2-Azanorbornyl Alcohols: Very Efficient Ligands for Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Aromatic Ketones

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2-Azanorbornyl-derived amino alcohols were prepared and evaluated as ligands in the Ru(II)-catalyzed asymmetric transfer hydrogenation of aromatic ketones. To improve selectivity and rate, the structure of the ligand was optimized. Acetophenone was reduced using 0.5 mol % catalyst in 40 min in 94% ee. This system was also able to reduce a wide range of aromatic ketones to the corresponding alcohols, while maintaining high enantioselectivities and yields. The effects of catalyst loading and the presence of cosolvents in the reaction vessel were examined, and a linearity study was also done.

Introduction

Catalytic asymmetric reduction of ketones to form chiral secondary alcohols is an important transformation in organic synthesis.[1] This enantioselective transformation can be accomplished by hydride reduction using the oxazaborolidine catalyst,[2] by hydrogenation with for example BINAP and DuPHOS ligands,[3] and by transfer hydrogenation.[4] The latter has been studied extensively during recent years because of the low cost, operational simplicity and favorable properties of the hydrogen donor—usually secondary alcohols or formic acid.[5] Ruthenium complexes are the most important catalysts in the asymmetric transfer hydrogenation of ketones, although other metal complexes of samarium,[6] rhodium,[7] and iridium[8] have been used successfully. Recently, Noyori developed an efficient and highly enantioselective ruthenium catalyst using diamines as chiral ligands.[9] Other types of chiral phosphorus and/or nitrogen ligands have also been used with varying levels of rate, yield, and selectivity.[10] A drawback of this methodology is the reversibility of the reaction. The equilibrium point depends on the redox potentials of the substrate and the hydrogen source.[1a] Consequently, long reaction times may lead to a drop in the enantiomeric excess. In a study of ligand acceleration effect in Ru(II)-catalyzed transfer hydrogenation, it was found that β-amino alcohols showed the highest reaction rate.[1a,11a] Despite these finding and the recent progress in this catalytic enantioselective

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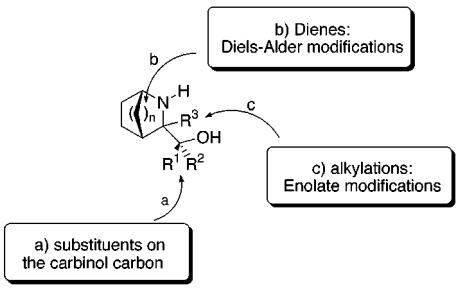


Figure 1.

process, there are only a few examples where simple amino alcohols are used as chiral ligands.[11] We recently reported the use of Ru(II)−2-azanorbornyl-3-methanol complexes as chiral ligands in this reaction.[12] These systems proved to be highly efficient for the reduction of aromatic ketones, using 2-propanol as the hydrogen source. The promising results regarding rates and enantioselectivities encouraged us to further investigate the limitations of this ligand and to optimize the 2-azanorbornyl structure in order to improve the catalytic activity and selectivity.

In this paper, we present the synthesis of new bicyclic β-amino alcohols and their use as chiral ligands in the transfer hydrogenation of aromatic ketones.

Results and Discussion

Synthesis of Chiral Amino Alcohol Ligands. An important feature in the preparation of new chiral ligands is their synthetic versatility, allowing a variety of modifications of their structures. These modifications can affect the performance of the ligand to a great extent. In this context, the methyl (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethylamino]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate derivative, obtained in high yield via a highly exo- and diastereoselective aza-Diels−Alder reaction between cyclopentadiene and the iminium ion derived from methyl glyoxylate and (*S*)-1-phenylethylamine,[13] presents the possibility of a wide variety of modifications in its structure. Three different ligand modification strategies were carried out and are shown in Figure 1.

Amino Alcohol Substitution Effects. We recently demonstrated that substitution of the carbinol carbon of the bicyclic amino alcohol ligands affects both the selectivity and the rate in the Ru(II)-catalyzed transfer hydrogenation of acetophenone.[14] It was shown that merely by introducing a methyl substituent in α-position to the alcohol the selectivity and the rate of the new ligands changed from a very active catalytic species (for the (*R*)-Me substitution) to a less active one ((*S*)-Me substitution). This could be explained by steric interactions between the substituent and the arene or between the substituent and the Ru-hydride in the metal hydride complex. To extend this study, not only were the (*R*)- and (*S*)-methyl substituted ligands synthesized, but also the bulkier phenyl-substituted analogues. These two new ligands were compared to the unsubstituted derivative **2** (Scheme 1), which had previously shown very high enantioselectivities and a large ligand acceleration effect.[12]

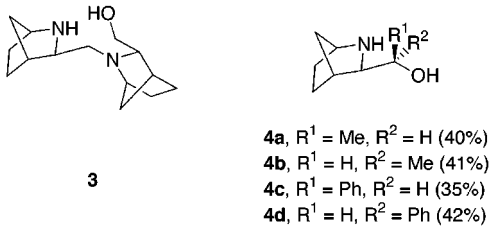
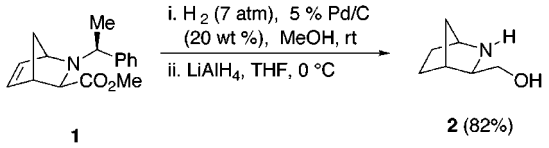


Figure 2.

Scheme 1



The already published synthesis of ligand **2** was optimized in the $LiAlH_4$ reduction step (Scheme 1) where a excess of reducing agent (6 equiv) and shorter reaction times were used in order to avoid the formation of a byproduct, which was found to be dimer **3** (Figure 2). The optimized synthesis and catalytic activity of **3** are currently being investigated in our group.[15]

Ligands **4a**−**d** were prepared[16] following a literature procedure and evaluated in the transfer hydrogenation of acetophenone, using [$RuCl_2$(*p*-cymene)][17] and isopropoxide as the base (acetophenone/Ru/chiral ligand/*i*-PrOK 200:1:4:5). The results are summarized in Table 1, entries 1−5.

As we expected, (*R*)-substitution in the carbinol carbon led to higher rates and enantioselectivities than the corresponding (*S*) forms (compare entries 2 and 4 with 3 and 5 in Table 1). In the case of phenyl-substituted ligands **4c** and **4d**, the selectivity was lower when compared with ligand **2**, probably due to an increase in the steric impediments that led to a less effective binding of the chiral ligand to the metal center. Ligand **4a** showed the highest rate (TOF = 1330 h^{-1}, 40 min reaction time) combined with a very good enantioselectivity (94% ee). It is important to mention that when using any of the ligands listed in Table 2, no decrease in optical purity of the product was observed during the course of the reaction.

Dienes: Diels−Alder Modifications. To investigate the influence of the bicyclic skeleton on the stereoselectivity, cyclopentadiene was replaced by 1,3-cyclohexadiene in the aza-Diels−Alder reaction.[13] Ligand **6** was then synthesized following the same procedure as for ligand **4**. Hydrogenation/hydrogenolysis of the Diels−Alder adduct **5** followed by LAH reduction of the amino ester intermediate afforded **6** in 90% yield (Scheme 2).

As shown in Table 1, entry 6, the ethylene-bridged ligand **6** is also highly enantioselective. Acetophenone

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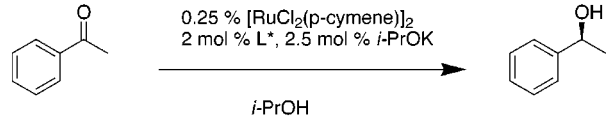
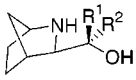
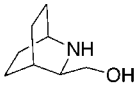
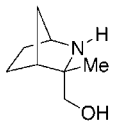
(17) For the synthesis of the Ru complexes, see: (a) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, 233. (b) Bennett, M. A.; Matheson, T. W.; Robertson, G. B.; Smith, A. K.; Tucker, P. A. *Inorg. Chem.* **1980**, *19*, 101.

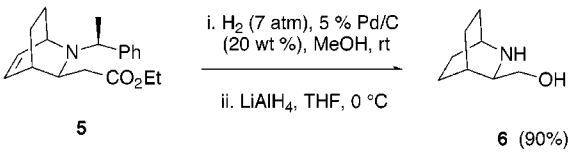
Table 1. Asymmetric Transfer Hydrogenation of Acetophenone Using Ligands 2, 4, 6 and 9[a]



entry	Chiral Ligand		Product Conv.[b](%)	t (h)	ee[c] (%)	Config.	TOF[d] (h^{-1})
1		**2**	92	1.5	94	*S*	450
2		**4a**	97	0.7	94	*S*	1330
3		**4b**	88	4.5	89	*S*	80
4		**4c**	94	1.0	81	*S*	690
5		**4d**	50	13	58	*S*	8
6		**6**	95	2.0	95	*S*	250
7		**9**	25	20	20	*R*	

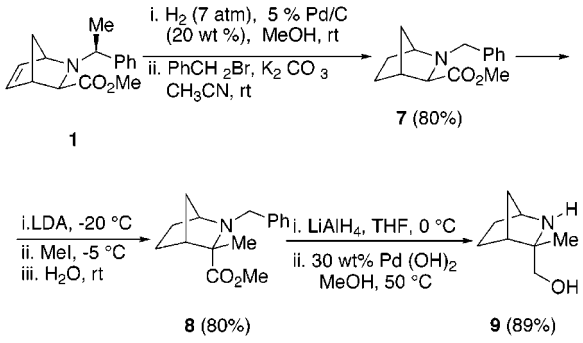
[a] Substrate to catalyst ratio 200 according to procedure 1 in the Experimental Section. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis. [d] Turnover frequencies [(mol product/mol catalyst)/h] were calculated at 50% conversion.

Scheme 2



5 6 (90%)

Scheme 3



1 7 (80%) 8 (80%) 9 (89%)

was reduced with 95% ee and in 95% yield, thus proving to be just as selective as the methylene-bridged analogue **2**. A drawback of this ligand is the decrease of the reaction rate.

Enolate Modifications. We were interested in how a 3,3-disubstitution in the 2-azanorbornyl skeleton affected the rate and the enantioselectivity in the transfer hydrogenation of aromatic ketones. We recently reported that a highly diastereoselective enolate alkylation of 2-azanorbornyl derivatives with different electrophiles such as alkyl halides, aldehydes, and acyl chlorides gave the corresponding exo addition products.[18] These reactions proceed with diastereoselectivities >98%. Taking advantage of this new strategy, we synthesized amino alcohol **9** (Scheme 3).

Hydrogenation/ hydrogenolysis followed by benzylation of **1** afforded **7** in 80% yield. Addition of LDA at −20 °C generated the enolate, which was diastereoselectively alkylated with MeI to give **8**. Reduction of the ester and debenzylation with $Pd(OH)_2$ under hydrogen atmosphere (1 atm) afforded ligand **9** in 89% yield. However, this transformation generated a poorly performing ligand that produced 1-phenylethyl alcohol with low and reversed enantioselectivity (*R* instead of *S*, entry 7, Table 1).

Transfer Hydrogenation of Aromatic Ketones. The reactions were run with a substrate-to-catalyst ratio of (S/C) 200. The chiral catalysts were prepared by refluxing 2 mol % ligand with 0.25 mol % [$RuCl_2$(*p*-cymene)]$_2$ in 2-propanol for 30 min. The 0.10 M solution of substrate in 2-propanol was mixed with 2.5 mol % *i*-PrOK used as cocatalyst before addition of the chiral catalyst. The transfer hydrogenations were done at room temperature, and the results are summarized in Table 2.

Due to the simple synthesis of ligand **2**, it was chosen for a more thorough study of the transfer hydrogenation of various alkyl aryl ketones; see Table 2. Our ligand shows a high capacity to hydrogenate most ketones with good conversion and ee at a high rate. The enantiomeric excess and the reaction rate in the reduction of alkyl aryl ketones were found to be dependent on both steric and electronic factors. Asymmetric transfer hydrogenation of sterically hindered ketones are often associated with loss of enantioselectivity and lower reaction rates. This is also the case with our catalytic systems, but the decrease is only moderate. The reduction of linear alkyl aryl ketones (entries 1−5) proceeds rapidly to the corresponding chiral alcohol with good ee's, ranging from 92 to 95%. Ketones with branched alkyl groups such as *tert*-butyl and isopropyl give lower yields of the reduced alcohol as well as lower ee's (entries 6 and 7).

The introduction of electron-withdrawing substituents, such as −Br and −CF_3 in the *ortho*, *meta*, and para positions of the aryl ketone, resulted in higher rates but

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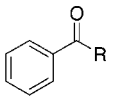
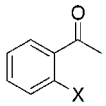
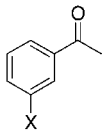
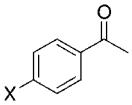
Table 2. Asymmetric Transfer Hydrogenation of Acetophenones Catalyzed by Ligand 2[a]

			Product		
entry	ketone		t (h)	conv. (%)[b]	ee (%)[c]
1		R = CH_3	1.5	91	94
2		R = C_2H_5	1.5	81	93
3		R = n-C_3H_7	2	90	92
4		R = n-C_4H_9	1.5	78	95
5		R = n-C_6H_{13}	2	85	95
6		R = *i*-C_3H_7	15	76	90
7		R = *t*-Bu	2	46	64
8		X = CH_3	2	100	91
9		X = MeO	2	96	90
10		X = Br	1	100	90
11		X = NH_2	20	<10	nd
12		X = NO_2	20	<5	nd
13		X = CH_3	2	94	94
14		X = MeO	2	96	94
15		X = Br	1	100	93
16		X = NH_2	3	100	93
17		X = NO_2	20	15	nd
18		X = CH_3	2	88	93
19		X = MeO	4	66	83
20		X = Br	1	100	87
21		X = NH_2	20	<10	nd
22		X = CF_3	1	100	88
23		X = NO_2	1	100	89
24	1-acetonaphtone		1.5	100	97
25	2-acetylpyridine		2	66	92
26	3-acetylpyridine		1	100	89

[a] Transfer hydrogenations were carried out using S/C 200 according to procedure 1 in the Experimental Section. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral GC analysis.

slightly lower enantioselectivities (entries 10, 15, 20, and 22). The reaction rate was moderately decreased with electron-donating substituents on the aromatic ring, but the high enantioselectivity was maintained. The exception was the *p*-methoxy-substituted acetophenone that gave a lower reaction rate and ee (entry 19). This substrate has proven to be difficult to reduce efficiently with other ligands as well; this is probably due to its lower redox potential.[11b]

The results obtained with nitrogen substituents strongly depend on their position in the aromatic ring. Neither amino nor nitro groups can be present in the ortho position for a successful hydrogenation to take place. However, amino substituents in the meta position give good yields and enantioselectivity (entry 16). Almost the same result was obtained when a nitro group was introduced in the para position (entry 23). Acetonaphthone and 2- and 3-acetylpyridine were reduced with good to excellent ee. Acetonaphthone gave the highest enantioselectivity reported in this paper (97%).

Generally, the best results were obtained when substituents were placed in the meta position. The yields were increased, and the enantioselectivities remained high. When reducing para-substituted acetophenone derivatives a slight decrease in selectivity was observed.

Unfortunately, when using the described procedure in the transfer hydrogenation reactions shown in Table 2 we were unable to reduce indanone and tetralone. Changing the proton source to the more potent formic acid/triethylamine failed. It is well-known that amino alcohols are not compatible with this solvent system.[4e] To overcome this problem, we developed an alternative procedure where the substrateswere added to the catalyst 5 min after the base. In addition, the chiral ligand and $[RuCl_2(p\text{-cymene})]_2$ were not refluxed for 30 min but simply stirred at room temperature for 5 min. Table 3 shows the optimized results with 1-indanone and 1-tetralone using S/C 50. When this procedure was used, ligand **2** induced high enantioselectivity, giving ee's as high as 95%. In all cases the reactions were substantially slower (18 h) compared to the reduction of acetophenone and the yields were low as well.

Table 3. Asymmetric Transfer Hydrogenation of 1-Indanone and 1-Tetralone Catalyzed by Ligands 2 and 6[a]

			product		
entry	ligand	ketone	*t* (h)	convn[b] (%)	ee[b] (%)
1	2	1-indanone	18	50	95
2	6	1-indanone	18	50	84
3	2	1-tetralone	18	72	95
4	6	1-tetralone	18	70	89

[a] Transfer hydrogenations were carried out according to procedure 2 in the Experimental Section using S/C = 50. [b] Determined by HPLC analysis.

Table 4. Solvent Effects[a]

entry	solvent	product		
		t (h)	yield[b] (%)	ee[c] (%)
1	THF (1 mol %)	6	95	92
2	THF/*i*-PrOH 1/1	6	73	93
3	DMF (1 mol %)	2	95	93
4	DMF/*i*-PrOH 1/1	20	27	92
5	toluene (1 mol %)	2	95	94
6	toluene//*i*-PrOH 1/1	2	85	91

[a] The transfer hydrogenations were carried out using S/C = 200 according to procedure 1 in the Experimental Section. [b] Determined by 1H NMR spectroscopy. [c] Determined by chiral HPLC analysis; see the Experimental Section.

Table 5. Catalyst Loading[a]

entry	substrate/Ru/L*/base	product		
		t (h)	convn[b] (%)	% ee[c]
1	200:1:4:5	1.5	91	94
2	400:1:4:5	2.5	94	94
3	800:1:4:5	18	81	94

[a] Transfer hydrogenations were carried out according to procedure 1 using 0.10 M solutions. [b] Determined by 1H NMR spectroscopy. [c] Determined by chiral HPLC analysis; see the Experimental Section.

Solvent Effect. Some substrates might not be soluble in 2-propanol, and therefore, we were interested in how an additional solvent (THF, DMF, and toluene) influenced the enantioselectivity and reactivity. It was found that all solvents when mixed 1:1 with 2-propanol slowed the hydrogenation of acetophenone. In addition, a 1−4% decrease in selectivity was generally observed.

Catalyst Loading. Reducing the catalyst loading did not affect the enantioselectivity (Table 5, entries 1 and 2). (*S*)-1-Phenylethanol is obtained in 81% yield after 18 h reaction time with S/C = 800 (entry 3); further increase in S/C molar ratio is accompanied with low conversions.

Nonlinearity Study. To examine the influence of ligand purity on the ee, we carried out a series of reactions with mixtures of the (*R*) and (*S*) enantiomers of ligand **2** (using acetophenone/Ru/chiral ligand/base molar ratio 200:1:1:5). When the ee of the (*S*)-1-phenyl ethanol was plotted against the ee of ligand **2**, a slight nonlinear effect was revealed as can be seen in Figure 3. The nonlinearity may in principle be caused by the formation of dimeric precatalyst species consisting of a mixture of so-called hetero- and homodimers.[19] In our case, the heterodimer seems to be more active, resulting in (*S*)-1-phenylethanol of lower enantiomeric purity.

In conclusion, we have demonstrated that simple amino alcohols can successfully be used as ligands in the Ru(II)-catalyzed transfer hydrogenation of a wide variety of aryl alkyl ketones. These chiral amino alcohols are obtained in good yields after simple transformations of an aza-Diels−Alder adduct derived from the highly diastereoselective reaction between cyclopentadiene and the iminium ion of methylglyoxylate and (*S*)-1-phenylethylamine. The reductions take place at a high rate, with good yield and enantioselectivity. We have also improved the performance of the system by altering the general procedure. Further investigations of the 2-azanorbornane structure and its use in asymmetric transfer hydrogenation are currently in progress.

(19) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2922.

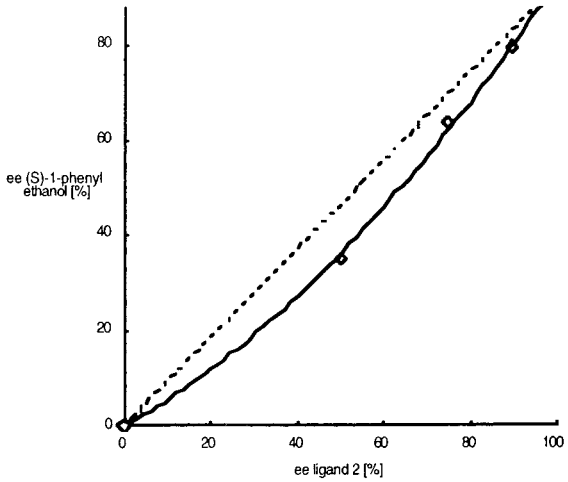


Figure 3. Asymmetric transfer hydrogenation of acetophenone: ee of (*S*)-1-phenylethanol as a function of ee off ligand **2**.

Experimental Section

For general experimental information see ref 20. Reactions were carried out under nitrogen using dried glassware. *i*-PrOH was dried over CaH_2 and freshly distilled under nitrogen prior to use. Acetophenone was distilled and stored over activated molecular sieves. *i*-PrOK **(**1 M) was prepared prior to use from freshly distilled *i*-PrOH and potassium. Reactions in Tables 2 and 4 were carried out in a Quest 210 supplied by Argonaut Technologies. Flash chromatography was performed on silica gel (Matrex 60A, 37−70 μm). Deactivated silica gel means that it was treated with 5% Et_3N in pentane and the column was eluted with the same solvent mixture until the eluent was basic according to pH paper. HPLC analysis were carried out using a chiral column (ChiralCel OD-H) and a diode-array detector with a flow rate of 0.5 mL/min using 5% *i*-PrOH in hexane as solvent. GC analysis was done on a Varian 3400 capillary gas chromatograph using a CP-Chirasil-Dex CB (25 m/0.25 mm i.d.) column with nitrogen as carrier gas and a flame ionization detector.

General Procedures for Transfer Hydrogenation of Aromatic Ketones. Procedure 1. Amino alcohol ligand (20 μmol) and $[RuCl_2(p\text{-cymene})]_2$ (1.53 mg, 2.5 μmol) were added to a round bottle flask. Any moisture was azeotropically removed via evaporation with benzene (3 × 4 mL) at reduced pressure. Reflux under nitrogen for 30 min in 2 mL of *i*-PrOH generated the precatalyst. The substrate (1 mmol) was dissolved in 8 mL of *i*-PrOH, and the base 1 M *i*-PrOK in *i*-PrOH (25 μL, 40 mmol) was added at room temperature, followed by the precatalyst. The resulting solution was stirred at room temperature, and the reaction was monitored by ^{1}H NMR.

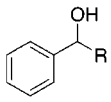
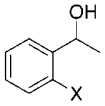
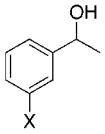
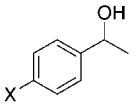
Procedure 2. Amino alcohol ligand (7.3 μmol) and $[RuCl_2(p\text{-cymene})]_2$ (2.03 mg, 3.3 μmol) were dissolved in 2 mL *i*-PrOH. After 5 min of stirring under nitrogen at room temperature, the substrate (0.33 mol, 0.1 M in *i*-PrOH) was added. Stirring was continued for 5 min, and NaOH (2.4 mL, 0.1 M in *i*-PrOH) was added.

Compounds **1**,[13] **2**,[12] **4a**−**d**,[14,15] **5**,[21] and **6**[22] were carried out following literature procedures.

(1*S*,3*R*,4*R*)-2-Benzyl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylic Acid Methyl Ester (7). Hydrogenation/debenzylation of compound **1** were performed according to a literature procedure.[23] The resulting amino ester (3.0 g, 19.3 mmol) was dissolved in acetonitrile (75 mL), and K_2CO_3 (5.3 g, 38.7 mmol) was added followed by benzylbromide (2.3 mL, 19.3

(20) Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518.
(21) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707.
(22) Pinho, P.; Guijarro, D.; Andersson, P. G.*Tetrahedron* **1998**, *54*, 7897.

Table 6. Analysis Methods and Retention Times for the Products Obtained in the Substrate Study

entry	alcohol	analysis method / program	rt_1 (min)	rt_2 (min)
1	 R = CH_3	HPLC	16.7	20.8
2	R = C_2H_5	HPLC	15.3	18.9
3	R = n-C_3H_7	HPLC	15.1	17.5
4	R = n-C_4H_9	HPLC	14.4	16.5
5	R = n-C_6H_{13}	HPLC	75.5	77.0
6	R = *i*-C_3H_7	GC / 1	47.7	48.3
7	R = *t*-Bu	GC/ 1	53.2	54.3
8	 X = CH_3	GC /1	44.2	48.8
9	X = MeO	GC / 1	51.9	53.8
10	X = Br	GC / 1	62.5	68.1
12	 X = CH_3	GC / 1	40.3	41.5
13	X = MeO	GC / 1	55.4	56.6
14	X = Br	GC / 1	62.7	64.2
15	X = NH_2	GC / 1	74.6	75.4
16	 X = CH_3	GC / 1	37.2	39.7
18	X = MeO	GC / 1	53.6	55.1
19	X = Br	GC / 1	63.7	65.8
20	X = NO_2	GC / 2	56.2	57.4
21	X = CF_3	GC / 1	40.0	43.4
22	1-naphthalen-1-yl-1-ethanol	HPLC	32.8	51.0
23	1-pyridin-2-yl-ethanol	GC / 1	49.6	49.0
24	1-pyridin-3-yl-ethanol	GC / 1	58.0	60.2
25	1-indan-1-ol	HPLC	18.5	20.9
26	1,2,3,4-tetrahydro-naphtalen-1-ol	HPLC	16.3	18.3

[a] Program 1: hold 90 °C for 10 min, heat to 150 °C/min, hold min, heat to 220 °C, 40 °C/min. Program 2: heat from 110 °C to 180 °C, 1 °C/min, hold 180 °C for 10 min, heat to 220 °C, 40 °C/min.

mmol). The reaction mixture was stirred under nitrogen overnight at room temperature. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (60 mL) and washed with brine (30 mL). Drying over $MgSO_4$, concentration under reduced pressure, and purification by flash chromatography (deactivated silica, pentane/ EtOAc 20/1−5/1) afforded pure **9** (4.0 g, 15.4 mmol) in 80% yield: $[\alpha]^{21}_D = +71.8$ (c = 0.11, CH_2Cl_2); IR (neat, cm^{-1}) 2952, 1745, 1156; ^1H NMR δ 1.25 (1H, d, J = 9.6 Hz), 1.30−1.42 (2H, m), 1.62−1.71 (1H, m), 1.91−2.03 (2H, m), 2.52 (1H, br s), 2.69 (1H, s), 3.33 (1H, s), 3.53 (3H, s), 3.74 (1H, s), 3.64−3.77 (1H, m), 7.19−7.36 (5H, m); ^{13}C NMR δ 22.3, 29.2, 36.5, 42.3, 51.4, 55.4, 59.6, 66.7, 126.8, 128.0, 129.0, 139.1, 173.9; MS (EI) *m/z* (rel intensity) 245 (M^+, 7), 186 (79), 158 (100), 92 (57).

(1*S*,3*S*,4*R*)-2-Benzyl-2-azabicyclo[2.2.1]hept-5-ene-3-methyl-3-carboxylic Acid Methyl Ester (8). A solution of compound **7** (100 mg, 0.41 mmol) in dry THF (1 mL) was slowly added to freshly prepared LDA (0.45 mmol) in dry THF (5 mL) at −20 °C. After 40 min, the reaction mixture was warmed to 5 °C, and MeI was added (0.43 mmol). The mixture was allowed to reach room temperature overnight. The reaction was quenched with brine and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (silica gel, pentane/ Et_2O) to afford compound **8** in 80% yield: $[\alpha]^{21}_D = -30.9$ (c = 0.11, CH_2Cl_2); IR (neat, cm^{-1}) 2966, 1735, 1113; ^1H NMR (400 MHz/$CDCl_3$) δ 1.21 (1H, d, J = 9.6 Hz), 1.30−1.49 (3H, m), 1.42 (3H, d, J = 4.4 Hz), 1.70−1.76 (1H, m), 1.85−1.95 (1H, m), 2.41 (1H, br s), 3.06 (1H, br s), 3.73 (3H, d, J = 4.4 Hz) 3.78 (1H, d, J = 3.6 Hz), 4.05 (1H, dd, J_1 = 3.2 Hz, J_2 = 14.4 Hz), 7.20−7.48 (5H, m); ^{13}C NMR (100 MHz/$CDCl_3$) δ 23.7, 26.2, 27.4, 35.5, 48.8, 51.3, 51.5, 60.0, 70.4, 126.6, 128.2, 128.4, 142.6, 177.3; MS (EI) *m/z* (rel intensity) 259 (M^+, 6), 200 (100), 186 (11), 172 (40), 91 (41). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.14; H, 8.16; N, 5.40. Found: C, 74.04; H, 8.30; N, 5.40.

(1*S*,3*S*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-methyl-3-methanol (9). Compound **8** (280 mg, 1.1 mmol) dissolved in THF (7 mL) was slowly added to a suspension of $LiAlH_4$ (42 mg, 1.1 mmol) in THF at 0 °C. The reaction mixture was stirred for 1 h and then quenched by slow addition of water (0.3 mL), 5% NaOH (0.3 mL), and water (0.8 mL). The reaction mixture was filtered and washed with THF, dried ($MgSO_4$), and concentrated under reduced pressure to afford the alcohol (239 mg) in 96% yield, pure by ^1H NMR.

Without further purification the alcohol was debenzylated. The alcohol was dissolved in MeOH and $Pd(OH)_2$ (120 mg, 50 wt %) was added. The reaction mixture was put under hydrogen pressure (1 atm), heated to 40−50 °C, and stirred overnight. After the mixture was cooled to room temperature, the $Pd(OH)_2$ was filtered off through a pad of Celite and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (30 mL), washed with brine (10 mL), dried with $MgSO_4$, and concentrated under reduced pressure to afford **9** (136 mg) in 93% yield. The amino alcohol was recrystallized from ether/ pentane: $[\alpha]^{21}_D = -2.7$ (c = 0.6, CH_2Cl_2); mp = 194−197 °C; IR (neat, cm^{-1}) 3328, 2900, 2750, 1392, 1063, 1052; ^1H NMR (400 MHz/$CDCl_3$) δ 1.49−1.61 (1 H, m), 1.51(3H, s), 1.60 (1H, d, J = 12.0 Hz), 1.78 (1 H, m), 1.86−2.04 (2H, m), 2.24 (1H, d, J = 11.2 Hz), 2.32 (1H, br s) 3.51(1 H, d, J = 12.8 Hz), 4.05 (1H, d, J = 12.8 Hz), 4.12 (1H, br s); ^{13}C NMR (100 MHz/$CDCl_3$) δ 22.30, 22.53, 25.09, 37.3, 44.29, 58.82, 64.91, 68.99; MS (EI) *m/z* (rel intensity) 142 (M^+, 10), 110 (66), 82 (100), 67 (17). Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.00; H, 10.54; N, 9.80.

(23) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *8*, 2530.

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