, 1583, 1563, 1506, 1260, 1227, 1029, 851, 825 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, J = 4.6 Hz, 1 H), 8.01 (d, J = 9.2 Hz, 1 H), 7.87 (dd, J = 9.2, 2.8 Hz, 1 H), 7.31 (d, J = 5.2 Hz, 1 H), 7.28 (m, 1 H), 6.95 (s, 1 H), 3.93 (s, 3 H), 3.27–3.15 (m, 4 H), 2.51 (s, 2 H), 2.06 (m, 1 H), 1.64 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 145.5, 147.3, 145.0, 140.3, 131.4, 127.8, 121.8, 120.4, 116.3, 101.9, 55.5, 49.6, 33.7, 26.0, 23.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{21}N_2O$ [M + H]$^+$ 281.1654; found 281.1649.

(*Z*)-2-Benzylidenequinuclidine (48): According to the general procedure, amine **35** (60 mg, 0.3 mmol) in toluene (1 mL) was treated with silver triflate (16 mg, 0.06 mmol). The mixture was stirred at 100 °C for 64 h. Purification by flash column chromatography (petroleum ether/EtOAc, 30:1) gave quinuclidine **48** (24 mg, 0.13 mmol, 42%) as a 9:1 mixture of (*Z*)/(*E*) isomers, as a colourless oil. IR (neat): $\tilde{\nu}$ = 2934, 2831, 1658, 1468, 694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.2 Hz, 1.8 H), 7.62 (d, J = 7.2 Hz, 0.2 H), 7.33–7.28 (m, 2.1 H), 7.16 (t, J = 7.4 Hz, 0.9 H), 6.13 (t, J = 4.4 Hz, 0.1 H), 5.88 (s, 0.9 H), 3.30 (m, 0.2 H), 3.22 (m, 0.2 H), 3.11 (m, 1.8 H), 3.02 (m, 1.8 H), 2.56 (t, J = 4.0 Hz, 0.2 H), 2.44 (s, 1.8 H), 2.00 (m, 1 H), 1.60 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 136.8, 128.8, 128.1, 128.0, 126.9, 125.9, 125.4, 122.9, 119.7, 49.7, 47.9, 38.3, 35.2, 27.6, 27.6, 26.2, 23.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}N$ [M + H]$^+$ 200.1434; found 200.1452.

(1*S*,2*R*,4*S*,5*R*)-5-Ethyl-2-[(6-methoxyquinolin-4-yl)methyl]-quinuclidine (49a) and (1*S*,2*S*,4*S*,5*R*)-5-Ethyl-2-[(6-methoxyquinolin-4-yl)methyl]quinuclidine (49b): Quinuclidine **39** (100 mg, 0.32 mmol) was dissolved in methanol (4 mL). Pd/C (17 mg, 0.016 mmol) was added, and the mixture was stirred at room temperature under H_2 for 1 h. The resulting mixture was filtered through Celite, and the solvent was evaporated in vacuo to give a 4:1 mixture of **49a/49b**. The diastereoisomers were purified by flash column chromatography (CH_2Cl_2/MeOH/NH_4OH, 100:3:1) to give **49a** and **49b** (92 mg, 0.29 mmol, 92%) as an inseparable mixture, as a colourless, sticky oil. IR (neat): $\tilde{\nu}$ = 2928, 2867, 1620, 1508, 1240, 1227 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, J = 4.4 Hz, 1 H), 8.02 (d, J = 9.2 Hz, 1 H), 7.38 (dd, J = 9.2, 2.7 Hz, 1 H), 7.31 (d, J = 2.7 Hz, 1 H), 7.25 (d, J = 4.4 Hz, 1 H), 3.97 (s, 3 H), 3.42–3.36 (m, 1 H), 3.25–3.16 (m, 1.6 H), 3.06–2.99 (m, 1.8 H), 2.96–2.88 (m, 1.4 H), 2.85 (m, 0.2 H), 2.68 (dd, J = 13.5, 4.8 Hz, 0.8 H), 2.52–2.43 (m, 0.2 H), 1.74–1.67 (m, 1.6 H), 1.58–1.40 (m, 5.4 H), 1.33–1.25 (m, 1 H), 0.95 (t, J = 7.3 Hz, 2.4 H), 0.85 (t, J = 7.3 Hz, 0.6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = δ = 157.6, 157.6, 147.5, 144.3, 143.9, 143.7, 131.6, 128.6, 121.7, 121.3, 57.8, 55.6, 55.5, 55.5, 55.4, 49.3, 49.3, 41.1, 38.4, 37.6, 37.4, 37.0, 28.5, 28.5, 28.0, 27.4, 27.1, 26.0, 25.7, 25.5, 12.0 ppm. HRMS (ESI): calcd. for $C_{20}H_{27}N_2O$ [M + H]$^+$ 311.2218; found 311.2127.

Dihydroquinidine (50) and Dihydroquinine (51): Sodium hydride (60% in mineral oil; 15 mg, 0.35 mmol) was dissolved in DMSO (1.4 mL). The mixture was heated to 70 °C and stirred for 1 h. Next, **49a** and **49b** (50 mg, 0.16 mmol) in DMSO (0.7 mL) were added, and – after stirring for 1 min – the solution became red. Oxygen was bubbled through the mixture for 45 min. Saturated aqueous $NaHCO_3$ (5 mL) was slowly added, followed by EtOAc (20 mL) and water (5 mL). The layers were separated, and the organic layer was washed with water and brine, dried with Na_2SO_4, and concentrated to give a mixture of dihydroquinidine (**50**)/dihydroquinine (**51**)/*epi*-dihydroquinidine/*epi*-dihydroquinine in a ratio of 10:2.5:3:0.5. Dihydroquinidine (**50**) and dihydroquinine (**51**) were separated from their *epi* analogues by flash column chromatography (CH_2Cl_2/MeOH/NH_4OH, 100:5:1) to give a 3:1 mixture of products **50/51** (27 mg, 0.085 mmol, 53%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, J = 4.5 Hz, 0.25 H), 8.69 (d, J = 4.5 Hz, 0.75 H), 8.02 (d, J = 9.2 Hz, 0.25 H), 7.99 (d, J = 9.2 Hz, 0.75 H), 7.62 (d, J = 4.5 Hz, 0.25 H), 7.58 (d, J = 4.5 Hz, 0.75 H), 7.39 (d, J = 2.6 Hz, 0.25 H), 7.36–7.32 (m, 1 H), 7.23 (d, J = 2.6 Hz, 0.75 H), 5.84 (br., 0.25 H), 5.73 (d, J = 3.0 Hz, 0.75 H), 3.97 (s, 0.75 H), 3.88 (s, 2.25 H), 3.70 (m, 0.25 H), 3.16–3.04 (m, 1.75 H), 2.92 (m, 1 H), 2.86 (m, 0.75 H), 2.79 (m, 0.75 H), 2.39 (m, 0.5 H), 2.00 (t, J = 11.5 Hz, 0.75 H), 1.84–1.78 (m, 0.75 H), 1.70 (s, 0.75 H), 1.55–1.33 (m, 4.5 H), 1.24 (m, 0.5 H), 1.10 (m, 0.75 H), 0.83 (t, J = 7.2 Hz, 2.25 H), 0.78 (t, J = 7.3 Hz, 0.75 H) ppm. All analytical data agree with those reported in the literature.[33]

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for new compounds.

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