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Synthesis of enantiopure 2-acyl azetidines and the application of amino alcohols derived therefrom in enantioselective catalysis

François Couty* and Damien Prim

SIRCOB, UPRESA CNRS 8086, Université de Versailles, 45, avenue des Etats-Unis, 78035, Versailles Cédex, France

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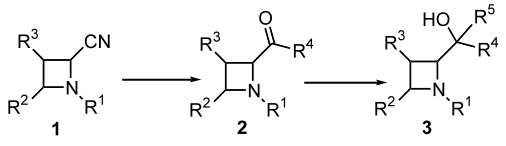
Abstract—Enantiopure 2-acyl azetidines were prepared in good yields from 2-cyano azetidines. The ketones produced were then stereoselectively reduced with sodium borohydride (with or without zinc bromide) or transformed into tertiary azetidinic amino alcohols by addition of phenyllithium. The latter compounds were found to be highly efficient catalysts for the enantioselective addition of diethylzinc to aldehydes, giving enantioselectivities up to 98%.

1. Introduction

2-Acyl azetidines of general structure **2** are scarcely reported heterocycles[1] and to our knowledge, not a single member of this family has been described in enantiomerically pure form. We recently reported a straightforward synthesis of 2-cyano azetidines **1** starting from readily available enantiopure β-amino alcohols.[2] Herein, we wish to describe a facile method for the preparation of 2-acyl azetidines **2** starting from **1**, and the transformation of the former ketones into 2-α-hydroxyaryl azetidines **3** (Scheme 1). We undertook the evaluation of these novel strained enantiopure β-amino alcohols as ligands for the catalytic addition of diethylzinc to aldehydes. This reaction, initially studied by Mukaiyama and Soai,[3] is now a benchmark for the evaluation of new ligands, and our results in this area are also presented.



Scheme 1. 2-Acyl azetidines are easily prepared from the corresponding amino nitrile.

2. Results

2.1. Synthesis of 2-acyl azetidines

2-Cyano azetidines **4** and **5**, readily prepared from (−)-ephedrine[2] were first used as substrates to investigate their transformations into the corresponding 2-acyl azetidines. Treatment of these compounds with phenyllithium in benzene cleanly afforded imines **6** and **7**. On purification by flash chromatography, these imines underwent hydrolysis, and complete epimerization at C-2 was observed when imine **7** was subjected to chromatography, so that ketone **8** forms when starting from either **4** or **5**. When the same reaction is performed using stereoisomer **9**, the imine **10** was formed and, after chromatography, a 7:3 mixture of epimeric ketones **11** and **12** was isolated. Finally, treatment of the (*R*)-phenylglycinol-derived azetidine **13** gave imine **14** and subsequently stereoisomerically pure ketone **15** after chromatography (Scheme 2).

It should be noted that no substitution of the nitrile moiety by the phenyl group is observed in these reactions. As a matter of fact, α-amino nitriles are considered as useful precursors of iminium ions through the loss of cyanide ion under the influence of Lewis acids[4] and treatment of such a functional group with an organometallic reagent usually yields the corresponding amine through an elimination/addition sequence. This old-standing Bruylants reaction[5] is disfavored in our case since it would generate a highly strained iminium ion intermediate, which accounts for the exclusive addi-

* Corresponding author. Tel.: 33(1)39254455; fax: 33(1)39254452; e-mail: couty@chimie.uvsq.fr

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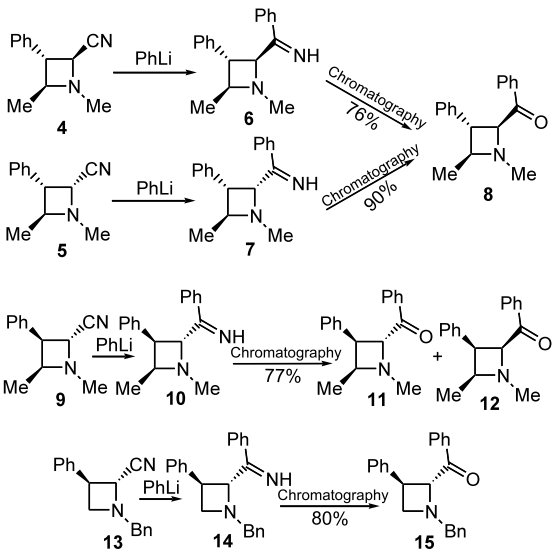


Scheme 2. Synthesis of 2-acyl azetidines.

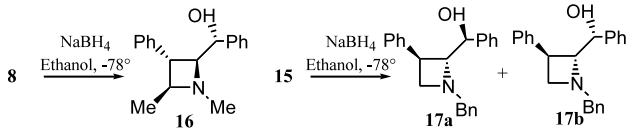
tion of the organolithium reagent to the cyano moiety in this case. The epimerization which occurs during chromatography of the intermediate imines highlights the ease of enolization of such aryl ketones. 2,3-t*rans*-Ketones were obtained either exclusively or as the major component of the epimeric mixture, and the relative stereochemistry of these compounds were determined by NMR[6] and indirectly by the sense of the enantioselectivities observed when their derivatives were used as ligands in enantioselective catalysis (vide supra). The ratio resulting from epimerization is reflective of the thermodynamic control in the system. Indeed, AM1 calculations performed with ketones **8** (and its C-2 epimer), **11** and **12** show that the 2,3-*trans* isomers are more stable by ca. 3–4 kcal mol^{-1} compared to their *cis* epimers, irrespective of the configuration of the tertiary amine.

Having in hand enantiopure 2-acyl azetidines, we began to investigate the outcome of nucleophilic additions of organometallic reagents on the keto moiety.

2.2. Synthesis of 2-α-hydroxyaryl azetidines

Reduction of the phenacyl moiety in **8** and **15** with sodium borohydride in ethanol at −78°C occurred stereoselectively to give **16** (de: 86%) and **17a**,**b** (de: 60%). In the first case, chromatography gave pure **16** in 74% yield whilst in the case of **17**, diastereoisomerically pure *anti*-**17a** and *syn*-**17b** were isolated in 66 and 17% yield, respectively (Scheme 3). When zinc bromide was used as an additive in these reactions, following a recently described procedure performed on a related aziridinic substrate,[7] the diastereoselectivity increased to >98% in both cases. The attribution of the relative *anti* stereochemistry in the alcohols produced was deduced from the following points.

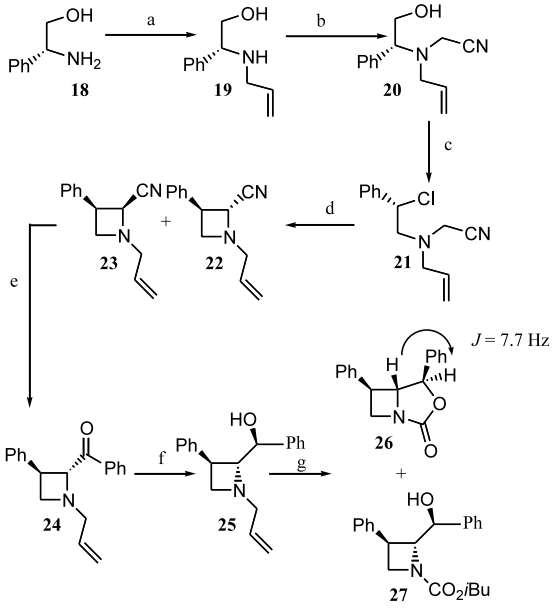
First, it is reported for closely related substrates that the addition of $ZnBr_2$ in such reductions favors chela-



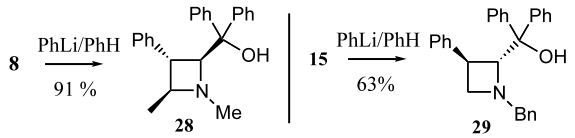
Scheme 3. Reduction of 2-acyl azetidines gives predominantly *anti* isomers.

tion control to give stereoselectively *anti* isomers.[7] Secondly, a cyclic derivative **26** of a close analogue[8] of **17a** was synthesized as shown in Scheme 4: (*R*)-phenylglycinol **18** was first *N*-monoallylated,[9] and transformed via a three-step sequence into a 64:35 epimeric mixture of 2-cyano azetidines **22** and **23** following our previously reported procedure.[2] Treatment of this mixture with phenyllithium followed by chromatography gave ketone **24** (de: 90%) that was reduced using zinc bromide as an additive to give alcohol **25** (de: 98%). The carbonate derivative of this alcohol, upon treatment with Grubb's catalyst,[10] underwent *N*-deallylation to give oxazolidinone **26** together with carbamate **27**. Examination of the ^3J coupling constant in the former compound establishes unambiguously the relative configuration of the two vicinal stereocenters.

Addition of phenyllithium to ketones **8** and **15** also afforded tertiary alcohols **28** and **29** (Scheme 5).



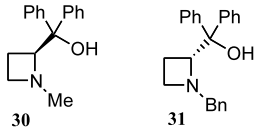
Scheme 4. Determination of the stereochemistry of the alcohols through the synthesis of a cyclic oxazolidinone derivative **26**. *Reagents and conditions*: (a) DBU, toluene, allyl bromide, 59%; (b) $BrCH_2CN$, K_2CO_3, CH_3CN, 65%; (c) $SOCl_2$, CH_2Cl_2, quant.; (d) LiHMDS, −78°C, THF, 90%; (e) PhLi, PhH, then chromatography, 69%; (f) $NaBH_4$, $ZnBr_2$, EtOH, 61%; (g) *i*-BuOCOCl, DMAP, CH_2Cl_2, reflux; (ii) Grubb's catalyst, toluene, reflux then chromatography.



Scheme 5. Addition of phenyllithium on 2-acyl azetidines.

2.3. Evaluation of 2-α-hydroxymethyl azetidines in enantioselective catalysis

Our newly synthesized azetidinic amino alcohols were then evaluated as chiral ligands during the catalytic enantioselective addition of diethylzinc on aldehydes. In this extensively studied field,[11] the unreported structural feature of our azetidinic ligands include the following points: (i) the presence of an extra substituent at C-4 and/or C-3 and (ii) the presence of a stereogenic center bearing the hydroxyl moiety (e.g. alcohols **16**, **17a**,**b**). Our results, using a standardized ratio of aldehyde/diethylzinc/ligand = 1/2/0.1 in toluene for 24 h at room temperature, are gathered in Table 1 and deserve some comments. First, modest enantioselectivities are obtained when secondary alcohols came to be used in this reaction (entries 1–3). It is interesting to note that the absolute configuration of the stereogenic center bearing the hydroxyl moiety has a dramatic influence on the outcome of the reaction since the enantioselectivity is *reversed* when isomers **17a** and **17b** are used as catalysts (entries 2, 3). Secondly, tertiary alcohols **28** and **29** are very efficient ligands in this reaction. As a matter of fact, the presence of substituents on the azetidinic ring at C-4 and/or C-3 has little effect on the enantioselectivity since compounds **30** and **31** depicted hereafter and that are devoid of extra substituents compared to **28** and **29** were reported[11a,d] to give respective enantioselectivities of 98 (*S* configuration) and 88% (*R* configuration) in this reaction. A modest match effect is however observed in case of **29** compared to **31**. The absolute configuration at C-2 on the azetidinic ring therefore seems to be the controlling factor for stereoinduction, and this observation, combined with the absolute configuration of the alcohols produced is indirect proof for the establishment of the relative configurations at positions 2 and 3 in **28** and **29**.



In conclusion, we have reported a new synthesis of enantiopure azetidinic amino alcohols, some of them being very efficient ligands for enantioselective catalysis. Further work is in progress in our group in order to get further insights in the chemistry of these understudied heterocycles.

3. Experimental

3.1. General comments

^1H and ^{13}C spectra ($CDCl_3$ solution) were respectively recorded on a Bruker ARX 300 spectrometer at 300 and 62.9 MHz; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin–Elmer 141 instrument. All reactions were carried out under argon. Column chromatography was performed on silica gel 230–400 mesh by using various mixtures of diethyl ether (E), ethyl acetate (AcOEt) and petroleum ether (PE). TLC were run on Merck Kieselgel $60F_{254}$ plates. Melting points are uncorrected. Benzene and THF were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Mention of 'usual workup' means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic phases over $MgSO_4$, (iv) solvent evaporation under reduced pressure. Composition of stereoisomeric mixtures was determined by NMR analysis on crude products before any purification.

Table 1.

Entry	Aldehyde	Ligand[a]	Yield[b] (%)	E.e.[c]	Abs. conf.
1	Benzaldehyde	**16**	97	62	*S*
2	Benzaldehyde	**17a**	88	50	*R*
3	Benzaldehyde	**17b**	98	57	*S*
4	Benzaldehyde	**28**	98	98	*S*
5	Benzaldehyde	**28**[d]	97	94	*S*
6	Benzaldehyde	**29**	97	98	*R*
7	2-Furylaldehyde	**28**	–[e]	93	*S*
8	Nonanal	**28**	–[e]	86[f]	*S*

[a] Unless otherwise stated, 10 mol% of catalyst were used.
[b] Determined by GC, using dodecane as internal standard.
[c] Unless otherwise stated, determined by GC using Lipodex-A as chiral phase.
[d] In this case, 5 mol% of ligand was used.
[e] Not determined.
[f] Determined on the benzoylated derivative by HPLC using (*R*,*R*) *whelk 01* as chiral column (isopropanol/heptane: 0.5/99.5).

3.2. (2*S*,3*S*,4*S*)-(1,4-Dimethyl-3-phenylazetidin-2-yl)-phenylmethanone, 8

To a solution of cyanoazetidine **5** (215 mg, 1.14 mmol) in dry benzene (10 mL) was added dropwise at 0°C a solution of phenyllithium in cyclohexane/ether (1.8 M sol., 1.25 mL, 2.27 mmol). The solution was stirred for 15 min at 0°C and hydrolyzed by addition of an aqueous saturated solution of NH_4Cl (10 mL). Addition of water and ether was then followed by usual workup to give crude imine **7** as an oil. Flash chromatography of this residue (E/PE: 7/3) gave ketone **8** as a white solid (275 mg, 91%). Intermediate crude imine **7**: ^{1}H NMR: 1.28 (d, $J=6.2$ Hz, 3H, Me), 2.49 (s, 3H, NMe), 2.84 (t, $J=7.7$ Hz, 1H, H_3), 3.32 (qd, $J=6.2$ and 7.7 Hz, 1H, H_4), 3.99 (d, $J=7.7$ Hz, 1H, H_2), 6.85–6.95 (m, 2H, Ar), 7.12–7.68 (m, 20H, Ar), 10.8 (bs, 1H, NH); ^{13}C NMR: 20.5, 42.1, 50.4, 53.0, 67.2, 75.4, 115.6 to 156.8: aromatic carbons including impurities from the reagent, 176.5. Ketone **8**: mp: 91°C; R_f: 0.6 (E/PE: 7/3); $[\alpha]_D^{20}$: +2.3 (*c* 0.3, $CHCl_3$); IR (film): 1680 (CO), 1444, 1229, 743 cm^{-1}; ^{1}H NMR: 1.28 (d, $J=5.9$ Hz, 3H, Me), 2.55 (s, 3H, NMe), 3.23–3.26 (m, 2H, H_3, H_4), 4.27 (d, $J=7.7$ Hz, 1H, H_2), 7.21–7.34 (m, 7H, Ar), 7.45 (t, $J=6.9$ Hz, 1H, Ar para), 7.65 (d, $J=6.9$ Hz, 2H, Ar *ortho*/*ortho'*); ^{13}C NMR: 29.7, 43.3, 50.4, 67.5, 75.4, 127.3, 128.1, 128.6, 128.7, 133.1, 135.3, 138.1, 197.7. Anal. calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.31; H, 7.39; N, 5.26%.

Starting from cyano azetidine **4** and following the same procedure, the same ketone was obtained in 76% yield. The intermediate crude imine **6** showed the following signals in NMR: ^{1}H NMR: 1.52 (d, $J=6.2$ Hz, 3H, Me), 2.41 (s, 3H, NMe), 3.47 (dd, $J=3.0$ and 8.8 Hz, 1H, H_3), 3.92 (qd, $J=6.6$ and 3.0 Hz, 1H, H_4), 4.71 (d, $J=8.8$ Hz, 1H, H_2), 7.11–7.78 (m, 18H, Ar), 10.6 (bs, 1H, NH); ^{13}C NMR: 15.4, 35.8, 49.5, 62.3, 70.3, 115.8 to 145.7: aromatic carbons including impurities from the reagent, 173.5.

3.3. (2*R*,3*R*,4*S*)- and (2*S*,3*R*,4*S*)-(1,4-Dimethyl-3-phenylazetidin-2-yl)phenylmethanone, 11 and 12

Following the above procedure and starting from cyanoazetidine **9** (250 mg, 1.34 mmol), crude imine **10** was obtained, that gave a 7:3 epimeric mixture of ketones **11**:**12** as an oil after chromatography (E/PE: 6/4) (274 mg, 77%). Major epimer **11**: R_f: 0.57 (E/PE: 7/3); ^{1}H NMR: 0.91 (d, $J=6.3$ Hz, 3H, Me), 2.51 (s, 3H, NMe), 3.50 (qd, 1H, $J=6.6$ and 7.7 Hz, 1H, H_4), 4.07 (bt, $J=7.7$ Hz, 1H, H_3), 4.48 (d, $J=8.1$ Hz, 1H, H_2), 7.01–7.15 (m, 2H, Ar), 7.20– 7.35 (m, 8H, Ar), 7.65 (d, $J=6.9$ Hz, 2H, Ar *ortho*/*ortho'*); ^{13}C NMR: 15.1, 36.7, 44.4, 69.7, 76.7, 126.7, 126.9, 127.7, 127.8, 127.9, 128.1, 128.5, 128.8, 132.8, 136.1, 197.9. The following selected signals belong to the minor epimer **12**: ^{1}H NMR: 0.90 (d, $J=6.3$ Hz, 3H, Me), 2.44 (s, 3H, NMe) 5.10 (d, $J=5.9$ Hz, 1H, H_2); ^{13}C NMR: 13.9, 36.7, 44.4, 73.8.

3.4. (2*R*,3*R*)-(1-Benzyl-3-phenylazetidin-2-yl)phenylmethanone, 15

Following the above procedure and starting from cyanoazetidine **13** (198 mg, 0.8 mmol), ketone **15** (287 mg, 80%) was obtained as an oil after chromatography (E/PE: 2/8). R_f: 0.32 (E/PE: 4/6); $[\alpha]_D^{20}$: −56.4 (*c* 1.1, $CHCl_3$); IR (film): 1690 (CO), 1450, 1380, 721 cm^{-1}; ^{1}H NMR: 3.27–3.36 (m, 1H, H_3), 3.76–3.86 (m, 3H, H_4, $H_{4'}$ and NCH*H*Ph), 3.90 (d, $J=12.9$ Hz, 1H, NC*H*HPh), 4.61–4.67 (broad d, $J=7.3$ Hz, 1H, H_2), 7.22–7.34 (m, 13H, Ar), 7.65 (d, $J=7.2$ Hz, 2H, Ar); ^{13}C NMR: 41.9, 57.2, 62.1, 75.8, 127.3, 127.4, 127.8, 128.2, 128.4, 128.6, 128.7, 129.3, 133.0, 135.5, 136.9, 140.0, 151.9, 197.8. Anal. calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.25; H, 6.55; N, 4.23%.

3.5. (2*R*,3*R*)-(1-Allyl-3-phenylazetidin-2-yl)phenylmethanone, 24

Following the above procedure and starting from various mixtures of cyanoazetidines **22** and **23** (300 mg, 1.5 mmol), ketone **24** was obtained as a 10:1 epimeric mixture after flash chromatography (E/PE: 4/6) (290 mg, 69%). Major epimer **24**: R_f: 0.36 (E/PE: 4/6); IR (film): 1680 (CO), 1598, 917, 743 cm^{-1}; ^{1}H NMR: 3.27 (dd, $J=8.7$ and 6.6 Hz, 1H, H_4), 3.37 (d, $J=6.5$ Hz, 2H, NCH_2CH), 3.92 (q, $J=7.5$ Hz, 1H, H_3), 4.01 (t, $J=5.8$ Hz, 1H, $H_{4'}$), 4.56 (d, $J=8.3$ Hz, 1H, H_2), 5.24–5.40 (m, 2H, CH_2CH), 5.88–6.01 (m, 1H, CH_2C*H*), 7.20–7.35 (m, 8H, Ar), 7.65 (d, $J=7.2$ Hz, 2H, Ar); ^{13}C NMR: 42.0, 57.5, 61.3, 77.9, 118.1, 127.3, 127.5, 127.8, 128.0, 128.1, 128.15, 128.2, 128.5, 128.6, 133.1, 133.9, 135.1, 139.6, 197.5.

3.6. (1′*R*,2*S*,3*S*,4*S*)-(1,4-Dimethyl-3-phenylazetidin-2-yl)phenylmethanol, 16

To a solution of **8** (197 mg, 0.74 mmol) in ethanol (8 mL) and cooled to −78°C was added in one portion sodium borohydride (33.7 mg, 0.891 mmol). After 1.5 h of stirring at −78°C, the reaction mixture was allowed to reach gradually rt and was quenched by addition of a saturated aqueous solution of NH_4Cl (2 mL). Water was then added and ethanol was evaporated under reduced pressure. Basification with an aqueous 1 M solution of NaOH and addition of diethylether was followed by usual workup to give an oil that was chromatographed (Et_2O). Amino alcohol **16** was obtained as a clear oil that crystallized on standing (146 mg, 74%). R_f: 0.50 (E/Ethanol: 9/1); mp: 37°C; $[\alpha]_D^{20}$: −26.1 (*c* 0.4, $CHCl_3$) IR (KBr): 3416 (OH), 1593, 1321, 1163 cm^{-1}; ^{1}H NMR: 1.31 (d, $J=6.3$ Hz, 3H, Me), 2.46 (s, 3H, NMe), 3.03–3.10 (m, 1H, H_4), 3.20 (t, $J=7.7$ Hz, 1H, H_3), 3.29 (dd, $J=3.4$ and 7.4 Hz, 1H, H_2), 4.30 (bs, 1H, OH), 4.79 (d, $J=3.5$ Hz, 1H, $H_{1'}$), 6.66 (dd, $J=1.5$ and 6.6 Hz, 2H, Ar), 7.05–7.42 (m, 8H, Ar). The following selected signals belong to the minor isomer in the crude reaction mixture: 2.13 (s, NMe), 4.65 (bs, H_2); ^{13}C NMR: 20.3, 41.3, 43.7, 66.5, 75.8, 125.8, 127.1, 127.2, 128.2, 139.7, 140.7. Anal. calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.77; H, 8.05; N, 5.11%. Following the procedure described in Ref. 7, the same product was obtained with >98% de.

3.7. (1′*S*,2*R*,3*R*)- and (1′*R*,2*R*,3*R*)-(1-Benzyl-3-phenylazetidin-2-yl)phenylmethanol, 17a and 17b

Following the above procedure and starting from ketone **15** (1.51 g, 4.6 mmol), alcohols **17a** and **17b** were obtained,

after chromatography (E/PE: 4/6) in 66 and 17% yield, respectively. **17a**: mp: 79°C; R_f: 0.35 (E/PE: 4/6); $[\alpha]_D^{20}$: +29 (*c* 0.9, $CHCl_3$); IR (KBr): 3401 (OH), 1598, 1490, 733 cm^{-1}; ^1H NMR: 3.11 (dd, $J=6.3$ and 7.2 Hz, 1H, H_2), 3.62–3.88 (m, 5H, H_3, H_4, $H_{4'}$ and NCH_2Ph), 4.53 (d, $J=3.7$ Hz, 1H, $H_{1'}$), 6.59–6.62 (m, 2H, Ar), 7.04–7.24 (m, 13H, Ar); ^{13}C NMR: 34.9, 57.5, 61.4, 71.0, 77.5, 125.8, 125.9, 127.0, 127.2, 127.5, 127.9, 128.2, 128.5, 128.8, 137.6, 139.4, 141.3. Anal. calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.74; H, 7.07; N, 4.10%.

Compound **17b**: mp: 95°C; R_f: 0.17 (E/PE: 4/6); $[\alpha]_D^{20}$: +109 (*c* 1, $CHCl_3$); IR (KBr): 3426 (OH), 1590, 1060, 743 cm^{-1}; ^1H NMR: 3.06 (dd, $J=6.6$ and 7.1 Hz, 1H, H_2), 3.35 (AB syst., $J=13.2$ Hz, 2H, H_5), 3.66–3.84 (m, 3H, H_4, $H_{4'}$, H_3), 4.25 (bs, 1H, OH), 4.74 (bs, 1H, $H_{1'}$), 7.16–7.26 (m, 15H, Ar); ^{13}C NMR: 38.5, 57.8, 62.3, 72.8, 78.5, 126.1, 127.5, 127.9, 128.0, 128.1, 129.1, 129.2, 129.3, 129.4, 138.3, 141.9, 144.1. Anal. calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.73; H, 7.10; N, 4.10%.

3.8. (2*S*,3*R*,4*S*)-(1,4-Dimethyl-3-phenylazetidin-2-yl)diphenylmethanol, 28

To a solution of **8** (211 mg, 0.796 mmol) in benzene (9 mL) cooled to 0°C was added dropwise was added dropwise at 0°C a solution of phenyllithium in cyclohexane/ether (1.8 M sol., 880 μL, 1.59 mmol). The solution was stirred for 15 min at 0°C and hydrolyzed by addition of water (10 mL). Extraction of the aqueous layer with diethylether, washing of the organic layer with aqueous 1M NaOH was then followed by usual workup to give crude alcohol that was chromatographed (E/PE: 15/85) to give **28** as a crystalline solid (248 mg, 91%). R_f: 0.45 (E/PE: 2/8); mp: 144°C; $[\alpha]_D^{20}$: −20.7 (*c* 0.8, $CHCl_3$); IR (KBr): 3288 (OH), 1490, 1450, 732 cm^{-1}; ^1H NMR: 1.25 (d, $J=5.9$ Hz, 3H, Me), 2.13 (s, 3H, NMe), 3.07–3.19 (m, 2H, H_3 and H_4), 4.13 (d, $J=7.3$ Hz, 1H, H_2), 5.29 (bs, 1H, OH), 6.94 (dd, $J=1.5$ and 6.6 Hz, 2H, Ar), 7.06–7.08 (m, 3H, Ar), 7.20–7.33 (m, 8H, Ar), 7.69 (d, $J=8$ Hz, 2H, Ar); ^{13}C NMR: 20.0, 42.2, 46.4, 66.7, 75.6, 78.2, 126.0, 126.1, 126.3, 126.5, 126.6, 127.7, 128.0, 128.1, 128.8, 139.7, 143.1, 146.9. Anal. calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.89; H, 7.34; N, 4.05%.

3.9. (2*R*,3*R*)-(1-Benzyl-3-phenylazetidin-2-yl)phenylmethanol, 29

Following the above procedure and starting from ketone **15**, alcohol **29** was obtained, after chromatography (E/PE: 2/8) in 63% yield. R_f: 0.6 (E/PE: 2/8); mp: 79°C; $[\alpha]_D^{20}$: +268 (*c* 2.6, $CHCl_3$); IR (KBr): 3288 (OH), 1588, 1480, 743 cm^{-1}; ^1H NMR: 3.10 (t, $J=7.5$ Hz, 1H,H_2), 3.35 3.35 (AB syst., $J=13.1$ Hz, 2H, H_5), 3.54–3.65 (m, 2H, H_4, $H_{4'}$), 4.48 (d, $J=6.9$ Hz, 1H, H_3), 5.46 (bs, 1H, OH), 6.87 (m, 2H, Ar), 7.06–7.18 (m, 16H, Ar), 7.70 (d, $J=8.1$ Hz, 2H, Ar); ^{13}C NMR: 37.7, 57.4, 60.9, 77.5, 79.5, 126.1, 126.2, 126.5, 126.7, 126.8, 127.2, 127.8, 128.0, 128.2, 128.25, 128.4, 128.7, 137.5, 141.6, 142.8, 146.7. Anal. calcd for $C_{29}H_{27}NO$: C, 85.89; H, 6.71; N, 3.45. Found: C, 85.92; H, 6.71; N, 3.33%.

3.10. (*R*)-2-Allylamino-2-phenylethanol, 19

To a stirred solution of (*R*)-phenylglycinol (2 g, 14.6 mmol) and DBU (2.2 mL, 14.6 mmol) in toluene (60 mL) was added dropwise allylbromide (1.3 mL, 15 mmol). The solution was stirred for 30 min at 40°C and hydrolyzed by addition of water (50 mL). Extraction of the aqueous layer with ether, was then followed by usual workup to give crude alcohol that was chromatographed (E/ethanol: 95/5) to give **19** (1.53 g, 59%). R_f: 0.74 (E/ethanol: 95/5); $[\alpha]_D^{20}$: −6.8 (*c* 1, $CHCl_3$) IR: 3421 (OH), 1634, 763 cm^{-1}; ^1H NMR: 2.86 (bs, 2H, NH, OH), 3.04–3.11 (m, 1H, NCH_2), 3.17–3.25 (m, 1H, NCH_2), 3.56 (dd, $J=10.8$ and 8.9 Hz, 1H, H_1), 3.75 (dd, $J=10.8$ and 4.3 Hz, 1H, $H_{1'}$), 3.81 (dd, $J=8.6$ and 4.3 Hz, 1H, H_2), 5.08–5.18 (m, 2H, CH_2CH), 5.82–5.88 (m, 1H, CH_2CH), 7.22–7.40 (m, 5H, Ar); ^{13}C NMR: 49.8, 63.9, 66.6, 116.2, 127.4, 127.6, 128.6, 140.5, 136.5, 140.5.

3.11. (*R*)-[Allyl-(2-hydroxy-1-phenylethyl)amino]-acetonitrile, 20

A suspension of **19** (1.5 g, 8.47 mmol), bromoacetonitrile (1.2 g, 11 mmol) and potassium carbonate (1.8 g, 13 mmol) in acetonitrile (70 mL) was stirred at rt for 4 h. Evaporation of the solvent under reduced pressure was followed by addition of water and diethylether to the residue. Usual workup and further flash chromatography (E/PE: 1/1) gave **20** (1.4 g, 65%). R_f: 0.56 (E/PE: 1/1); $[\alpha]_D^{20}$: −11.6 (*c* 0.4, $CHCl_3$); IR (film): 3431 (OH), 2233 (CN), 1644, 758 cm^{-1}; ^1H NMR: 2.28 (bs, 1H, OH), 3.18–3.25 (m, 2H, NCH_2CH), 3.51 (dd, $J=17.4$ and 0.7 Hz, 2H, CH_2CN), 3.72–3.78 (m, 1H, H_2), 3.78 (d, $J=5.3$ Hz, 2H, H_1), 5.21–5.35 (m, 2H, CH_2CH), 5.69–5.75 (m, 1H, CH_2CH), 7.22–7.41 (m, 5H, Ar); ^{13}C NMR: 39.2, 54.6, 63.9, 67.6, 115.6, 119.4, 128.9, 129.3, 134.1, 138.3. Anal. calcd for $C_{13}H_{16}N_2O(+0.5H_2O)$: C, 69.31; H, 7.61; N, 12.43. Found: C, 69.55; H, 7.50; N, 12.70%.

3.12. (*R*)-[2-Allyl-(2-chloro-2-phenylethyl)-amino]-acetonitrile, 21

To a solution of **20** (1.28 g, 5.9 mmol) in dichloromethane (60 mL) was added dropwise thionyl chloride (0.86 mL, 11.8 mmol) at 0°C. The mixture was then heated under reflux for 4 h and hydrolyzed by addition of a saturated aqueous solution of $NaHCO_3$ (50 mL). Usual workup followed by flash chromatography (E/PE: 1/1) gave quantitatively **21**. R_f: 0.60 (E/PE: 1/1); $[\alpha]_D^{20}$: +10 (*c* 1.1, $CHCl_3$); IR (film): 2228 (CN), 1639, 1495, 763 cm^{-1}; ^1H NMR: 3.07 (dd, $J=14.0$ and 6.6 Hz, 1H, H_2), 3.17 (dd, $J=14.0$ and 7.7 Hz, 1H, $H_{2'}$), 3.23 (d, $J=6.2$ Hz, 2H, NCH_2CH), 3.46 (d, $J=17.6$ Hz, 1H, CH_2CN), 3.60 (d, $J=17.6$ Hz, 1H, CH_2CN), 4.91 (d, $J=7.7$ Hz, 1H, H_1), 5.21–5.33 (m, 2H, CH_2CH), 5.68–5.79 (m, 1H, CH_2CH), 7.36–7.41 (m, 5H, Ar); ^{13}C NMR: 42.3, 57.9, 60.7, 61.5, 115.1, 119.7, 127.3, 128.7, 133.7, 139.5. Anal. calcd for $C_{13}H_{15}ClN_2$: C, 66.52; H, 6.44; N, 15.10. Found: C, 66.51; H, 6.62; N, 15.21%.

3.13. (2*R*,3*R*)- and (2*S*,3*R*)-1-Allyl-3-phenylazetidin-2-carbonitrile, 22 and 23

To a solution of **21** (1 g, 4.27 mmol) in THF (70 mL) was added dropwise at −90°C a THF solution of lithium bis-trimethylsilylamide (1 M, 5.6 mL, 5.6 mmol). The mixture was then gradually (3 h) allowed to reach 0°C and hydrolyzed by addition of saturated aqueous solution of NH_4Cl. Usual workup followed by flash chromatography (E/PE: 2/8) gave azetidines **22** and **23** as a 2/1 mixture of isomers (780 mg, 90%). Faster eluting isomer **22**: R_f: 0.43 (E/PE: 20/80); $[\alpha]_D^{20}$: −19.6 (*c* 7.4, $CHCl_3$); IR (film): 2233 (CN), 1639, 917, 748 cm^{-1}; ^1H NMR: 3.19 (dd, $J=7.9$ and 6.5 Hz, 1H, H_4), 3.24 (d, $J=6.2$ Hz, 2H, NCH_2CH), 3.79 (m, 2H, $H_{4'}$ and H_2), 3.95 (q, $J=7.5$ Hz, 1H, H_3), 5.24–5.40 (m, 2H, CH_2CH), 5.85–5.91 (m, 1H, CH_2CH), 7.28–7.37 (m, 5H, Ar); ^{13}C NMR: 41.3, 58.2, 58.4, 60.3, 118.9, 119.1, 126.9, 127.7, 128.9, 132.8; 138.4. Anal. calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.52; H, 7.23; N, 14.05. Slower eluting isomer **23:** R_f: 0.43 (E/PE: 20/80); $[\alpha]_D^{20}$: −3.2 (*c* 0.1, $CHCl_3$); IR (film): 2233 (CN), 1644, 927, 748 cm^{-1}; ^1H NMR: 3.29 (d, $J=6.2$ Hz, 2H, NCH_2CH), 3.87–3.91 (m, 1H, H_3), 3.57 (d, $J=6.6$ Hz, 2H, H_4), 4.39 (d, $J=8.1$ Hz, 1H, H_2), 5.26 (m, 2H, CH_2CH), 5.84 (m, 1H, CH_2CH), 7.36 (m, 5H, Ar); ^{13}C NMR: 38.9, 57.9, 58.4, 59.0, 116.8, 118.8, 126.8, 127.9, 128.7, 132.9; 137.4.

3.14. (1′*S*,2*R*,3*S*)-(1-Allyl-3-phenylazetidin-2-yl)-phenylmethanol, 25

Following the procedure described in Ref. 7 and starting from ketone **24**, alcohol **25** was obtained, after chromatography (E/pentane: 1/1) in 68% yield. R_f: 0.5 (E/pentane: 1/1); mp: 55°C; $[\alpha]_D^{20}$: +9.4 (*c* 6.6, $CHCl_3$); IR (film): 3405 (OH), 2245 (CN), 1454, 1373, 732 cm^{-1}; ^1H NMR: 2.70 (bs, H, OH), 3.07 (t, $J=7.3$ Hz, 1H, H_4), 3.20 (m, 1H, NCH_2CH), 3.33 (m, 1H, NCH_2CH), 3.55 (m, 1H, H_2), 3.70 (q, $J=7.3$ Hz, 1H, H_3), 4.01 (t, $J=6.1$ Hz, 1H, $H_{4'}$), 4.82 (d, $J=3.3$ Hz, 1H, $CH(OH)$), 5.17–5.31 (m, 2H, CH_2CH), 5.82–5.93 (m, 1H, CH_2CH), 6.60 (m, 2H, Ar), 7.04 (m, 3H, Ar), 7.17–7.25 (m, 5H, Ar), ^{13}C NMR: 34.8, 57.1, 59.9, 71.1, 77.5, 117,8, 125.8, 125.9, 127.0, 127.2, 127.9, 128.1, 134.2, 139.5, 141.2. Anal. calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.41; H, 7.54; N, 5.01%.

3.15. (4*S*,5*R*,6*S*)-4,6-Diphenyl-3-oxa-1-aza-bicyclo[3.2.0]-heptan-2-one, 26

To a solution protected from light of compound **25** (0.130 g, 0.34 mmol) in anhydrous toluene (8 mL), was added in portions $Cl_2(Cy_3P)_2Ru{=}CHPh$ (0.024 g, 0.03 mmol) under argon. The resulting mixture was heated at reflux until complete disappearance of the starting material and was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and silica gel followed by water were added. The resulting mixture was then vigorously stirred for 30 min, filtered over a Celite pad and dried over $MgSO_4$. Flash chromatography (E/pentane: 6/4) followed by preparative TLC (E/cyclohexane: 5/5) gave a mixture of **26** and **27** (0.080 g). **26** and **27** have been undoubtedly identified by HRMS: **26** (*m*/*z*) $[M+H]^+$ calcd for $C_{17}H_{16}O_2N$, 266.1181; found, 266.1172 and **27** (*m*/*z*) $[M+H]^+$ calcd for $C_{21}H_{26}O_3N$, 340.1913; found, 340.1910.

^1H NMR: the following signals belong to oxazolidinone **26**: 3.99 (m, 1H, H_6), 4.16 (t, $J=9$ Hz, 1H, H_7), 4.32 (t, $J=9.1$ Hz, 1H, $H_{7'}$), 4.85 (t, $J=7.7$ Hz, 1H, H_5), 5.85 (d, $J=7.7$ Hz, 1H, H_4), 6.77 (m 2H, Ar), 7.22 (m, 2H, Ar), 7.33 (m, 2H, Ar), 7.42 (m, 4H, Ar); ^{13}C NMR (DEPT 135): 44.0 (CH), 57.8 (CH_2), 72.0 (CH), 78.6 (CH), 124.9, 126.6, 127.5, 128.7, 128.7, 129.0 (aromatic CH).

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