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Cinchona alkaloid derived ligands in catalytic asymmetric transfer hydrogenation

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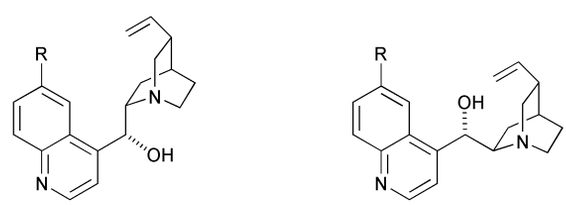
A collection of chiral quinuclidine ligands, derived from the *Cinchona* alkaloids quinine and quinidine, has been evaluated in the catalytic asymmetric transfer hydrogenation of aromatic ketones. It was fond that $[IrCl(COD)]_2$ complexes of the diamines QCI-Amine and QCD-Amine gave the most active catalysts, capable of reducing a range of aromatic ketones with excellent conversions and good enantioselectivities (up to 95% ee). These are the best selectivities reported for ligands based on the quinuclidine core in an asymmetric transformation, and advocate that these ligands, commercially available in both *pseudo*-enantiomeric forms, will find practical use in this and other catalytic processes.

Introduction

The naturally occurring *Cinchona* alkaloids quinine, quinidine, cinchonine, and cinchonidine (Fig. 1) have a long and proud history in the field of asymmetric synthesis.[1] These inexpensive and readily available alkaloids have been used in processes ranging from classical resolution of optically active acids,[2] to chiral reagents and auxiliaries, and as chiral catalysts.[3–5] Moreover, synthetic derivatives of these molecules are among the most useful chiral catalysts in use today, *e.g.* for Sharpless' dihydroxylation[6–8] and enolate alkylation under phase-transfer conditions.[9–13]



Quinine (R = OMe)
Cinchonidine (R = H)

Quinidine (R = OMe)
Cinchonine (R = H)

Fig. 1 Structural formula of the *Cinchona* alkaloids quinine, quinidine, cinchonidine, and cinchonine.

Although a wealth of studies have addressed ligand design on the intact quinine skeleton, only a handful of studies on the quinuclidine portion of the molecule have been reported.[14–17] Following a procedure reported by Hoffmann *et al.*,[18] quinine and quinidine may be transformed into the enantiomerically pure quinuclidine derivatives quincorine (QCI) **1** and quincoridine (QCD) **2**, respectively (Fig. 2). Although formally diastereoisomers, these bicyclic β-amino alcohols are classified as *pseudo*-enantiomers and contain four stereogenic centers each, including a fixed stereogenic (*S*)-configured *N*-bridgehead.[19–21] Further transformation of these substances, *i.e.* replacement of the β-hydroxy function by a primary amine, yields the corresponding β-diamines QCI-Amine **3** and QCD-Amine **4**.[22]

The low cost and the commercial availability of these β-substituted amino alcohols and diamines, in both *pseudo*-enantiomeric forms, encouraged us to investigate their utility as ligands in asymmetric catalysis. In this contribution we report our studies on the use of QCI and QCD derived ligands for the catalytic asymmetric transfer hydrogenation of aromatic ketones.

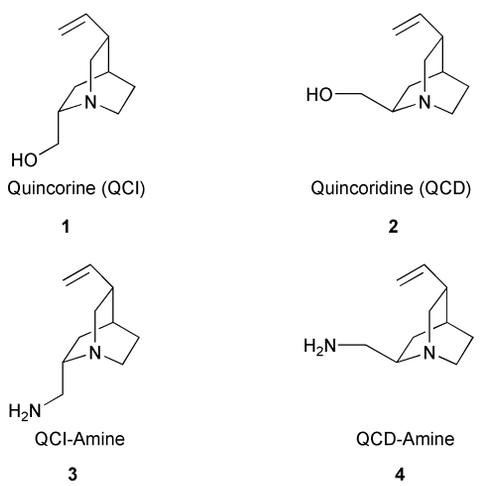
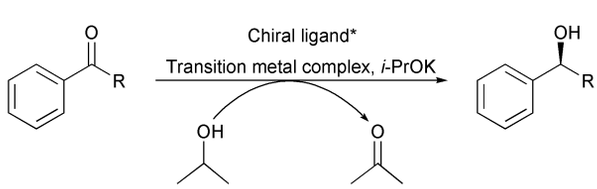


Fig. 2 Structural formula of the *pseudo*-enantiomeric β-amino alcohols quincorine **1** and quincoridine **2**, and the β-diamines **3** and **4** derived from them.

Results and discussion

Transfer hydrogenation of prochiral ketones by 2-propanol (Meerwein–Pondorf–Verley reduction) is a safe, inexpensive, and efficient complementary procedure to hydrogenation using molecular hydrogen, Scheme 1.[23] Highly enantioselective versions of this reaction have also recently been developed.[24–27] The most efficient systems developed today utilize Ru, Rh, or Ir as metal catalysts and achieve up to 98% conversion in <1 hour, with >95% enantiomeric excess, for the benchmark reduction of acetophenone.[28,29]



Scheme 1 Asymmetric transfer hydrogenation of aromatic ketones mediated by chiral transition metal complexes.

To avoid possible side reactions with the alkene functionality, and to prevent potential alkene–metal interactions during preparation of the catalyst we initially investigated the dihydro derivatives **5** and **6**, quantitatively obtained from QCI- and QCI-Amine after hydrogenation over Pd/C, Scheme 2.

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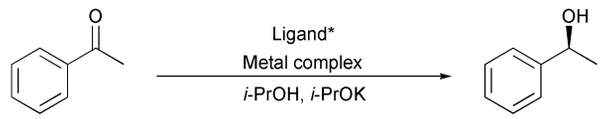
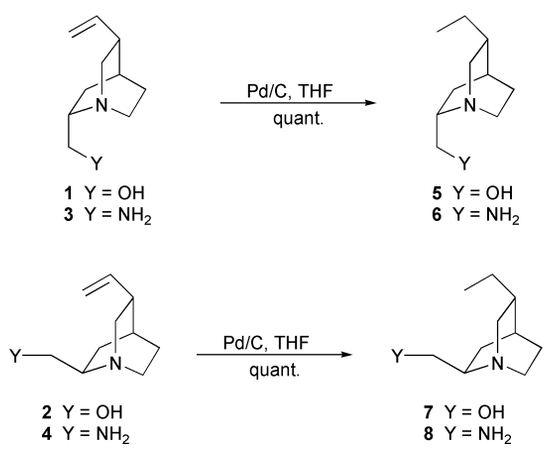
Table 1 Asymmetric transfer hydrogenation of acetophenone[a]



Entry	Metal complex	Ligand	Conv. (%)[b] 1 h	Conv. (%)[b] 10 h	ee (%)[b] 1 h	ee (%)[b] 10 h	Config.
1	$[RuCl_2(p\text{-cym})]_2$	**5**	—	—	—	—	
2	$[RuCl_2(p\text{-cym})]_2$	**6**	—	3	—	*rac*	
3	$RuCl_2(PPh_3)_3$	**5**	—	—	—	—	
4	$RuCl_2(PPh_3)_3$	**6**	—	—	—	—	
5	$RuCl_2(DMSO)_4$	**5**	—	—	—	—	
6	$RuCl_2(DMSO)_4$	**6**	—	—	—	—	
7	$[IrCl(COD)]_2$	**5**	—	—	—	—	
8	$[IrCl(COD)]_2$	**6**	81	96	80	73	(*S*)
9	$RhCl(PPh_3)_3$	**5**	—	—	—	—	
10	$RhCl(PPh_3)_3$	**6**	—	—	—	—	
11	$[RhCl(COD)]_2$	**5**	—	—	—	—	
12	$[RhCl(COD)]_2$	**6**	4	36	48	51	(*S*)

[a] Metal–ligand–base–substrate = 1 : 1.2 : 5 : 200. [b] Determined by GC analysis on chiral stationary phase.



Scheme 2 Catalytic hydrogenation of commercially available QCI **1** and QCD **2**, and their corresponding amino derivatives **3** and **4**, to the dihydro derivatives **5**–**8**.

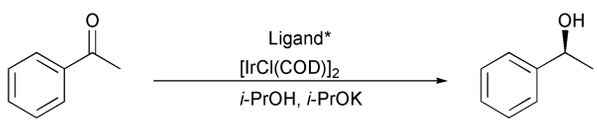
In order to evaluate the optimal metal for the quinuclidine ligands in transfer hydrogenation, we initially tested the QCI-derived ligands **5** and **6** with six different metal complexes, Table 1.

As seen in Table 1, the β-amino alcohol **5** did not result in a catalytically active complex with any of the investigated metals. This finding is in accordance with previous studies showing that an N–H moiety is crucial for catalytic activity where amino alcohols are employed as chiral ligands; nevertheless, this information is important since discrete mechanisms have been suggested for different metal complexes and ligand structures.[30,31]

Diamine ligand **6**, on the other hand, showed modest activity (36% conversion after 10 h) with $[RhCl(COD)]_2$ (entry 12), and good activity (96% conversion after 10 h) when $[IrCl(COD)]_2$ was used as pre-catalyst (entry 8). The enantioselectivity of the Ir-catalyzed reaction is also fair, affording (*S*)-1-phenylethanol in 80% ee at 81% conversion. Since the transfer hydrogenation is a reversible process, the maximum enantiomeric excess of the product is attained at lower conversion. No attempts were made to optimize the catalysts loading, although this could have a favorable bearing on the reactivity/selectivity; instead identical reaction conditions were used throughout the present study.

Having established that $[IrCl(COD)]_2$ is the metal complex of choice, we turned our attention to variations in the ligand structure. Use of the *pseudo*-enantiomeric ligand **8**, derived from QCD-Amine **4**, in the enantioselective reduction of

Table 2 Asymmetric transfer hydrogenation of acetophenone[a]



Entry	Ligand	Conv. (%)[b] 1 h	Conv. (%)[b] 10 h	ee (%)[b] 1 h	ee (%)[b] 10 h	Config.
1	**6**	94	97	80	76	(*S*)
2	**8**	76	96	85	84	(*R*)
3	**9**	31	94	82	81	(*S*)
4	**10**	28	91	81	80	(*R*)
5	**3**	42	95	75	69	(*S*)
6	**4**	66	95	81	74	(*R*)

[a] Metal–ligand–base–substrate = 1 : 1.2 : 5 : 200. [b] Determined by GC analysis on chiral stationary phase.

acetophenone afforded (*R*)-1-phenylethanol in 84% ee at 97% conversion, Table 2 (entries 1 and 2). The reversal in enantioselectivity is notable, and verifies that only the configuration at the 2-position of the quinuclidine is responsible for the selectivity. Further, this verifies the *pseudo*-enantiomeric relationship between QCI-Amine and QCD-Amine. The somewhat higher selectivity of the QCD-based ligand reflects the slightly faster reaction rate of this system, as compared to the QCI-based system. (Again, a too long reaction time leads to loss of enantioselectivity due to the equilibrium of this transformation.)

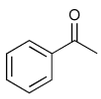
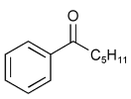
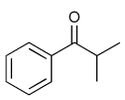
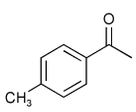
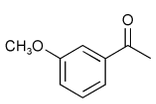
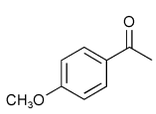
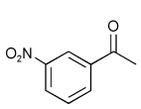
To probe the influence of substitution at the primary amine, two *N*-alkylated derivatives, *i.e.* **9** and **10**, were readily prepared by reductive amination of the quinuclidine amines with acetone, Scheme 3.

Examination of these ligands in the asymmetric transfer hydrogenation of acetophenone gave the product in comparable enantioselectivity, albeit with a lower reaction rate (Table 2, entries 3 and 4). Clearly, the selectivities of these ligands are insensitive to structural variation at the pendant *N*-center.

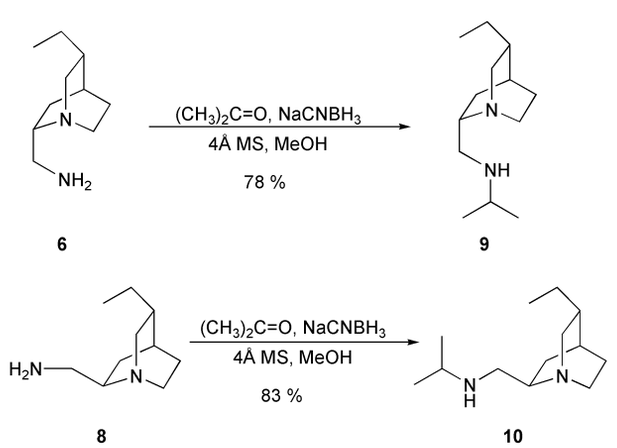
A new screening of the different metal complexes, in Table 1 above, with the secondary amine ligand **9** did not yield any improvements (data not shown). Again, only $[IrCl(COD)]_2$ and $[RhCl(COD)]_2$ showed catalytic activity, although both the conversion and the enantioselectivity were lower than with the primary amines **6** and **8**.

In summary, the bulky *N*-isopropyl substituent dramatically reduced the reaction rate, while having a surprisingly weak

Table 3 Asymmetric Transfer Hydrogenation of various aromatic ketones[a]

Entry	Ketone	Ligand	Conv. (%)[b] 1 h	Conv. (%)[b] 10 h	ee (%)[b] 1 h	ee (%)[b] 10 h	Config.[c]
1		**6**	97	98	80	76	(*S*)
2		**8**	93	97	82	80	(*R*)
3		**6**	60	96	83	78	(*S*)
4		**8**	56	80	90	88	(*R*)
5		**6**	42	49	(93)[d]	(92)[d]	(*S*)
6		**8**	35	48	95	94	(*R*)
7		**6**	99	99	82	80	(*S*)
8		**8**	81	99	89	89	(*R*)
9		**6**	99	99	75	65	(*S*)
10		**8**	92	99	83	80	(*R*)
11		**6**	74	76	80	70	(*S*)
12		**8**	45	68	84	79	(*R*)
13		**6**	99	99	70	65	(*S*)
14		**8**	68	91	69	66	(*R*)

[a] Metal–ligand–base–substrate = 1 : 1.2 : 5 : 200. [b] Determined by GC analysis on chiral stationary phase. [c] Only the absolute configuration of 1-phenylethanol is established. Here the (*S*)-enantiomer elutes first; the reported configuration of the other alcohols relate to the first eluting peak in the chromatogram (which is not necessarily the same as for 1-phenylethanol). [d] Uncertain value due to partial overlap of the small peak, eluting second, by the major peak, eluting first.



Scheme 3 Preparation of *N*-alkylated QCI- and QCD-derivatives **9** and **10**.

influence on the enantioselectivity. These findings made us hesitate to evaluate further *N*-substituted derivatives. Instead we investigated if the commercially available derivatives **3** and **4** could be used directly for the reduction. As seen in Table 2 (entries 5 and 6), the parent QCI- and QCD-Amines perform somewhat worse than their hydrogenated analogues **6** and **8**. The reason for this remains tentative, but presumably the double bond perturbs the stability and/or influences the structure of the metal complex by coordination to the metal center, possibly at the COD-ligand binding site.

To examine further the utility of the QCI- and QCD-Amine ligands we performed the asymmetric transfer hydrogenation with a selected set of aromatic ketones as substrates.

As seen in Table 3, making the aliphatic group of the ketone larger than methyl (*i.e.* entries 3–6) gives the product in higher selectivity than acetophenone, albeit at a lower rate.

Likewise, *o*- and *m*-substituted ketones generally furnish quantitative conversion of the substrate within 10 h with a fair enantioselectivity (typically above 80% ee). Electron donating substituents in the *p*-position, on the other hand, gives the product in fair selectivity but with low conversions (entries 11 and 12).

Aromatic ketones incorporating electron-withdrawing substituents, *e.g.* nitro-groups, in the *m*-position are notoriously bad substrates in asymmetric transfer hydrogenation reactions.[32] Nevertheless, the QCI-/QCD-based system performance was fair on this demanding substrate, yielding the product in quantitative yield, although with reduced enantioselectivity (70% ee), entries 13 and 14.

As previously noted, the QCI-derived ligand reacts faster than the QCD-derived analogue (conversion at 1 h always

Table 4 Analytical methods and retention times for the chiral product alcohols

Entry	Product alcohol	GC Program[a]	Retention time/min	
			t_1 (*S*)[b]	t_2 (*R*)[b]
1	1-Phenylethanol	1	9.12	9.58
2	1-Phenylhexan-1-ol	2	56.9	57.7
3	2-Methyl-1-phenylpropan-1-ol	2	31.5	31.7
4	1-*p*-Tolylethanol	2	35.6	37.9
5	1-(3-Methoxyphenyl)ethanol	2	39.1	40.2
6	1-(4-Methoxyphenyl)ethanol	2	37.5	38.7
7	1-(3-Nitrophenyl)ethanol	3	48.4	49.5

[a] GC program 1: 100–135 °C (3 °C min^{-1}) then 135–220 °C (40 °C min^{-1}), hold 1 min. GC program 2: 90 °C, hold 10 min, 90–150 °C (1 °C min^{-1}), then 150–220 °C (40°C min^{-1}), hold 1 min. GC program 3: 90 °C, hold 10 min, 90–150 °C (1 °C min^{-1}), hold 10 min, then 150–220 °C (40 °C min^{-1}), hold 1 min. [b] Only the absolute configuration of 1-phenylethanol is established. Here the (*S*)-enantiomer elutes first; the reported configuration of the other alcohols relate to the first eluting peak in the chromatogram (which is not necessarily the same as for 1-phenylethanol).

higher). This difference affects the enantioselectivity observed after 10 h, and emphasizes the importance of terminating the transfer hydrogenation process as soon as possible after full conversion has been obtained.

Conclusion

In conclusion, we have demonstrated that commercially available QCI- and QCD-Amine, originating from the *Cinchona* alkaloid degradation products quincorine and quincoridine, respectively, are potent ligands in asymmetric transfer hydrogenation of ketones. After initial screening of various metal complexes it was found that $[IrCl(COD)]_2$ gave the most active catalyst, capable of reducing a range of aromatic ketones with excellent conversions and fair enantioselectivity (up to 95% ee). Modification of the ligand structure by *N*-alkylation did not lead to an improved catalyst. The commercial availability of these ligands, in both *pseudo*-enantiomeric forms, suggests that these ligands will find practical use in asymmetric transfer hydrogenation reactions.

Experimental

General

All reactions were carried out under argon or nitrogen using dry glassware and magnetic stirring. Tetrahydrofuran was freshly distilled under nitrogen from a blue solution of sodium–benzophenone ketyl radical prior to use. Dichloromethane and isopropanol were freshly distilled under nitrogen from powdered calcium hydride just before use. Analytical TLC was carried out using 0.25 mm precoated plates from Macherey-Nagel, silica gel 60 UV_{254} and spots were visualised by the use of UV light and ethanolic phosphomolybdic acid followed by heating. ^{1}H NMR 500 MHz spectra were recorded on a Varian Unity 500 and ^{13}C NMR 100 MHz spectra were recorded on a Varian Unity 400 spectrometer at ambient temperature using deuterated chloroform as solvent. Chemical shifts (δ) in ppm are reported using residual chloroform as internal reference (^{1}H δ 7.26, ^{13}C δ 77.0), and coupling constants (J) in Hz. Infrared spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer. Mass spectra were recorded by the direct infusion technique using a Finnigan MAT GCQ PLUS system using electron impact ionisation (EI, 70 ev). The high pressure liquid chromatography (HPLC) coupled with mass detection analysis was done on a Gilson HPLC system equipped with a Thermoquest AQA mass spectrometer with electrospray ionization (ESI), using a Phenomenex Luna C8-RP-column (5 μ, 4.6 × 100 mm) with acetonitrile–water (both containing 0.1% TFA) as mobile phase (Gradient: MeCN–H_2O 10 : 90 for 10 min then 10–50% MeCN during 5 min). GC analysis was performed using a Varian 3400 instrument equipped with a CP-Chirasil-Dex CB column (25 m, ∅ 0.25 mm, 25 μm) with nitrogen as carrier gas at 15 psi and a flame-ionizing detector. The retention times for the chiral product alcohols are shown in Table 4.

General procedure for transfer hydrogenation reactions

All transfer hydrogenations were carried out in a Chemspeed® ASW 2000, equipped with two reaction blocks, under a nitrogen atmosphere. The reaction vessels (13 ml) were filled with the metal complex (5.00 μmol), and mounted in the reaction block. *i*-PrOH (2760 μl) and ligand (6.00 μmol) were added to the metal complexes and the resulting mixture was heated to reflux for 30 min. Meanwhile, *i*-PrOH (3428 μl) and substrate (59.0 μl, 0.50 mmol) was added to the other block of reaction vessels. After cooling to 25 °C, the catalyst solution (1500 μl; 2.5 μmol) was transferred from each catalyst preparation site to the corresponding reaction vessel. Base (1M *i*-PrOK in *i*-PrOH, 25.0 μl, 12.5 μmol) was added to each reaction vessel to initiate the hydrogenation reaction. Samples were taken from the reaction mixture after 1 h and after 10 h.

All reactions were run in triplicate. Two control reactions were performed in each run, and the results from the whole run were discarded if these controls did not perform satisfactorily.

Synthesis

General procedure for catalytic hydrogenation. The vinylic function of the QCI/QCD-core was catalytically hydrogenated by dissolving the molecule (5 g) in dry THF (80 ml). Pd/C (10% loading, 10 mole% catalyst) was added, and the resulting mixture was shaken in a Parr-apparatus for 8 h at 4 atm. The reaction mixture was filtered through a pad of Celite, and evaporated to yield the pure dihydro derivative in nearly quantitative yield.

(1*S*,2*S*,4*S*,5*R*)-2-(Hydroxymethyl)-5-ethyl-1-azabicyclo-[2.2.2]octane 5. QCI **1** was hydrogenated according to the general procedure (half scale). (1*S*,2*S*,4*S*,5*R*)-2-(Hydroxymethyl)-5-ethyl-1-azabicyclo[2.2.2]octane **5** was isolated as a colourless viscous oil (2.5 g; 98%). Spectral data were identical to those reported in ref. 22.

(1*S*,2*S*,4*S*,5*R*)-2-(Aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]-octane 6. QCI-Amine **3** was hydrogenated according to the general procedure. (1*S*,2*S*,4*S*,5*R*)-2-(Aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane **5** was isolated as a light brown viscous oil (5.1 g, 97%). $[a]_D^{rt} = +17.8$ (c = 1, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) 2932, 2865, 1455, 1379, 1050, 980, 928; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.95–2.76 (m, 3H), 2.74–2.67 (dd, J = 12.7 Hz, J= 9.5 Hz, 1H), 2.62–2.56 (m, 1H), 2.51–2.46 (dd, J = 12.7 Hz, J = 4.9 Hz, 1 H), 2.37–2.31 (m, 1H), 1.68–1.32 (m, 7H), 1.31–1.22 (pent, 2H) 1.12–1.04 (m, 1H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 25.5, 26.7, 27.7, 28.9, 37.8, 40.7, 45.8, 57.8, 58.9; HPLC-MS: t_R = 2.1 min, ESI *m*/*z* (rel. inten-

sity): 168.8 (M^+, 100); Direct infusion MS (EI) *m*/*z* (rel.intensity): 169.2 (M + 1, 20), 153.3 (22), 138.4 (32), 110.6 (100), 96.7 (26), 82.3 (36).

(1*S*,2*R*,4*S*,5*R*)-2-(Hydroxymethyl)-5-ethyl-1-azabicyclo-[2.2.2]octane 7. QCD **2** was hydrogenated according to the general procedure (half scale). (1*S*,2*R*,4*S*,5*R*)-2-(Hydroxymethyl)-5-ethyl-1-azabicyclo[2.2.2]octane **7** was isolated as a colourless viscous oil (2.5 g; 98%). Spectral data were identical to those reported in ref. 22.

(1*S*,2*R*,4*S*,5*R*)-2-(Aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]-octane 8. QCD-Amine **4** was hydrogenated according to the general procedure. (1*S*,2*R*,4*S*,5*R*)-2-(Aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane **8** was isolated as a pale yellow viscous oil (5.3 g, 98%). $[\alpha]_D^{rt} = +152.9$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) 2937, 2873, 1575, 1520, 1461, 1380, 1051, 929; ^1H NMR (500 MHz, $CDCl_3$): δ 2.95–2.76 (m, 3H), 2.74–2.66 (dd, *J*= 12.7 Hz, *J* = 9.6 Hz, 1H), 2.56–2.64 (m, 1H), 2.51–2.46 (dd, *J* = 12.7 Hz, *J* = 4.9 Hz, 1H), 2.37–2.31 (m, 1H), 1.68–1.30 (m, 7H), 1.27 (pent, 2H), 1.12–1.04 (m, 1H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 25.6, 26.9, 27.8, 29.0, 37.8, 40.8, 45.9, 57.9, 59.0; HPLC-MS: t_R = 2.1 min, ESI *m*/*z* (rel.intensity): 168.8 (M^+, 100); Direct infusion MS (EI) *m*/*z* (rel.intensity): 169.2 (M + 1, 30), 138.3 (52), 110.3 (100), 82.3 (62).

(1*S*,2*S*,4*S*,5*R*)-2-(*N*-(Isopropyl)aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane 9. Sodium cyanoborohydride (0.189 g, 3.0 mmol), methanol (2.76 ml) and 4 Å molecular sieves (0.15 g) were mixed. To the mixture was added acetone (0.44 ml, 6.0 mmol) and (1*S*,2*S*,4*S*,5*R*)-2-(aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane **6** (0.51 g, 3.0 mmol) in a solution of 2.8 ml methanol. The mixture was stirred for 24 h in room temperature and then quenched with 3.3 ml water and 3.3 ml 10% sodium hydroxide solution. The mixture was filtered and then extracted three times with 15 ml dichloromethane. The combined organic phases were washed with 10% aqueous sodium hydroxide solution (3 × 15 ml), and subsequently extracted with 0.5 M aqueous hydrochloric acid (3 × 15 ml). The combined water phases were made basic and then extracted three times with dichloromethane. The organic phases were dried with sodium sulfate and then concentrated under reduced pressure to give (1*S*,2*S*,4*S*,5*R*)-2-(*N*-(isopropyl)aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane **9** a slightly yellowish oil (0.50 g, 78%). $[\alpha]_D^{rt} = +3.2$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) 2961, 2932, 2865, 1520, 1455, 1383, 1339, 1126, 1051, 922; ^1H NMR (500 MHz, $CDCl_3$): δ 3.15–3.08 (dd, *J* = 13.4 Hz, 9.5 Hz, 1H), 2.8–2.6 (m, 2H), 2.75 (sep, *J* = 6.2 Hz, 1H), 2.64–2.5 (m, 5H), 2.38 (m, 1H), 1.81 (m, 1H), 1.65 (m, 1H), 1.5–1.3 (m, 5H), 1.04 (dd, *J* = 6.9 Hz, *J* = 6.6 Hz, 6H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 22.5, 23.3, 25.7, 27.3, 27.8, 28.5, 37.8, 40.8, 49.1, 51.2, 55.8, 57.5; HPLC-MS: t_R = 2.2 min, ESI *m*/*z* (rel.intensity): 210.9 (M^+, 100); Direct infusion MS (EI) *m*/*z* (rel.intensity): 211.2 (M + 1, 26), 153.3 (30), 110.3 (100), 82.3 (46).

(1*S*,2*R*,4*S*,5*R*)-2-(*N*-(Isopropyl)aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane 10. (1*S*,2*R*,4*S*,5*R*)-2-(Aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane **8** (0.5 g, 3.0 mmol) was reductively alkylated with acetone following the same procedure as described for the QCI-amine **9**. (1*S*,2*R*,4*S*,5*R*)-2-(*N*-(isopropyl)aminomethyl)-5-ethyl-1-azabicyclo[2.2.2]octane **10** was isolated as a pale yellow oil (0.52 g, 83%). $[\alpha]_D^{rt} = +191.1$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$, cm^{-1}) 2961, 2935, 2873, 1463, 1382, 1339, 1082, 1055, 920; ^1H NMR (500 MHz, $CDCl_3$): δ 2.9–2.7 (m, 5H), 2.75–2.71 (t, *J* = 6.2 Hz, 1H), 2.56 (dd, *J* = 11.7 Hz, *J* = 9.9 Hz, 1H), 2.48 (dd, *J* = 11.7 Hz, *J* = 4.6 Hz, 1H), 2.35 (m, 1H), 1.62–1.5 (m, 2H), 1.5–1.4 (m, 2H), 1.4–1.25 (m, 4H), 1.17–1.10 (m, 1H), 1.03 (dd, *J* = 9.1 Hz, *J* = 6.2 Hz, 6H), 0.83 (t, *J* = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 22.8, 23.2, 25.6, 26.0, 26.2, 27.8, 38.2, 48.5, 48.8, 49.2, 50.1, 50.6; t_R = 2.2 min, ESI *m*/*z* (rel.intensity): 210.9 (M^+, 100); Direct infusion MS (EI) *m*/*z* (rel.intensity): 211.2 (M + 1, 100), 195.4 (42), 153.3 (42), 110.2 (58), 82.2 (30).

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