JOC The Journal of Organic Chemistry

Article

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N-Arylazetidines: Preparation through Anionic Ring Closure

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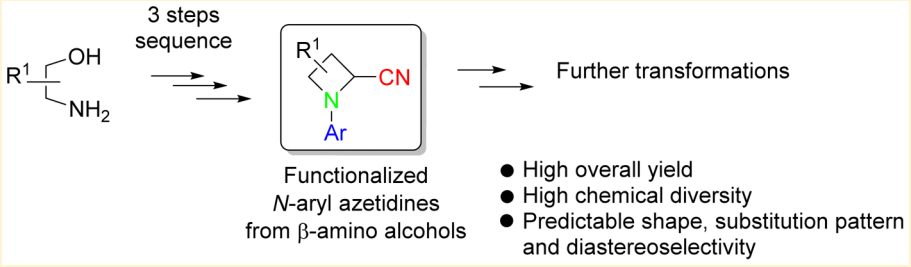
Supporting Information



ABSTRACT: We report herein an efficient synthesis of diversely substituted *N*-aryl-2-cyanoazetidines based on an anionic ring-closure reaction. These compounds can be prepared from *β*-amino alcohols in enantiomerically pure form through a three-step sequence involving (i) copper-catalyzed *N*-arylation, (ii) *N*-cyanomethylation of the secondary aniline, and (iii) one-pot mesylation followed by ring closure induced by a base. This high-yielding sequence gives access to azetidines with a predictable and adjustable substitution pattern and also with predictable diastereoselectivity. These compounds are susceptible to multiple further derivatizations through Suzuki coupling or nitrile transformation, thus appearing as valuable new scaffolds for medicinal chemistry. Their rigid shape, featuring an almost planar *N*-arylamine and a planar four-membered ring, was revealed by both AM1 calculations and X-ray crystallography.

INTRODUCTION

Azetidines have emerged as privileged scaffolds in medicinal chemistry within the past decade, which can be ascribed to patent strategies based on novelty, promoted by the recent commercial availability of azetidinyl building blocks,[1] coupled with the increasing number of methods for their preparation.[2] Thus, in this area, new rigid spiro-azetidinyl scaffolds for the exploration of chemical space have been developed by Carreira's group,[3] while new methodologies based on organocatalysis have appeared to prepare these heterocycles in optically enriched form.[4] At the same time, while these nitrogen heterocycles are becoming very popular, the design and synthesis of more complicated azetidinyl scaffolds with a predictable shape, taking into account the key problem of absolute stereochemistry, and fitted with functional groups allowing further functionalization still remains a challenge. Such stereodefined scaffolds appear to be ideal platforms for diversity-oriented synthesis (DOS), with the aim to explore chemical space.[5]

This paper reports the synthesis of diversely substituted *N*-aryl-2-cyanoazetidines **4** via a three-step sequence involving (i) *N*-arylation of a *β*-amino alcohol **1**, (ii) *N*-cyanomethylation of **2**, and (iii) a one-pot mesylation/intramolecular alkylation promoted on the corresponding adduct **3** by a base (Scheme 1). The produced *N*-aryl-2 cyanoazetidines **4** offer high structural diversity considering the large array of available precursors and can be further derivatized through Pd-catalyzed coupling reactions, if R′ = Br or R″ = 4-C_6H_4Br or through nitrile transformations. We also demonstrate herein that these azetidines display a rigid shape, with an almost planar four-membered ring and heterocyclic nitrogen atom, as demonstrated by X-ray crystallography and AM1 calculations. This rigid shape is a key point for the use of these platforms for the exploration of chemical space in medicinal chemistry.

The synthesis of the *N*-arylated azetidines[6] described herein relies on a key anionic ring-closure step, which had previously been explored only with *N*-alkyl substrates.[7] The adaptation of this powerful, yet under-used, synthetic strategy to *N*-arylated substrates was not straightforward because of fundamental differences between tertiary amines and anilines, including lower basicity and nucleophilicity and flattening of the nitrogen atom in tertiary anilines compared to tertiary amines. This last point is a crucial parameter for the key projected ring closure, since this flattening would potentially increase the distance between the reacting anion and the electrophilic carbon, thus rendering the 4-*exo-tet* cyclization step more difficult.[8]

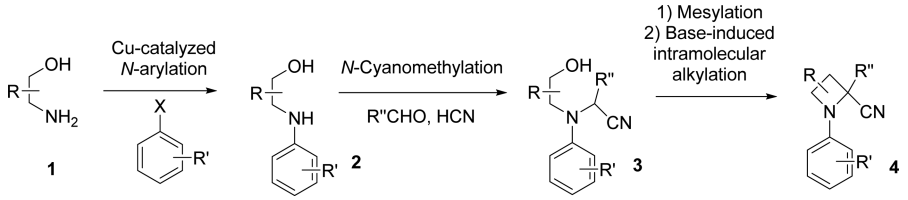
RESULTS AND DISCUSSION

The *N*-aryl *β*-amino alcohols required as substrates for the synthesis of *N*-arylazetidines following Scheme 1 were prepared by Cu-catalyzed *N*-arylation of the corresponding *β*-amino alcohols. This coupling reaction is particularly efficient with *β*-amino alcohols and does not require an additional ligand, as shown by Buchwald.[9] When the amino alcohol could not be used

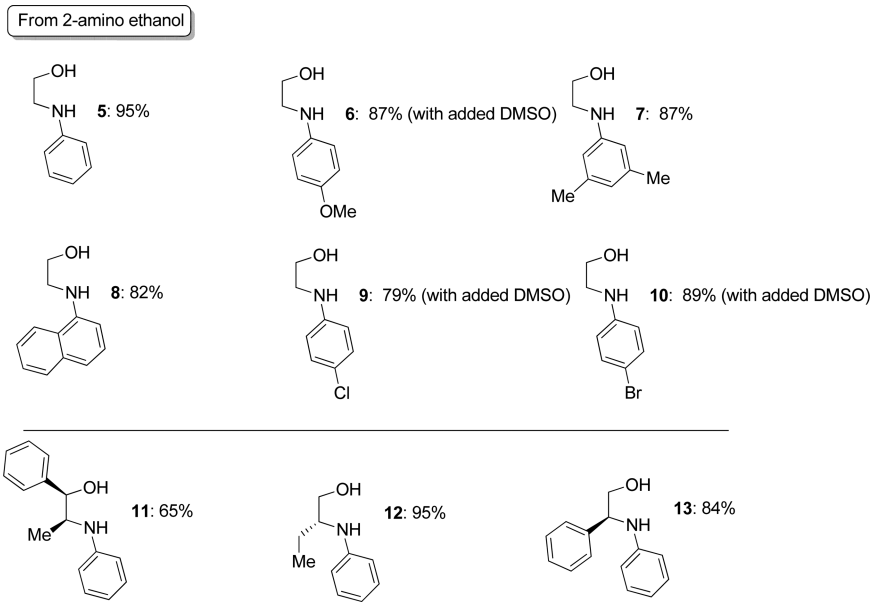
Received: January 25, 2016
Published: March 1, 2016

DOI: 10.1021/acs.joc.6b00169
J. Org. Chem. 2016, 81, 2899−2910

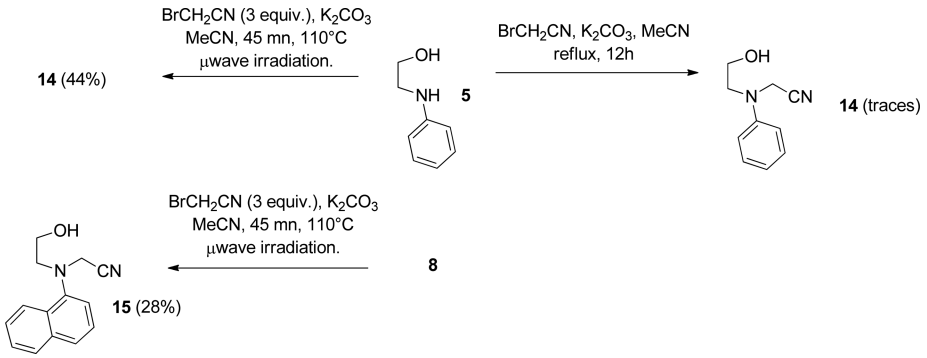
Scheme 1. Three-Step Synthesis of *N*-Aryl-2-cyanoazetidines through Anionic Ring Closure



Scheme 2. Structures and Yields of Prepared *N*-Arylamino Alcohols



Scheme 3. *N*-Alkylation with Bromoacetonitrile Gives Low Yields of *N*-Cyanomethylated Products



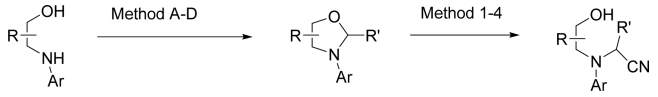
in excess for economic reasons, Buchwald's procedure was used (ArI, 5 mol % of CuI, NaOH 2 equiv in *i*-PrOH). Otherwise, starting from ethanolamine **1** (R = H, 3 equiv), the reaction was conducted without solvent (ArI, CuCl, 10 mol %, KOH, 2 equiv) following Han's procedure,[10] with a limited addition of DMSO (0.4 mL/mmol) in some cases to aid solubility. The structures and yields of the prepared *N*-arylamino alcohols are shown in Scheme 2.

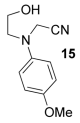
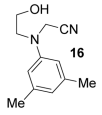
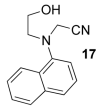
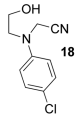
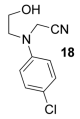
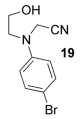
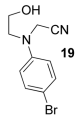
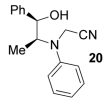
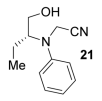
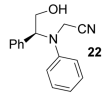
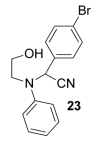
The second step of the synthesis was *N*-cyanomethylation. This step is usually carried out in the case of *N*-alkylamino alcohols by alkylation with the required α-bromonitrile,[11] but we found that the lowered nucleophilicity of *N*-arylamines considerably reduced the efficiency of this alkylation step, even with unsubstituted **5**. Thus, conventional heating (MeCN, $BrCH_2CN$, K_2CO_3, reflux) only gave trace amounts of **14** starting from **5**, and protracted reaction time or solvent change (DMF, 100 °C) only led to low isolated yields. After extensive optimization, the best conditions were found to involve microwave activation for 45 min at 110 °C in MeCN to afford **14** in a modest 44% yield. However, under these conditions, *N*-naphthyl-substituted amino alcohol **8** led to **15** with an unsatisfactory yield of 28% (Scheme 3).

Gratifyingly, a two-step procedure involving the formation of an intermediate oxazolidine followed by acid-catalyzed opening by cyanide anion proved much more efficient and allowed the preparation of nonsubstituted amino nitriles **14**–**21** in high yields. Alternatively, when an aryl aldehyde was used instead of paraformaldehyde, the intermediate 2-aryloxazolidine was also cleanly opened with HCN (KCN/AcOH) to give the substituted amino nitrile **22**. The conditions used for each substrate were modulated in order to optimize yields, and the structures of the products are shown in Table 1.

DOI: 10.1021/acs.joc.6b00169
J. Org. Chem. 2016, 81, 2899–2910

Table 1. Cyanomethylation via an Oxazolidine

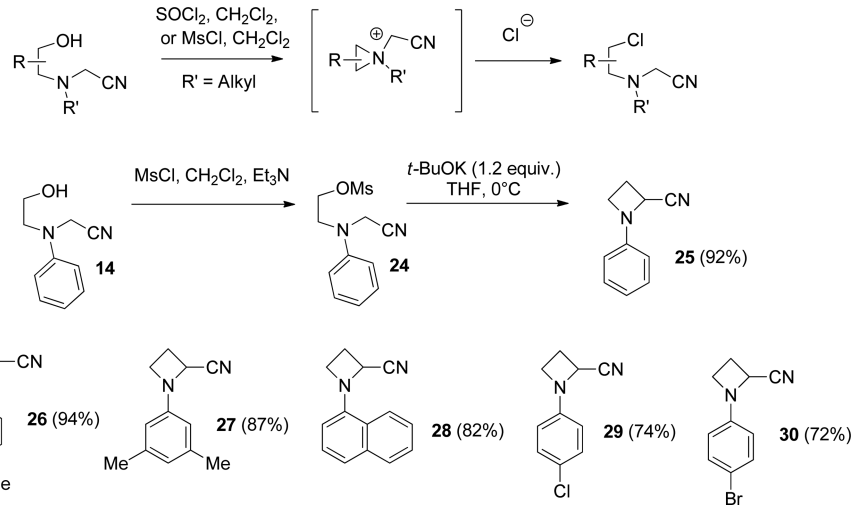


Substrate	Oxazolidine (Method)[a]	Opening of the oxazolidine (Method)[b]	Product structure	Overall yield
5	A	1	 **14**	82
6	A	1	 **15**	84
7	A	1	 **16**	80
8	A	1	 **17**	82
9	A	4	 **18**	44
9	B	3	 **18**	81
10	A	1	 **19**	degradation
10	B	4	 **19**	64
11	A	4	 **20**	81
12	A	4	 **21**	85
13	C	2	 **22**	82
5	D	2	 **23**	79

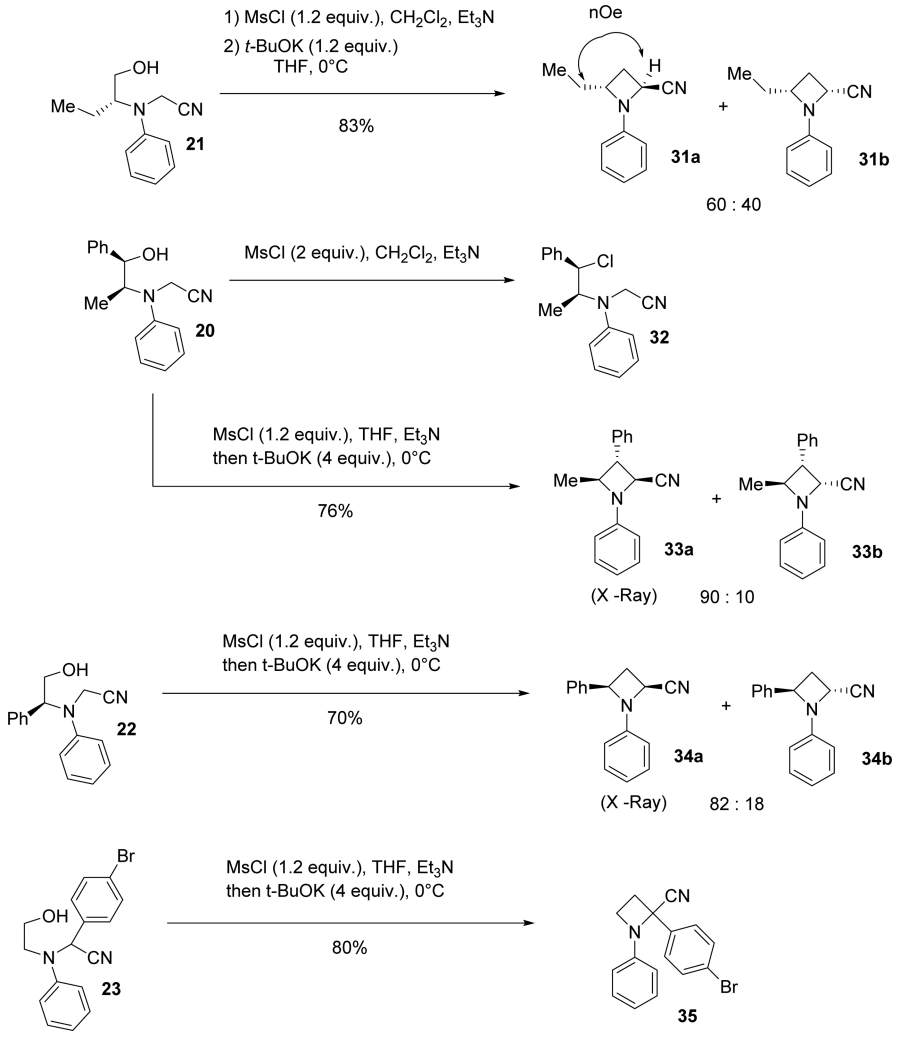
[a]Method A: paraformaldehyde (2 equiv), MeCN, reflux, 12 h. Method B: 40% aqueous formaldehyde (1.2 equiv), CH_2Cl_2, 4 Å MS, rt, 12 h. Method C: paraformaldehyde (2 equiv), azeotropic reflux, benzene, APTS cat. 12 h. Method D: 4-BrC_6H_4CHO (1 equiv), azeotropic reflux, benzene, APTS cat. 12 h. [b]Method 1: MeCN, TMSCN (2equiv), AcOH (2 equiv), reflux, 12 h. Method 2: AcOH, KCN (8 equiv), 70 °C, 1 h. Method 3: AcOH, TMSCN (2 equiv), 70 °C, 1 h. Method 4: $BF_3{\cdot}Et_2O$, TMSCN (2 equiv) rt, 15 min. For combination of methods A/1 and A/4, the reaction was conducted in one pot. For other combinations, intermediate oxazolidine was isolated before the opening step.

DOI: 10.1021/acs.joc.6b00169
J. Org. Chem. 2016, 81, 2899−2910

Scheme 4. Synthesis of *N*-Aryl-2-cyanoazetidines 25−30 via an Isolable Intermediate Mesylate



Scheme 5. Diastereoselectivity Issues in Anionic Ring-Closure Reactions



The crucial intramolecular alkylation step was studied next. When *N*-alkyl substrates are used, activation of the alcohol is usually carried out by chlorination ($SOCl_2$) and involves participation of the lone pair of the nitrogen atom to produce an aziridinium ion, which results in a stereospecific chlorination via a double S_N2 process.[11,12] It should be noted that with such

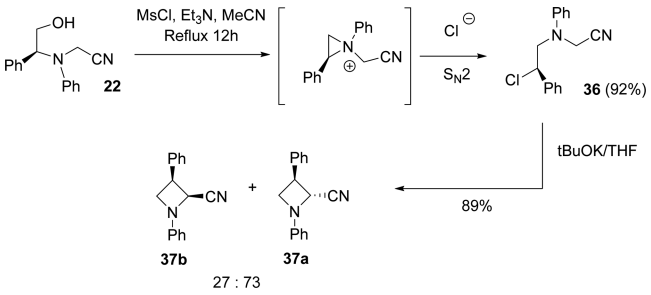
DOI: 10.1021/acs.joc.6b00169
J. Org. Chem. 2016, 81, 2899−2910

nucleophilic amines activation of the alcohol as a mesylate ($MeSO_2Cl$, Et_3N) also gives the corresponding chloride via the same aziridinium intermediate and its opening by chloride anion.[13] Since the opening of the produced intermediate aziridinium ion might not be regioselective, this activation can lead to mixtures of chloride isomers.[12] In the case of *N*-aryl substrates, different behavior was observed since mesylation of **14** (MsCl, 1.2 equiv, Et_3N, CH_2Cl_2, 0 °C) quantitatively gave the corresponding mesylate **24**, without any trace of the corresponding chloride, and was found to be stable enough to be isolated. This crude compound was then treated with *t*-BuOK (1.2 equiv in THF), which gave a high overall yield of 2-cyanoazetidine **25**. This two-step procedure was next applied to alcohols **15**−**19** to afford good yields of 2-cyanoazetidines **26**−**30** (Scheme 4).

With the ethyl-substituted amino alcohol **21**, this procedure gave a 6/4 epimeric mixture of azetidines **31a** and **31b** that could be separated by preparative TLC and whose relative configurations were determined by NOESY experiments. Only the 4-ethyl-substituted azetidine was produced, confirming that the rearrangement of the carbon chain via an aziridinium ion did not occur. However, when mesylation of **20** with a more reactive secondary benzylic alcohol was performed, only the chloride **32** was produced (isolated as a 1:1 mixture together with starting **20**). In this case, the previously mentioned participation of the lone pair of the nitrogen aniline and formation of an intermediate aziridinium ion took place, followed by exclusive ring-opening at the benzylic position. When this mesylation was conducted in THF instead of dichloromethane, the intermediate chloride was not isolated and subsequent addition of *t*-BuOK at 0 °C (4 equiv) smoothly generated an epimeric mixture of **33a** and **33b** in a 10/90 ratio in good overall yield. This one-pot procedure was next applied to **22** and **23**, producing a mixture of epimeric azetidines **34a,b** and azetidine **35** as shown in Scheme 5. The relative configuration of the major epimers **33a** and **34a** was confirmed by X-ray crystallography (Scheme 5).

The position of the phenyl substituent in **34a,b** could also be modulated. When starting **22** was mesylated in MeCN and the produced mesylate was heated for 12 h at reflux, the chloride **36** was isolated as a single isomer in good yield. This compound results from regioselective ring-opening of the intermediate aziridinium by the chloride anion at the benzylic position, a rearrangement which spontaneously occurs without heating in case of the more nucleophilic *N*-Bn substrates.[11] Anionic ring closure of this compound then gave epimeric **37a,b** in a 73/27 ratio (Scheme 6). The relative configurations of these compounds were assigned by comparison with the ^{1}H NMR spectra of **33a,b**, as the H-2 signal in the 2,3-*cis* isomers appears more deshielded (5.02 and 5.21 ppm) than in the 2,3-*trans* isomers (4.38 and 4.56 ppm).

Scheme 6. Regioselective Rearrangement by Heating of the Mesylate Derived from 22



AM1 calculations (B3LYP 6.31G +) were performed in order to evaluate the thermodynamic stabilities of the epimeric mixtures of 2-cyanoazetidines **31a,b**, **33**−**34a,b**, and **37a,b** (Table 2; see the SI for details). The optimized structures showed a slight preference for the *cis* compounds in the case of 2,4-disubstituted azetidines **31a,b** and **34a,b**. In the case of norephedrine-derived azetidines **33a,b** and phenylglycinol-derived **37a,b**, calculation predicts that the 2,3-*trans* compounds **33a** and **37a** would be more stable. The experimental distribution of diastereoisomers fits quite well with those calculated for **33a,b**, **34a,b**, and **37a,b**, suggesting that diastereoselectivity results in these cases from rapidly attained thermodynamic control. However, in the case of **31a,b**, the calculated ratio does not correspond with the experimental results, suggesting that the two-step procedure used to prepare these compounds does not allow complete thermodynamic equilibrium to be reached.

The structures of the optimized calculated structures (MP2 level) are shown in Figure 1 for **33a** (right) and **34a** (left). Particularly noteworthy is the marked planarity of the four-membered ring, which adopts a more pronounced envelope form in the related *N*-alkylazetidines,[11] and the flattening of the heterocyclic nitrogen atom, with a deviation angle from planarity of ca. 25° in **33a** and 23° in **34a**. These calculations suggest a quite rigid structure with limited conformational exchange, and these minimized structures fit very well with the X-ray data obtained from both **33a** and **34a** (see the SI for ORTEP figures),[14] which show an average angle of deviation from planarity of 32°.[15]

The reactivity of these compounds was evaluated through several transformations. *N*-Alkylation of **25** with methyl trifluoromethanesulfonate gave azetidinium ion **38** with moderate diastereoselectivity. The latter could be opened by an azide anion, yielding a mixture of **39** and **40**. The nitrile moiety in **25** reacted with butyllithium to give the corresponding ketone **41** that could be reduced with high diastereoselectivity (88% de) to afford the corresponding *anti* amino alcohol **42**. The structure of the major diastereoisomer in **42** was assigned on the basis of a chelated model operating with similar *N*-alkylazetidines.[16] These experiments demonstrate that the *N*-arylazetidines show a roughly similar reactivity profile as the *N*-alkyl-2-cyanoazetidines. Additionally, Suzuki couplings were evaluated with substrates **30** and **35**, and phenyl coupling was successfully achieved to give **43** and **44** (Scheme 7).

■ CONCLUSIONS

In conclusion, we have demonstrated that *N*-aryl-2-cyanoazetidines can be prepared in good overall yields from *β*-amino alcohols. Considering the large panel of commercially available *β*-amino alcohols and aryl halides, coupled with the multiple possible chemical transformations of the cyano moiety, this simple procedure gives access to a vast array of azetidines fitted with substituents displaying predictable spatial orientation. This work further demonstrates that the synthetic route toward azetidines based on anionic ring closure is particularly appealing.

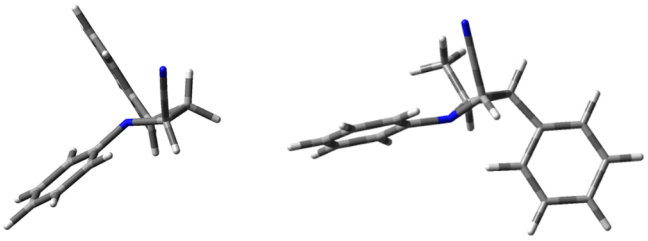
■ EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 and 75 MHz, respectively; chemical shifts (δ) are reported in ppm and coupling constants (J) reported in hertz and rounded up to 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septuplet (sep), multiplet (m), broad (br), or a combination of these. Solvents were used as internal standard when assigning NMR

DOI: 10.1021/acs.joc.6b00169
J. Org. Chem. 2016, 81, 2899−2910

Table 2. Calculated Thermodynamic Stabilities of 2-Cyanoazetidines

optimized structure	**31a**	**31b**	**33a**	**33b**
calcd energies (au)	−572.08178889	−572.082558243	−762.78836669	−762.78550949
calcd thermodynamic distribution at 25 °C	70	30	95	15
exptl distribution	40	60	90	10
optimized structure	**34a**	**34b**	**37a**	**37b**
calcd energies (au)	−723.68316775	−723.68207657	−723.7780645	−723.67599308
calcd thermodynamic distribution at 25 °C	76	24	85	15
exptl distribution	82	18	73	27



34a (calculated) **33a** (calculated)

Figure 1. Minimized conformations (MP2 level) for **33a** and **34a**.

spectra (δ H: $CDCl_3$ 7.26 ppm; δ C: $CDCl_3$ 77.0 ppm). Assignments for signals from ^{1}H and ^{13}C in the NMR spectra were validated by two-dimensional correlated spectroscopy (2D COSY) and heteronuclear multiple bond correlation (HMBC). IR data were collected with an ATR-FT-IR spectrometer. All reactions were carried out under argon. Column chromatography was performed on silica gel (230−400 mesh) with use of various mixtures of CH_2Cl_2, EtOAc, petroleum ether (35−60 °C fraction) (PE), and methanol. TLC was performed on Merck Kieselgel 60 F254 plates. Melting points are uncorrected. THF was distilled under argon from sodium using benzophenone as indicator. Dichloromethane was distilled from calcium hydride. Isomeric ratios were determined by NMR analysis of crude reaction mixtures before purification.

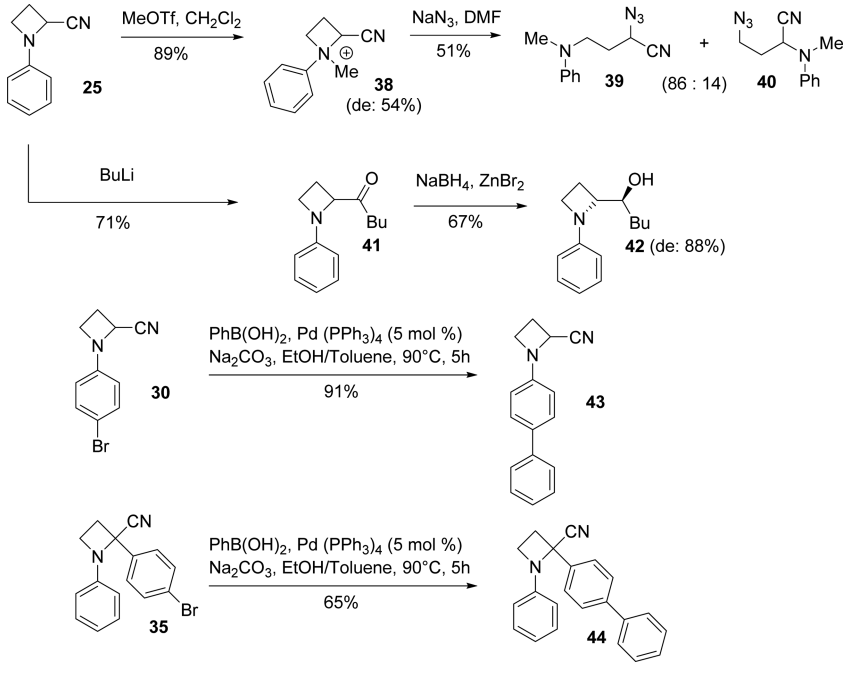
General Procedure for the *N*-Arylation of *N*-Ethanolamine.[10] In a dried, round-bottomed flask were mixed the required iodoaryl compound (10 mmol, 1 equiv), ethanolamine (3 equiv), copper chloride (0.1 equiv), and freshly crushed potassium hydroxide (2 equiv). In the case of substrates **6**, **9**, and **10**, additional DMSO (0.4 mL/mmol) was also added. The mixture was stirred overnight at room temperature and then poured into saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layers were then washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography on silica gel with a mixture of PE/EtOAc/MeOH as eluent.

*2-(Phenylamino)ethanol (**5**).* Yield: 1.30 g, 95%. Colorless oil. R_f: 0.2 (PE/EtOAc 7/3). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.22 (t, J = 7.9 Hz, 2H, Ph), 6.78 (t, J = 7.3 Hz, 1H, Ph), 6.67 (d, J = 7.6 Hz, 2H, Ph), 3.80 (t, J = 5.2 Hz, 2H, CH_2OH), 3.38 (bs, 2H, OH and NH), 3.28 (t, J = 5.1 Hz, 2H, NCH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.0 (C_q), 129.4 (C_{Ar}), 118.1 (C_{Ar}), 113.4 (C_{Ar}), 61.1 (CH_2OH), 46.2 (NCH_2) ppm. IR: ν_{max} = 3350 (b), 2932, 2872, 1600, 1500, 1318, 1260, 1047, 747, 691, 505 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_8H_{12}NO$ $[MH]^+$: 138.0919, found 138.0922.

*2-(4-Methoxyphenyl)aminoethanol (**6**).* Yield: 1.45 g, 87%. White solid. Mp: 42−44 °C, R_f: 0.4 (PE/EtOAc 1/1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.79 (d, J = 9.0 Hz, 2H, Ar), 6.61 (d, J = 8.9 Hz, 2H, Ar), 3.89−3.63 (m, 5H, OMe and CH_2OH), 3.58−3.36 (m, 2H, NH and OH), 3.18 (t, J = 5.2 Hz, 2H, CH_2N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5 (C_q), 142.3 (C_q), 114.93 (C_{Ar}), 114.89 (C_{Ar}), 61.1 (CH_2OH), 55.8 (OMe), 47.2 (CH_2N) ppm. IR: ν_{max} = 3300, 2926, 2831, 1509, 1229, 1035, 899, 818, 544 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_9H_{14}NO_2$ $[MH]^+$: 168.1025, found 168.1020.

*2-(3,5-Dimethylphenyl)aminoethanol (**7**).* Yield: 1.44 g, 87%. Colorless oil, R_f: 0.6 (PE/EtOAc 1/1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.47 (s, 1H, Ar), 6.33 (s, 2H, Ar), 3.80 (t, 2H, J = 5.3 Hz, CH_2OH),

Scheme 7. Synthetic Transformations of *N*-Aryl-2-cyanoazetidines



DOI: 10.1021/acs.joc.6b00169
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3.34 (s, 2H, NH and OH), 3.28 (t, 2H, J = 5.3 Hz, NCH_2), 2.30 (s, 6H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.3 (C_q), 139.0 (C_q), 120.1 (C_{Ar}), 111.4 (C_{Ar}), 61.2 (CH_2OH), 46.3 (NCH_2), 21.5 (Me) ppm. IR: ν_{max} = 3374 (b), 2912, 2850, 1599, 1459, 1334, 1188, 1055, 820, 690 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{10}H_{16}NO$ $[MH]^+$: 166.1232, found 166.1227.

*2-(Naphthalen-1-ylamino)ethanol (**8**).* Yield: 1.54 g, 82%. White solid. Mp: 44−46 °C, R_f: 0.4 (PE/EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96−7.88 (m, 1H, Ar), 7.86−7.78 (m, 1H, Ar), 7.53−7.44 (m, 2H, Ar), 7.41−7.30 (m, 2H, Ar), 6.60 (t, J = 6.9 Hz, 1H, Ph), 4.02 (t, J = 5.1 Hz, 2H, CH_2OH), 3.50 (t, J = 5.1 Hz, 2H, NCH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3 (C_q), 134.4 (C_q), 128.7 (C_{Ar}), 126.6 (C_{Ar}), 125.9 (C_{Ar}), 124.9 (C_{Ar}), 123.8 (C_{Ar}), 120.1 (C_{Ar}), 118.0 (C_{Ar}), 104.9 (C_{Ar}), 61.0 (CH_2OH), 46.2 (NCH_2) ppm. IR: ν_{max} = 3329, 3217 (b), 2863, 1582, 1516, 1464, 1454, 1451, 1274, 1210, 1061, 790, 757, 674 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{12}H_{14}NO$ $[MH]^+$: 188.1075, found 188.1070.

*2-(4-Chlorophenyl)aminoethanol (**9**).* Yield: 1.36 g, 79%. White solid. Mp: 75−77 °C, R_f: 0.3 (PE/EtOAc/MeOH: 70/30/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (d, J = 8.8 Hz, 2H, Ar), 6.57 (d, J = 8.8 Hz, 2H, Ar), 3.81 (t, J = 5.3 Hz, 2H, CH_2OH), 3.25 (t, J = 5.0 Hz, 2H, NCH_2), 3.08 (s, 2H, NH and OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.7 (C_q), 129.1 (C_q), 122.5 (C_{Ar}), 114.3 (C_{Ar}), 61.1 (CH_2OH), 46.2 (NCH_2) ppm. IR: ν_{max} =3301, 3174, 2932, 2847, 1596, 1495, 1269, 1060, 900, 811, 709, 623, 499 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_8H_{11}ClNO$ $[MH]^+$: 172.0529, found 172.0531.

*2-(4-Bromophenyl)aminoethanol **10**.* Yield: 1.92 g, 89%. White solid. Mp: 80−82 °C, R_f: 0.4 (PE/EtOAc/MeOH: 70/30/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.9 Hz, 2H, Ar), 6.52 (d, J = 8.9 Hz, 2H, Ar), 3.81 (t, J = 5.3 Hz, 2H, CH_2OH), 3.25 (t, J = 5.0 Hz, 2H, NCH_2), 3.07 (s, 2H, NH and OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.1 (C_q), 132.0 (C_{Ar}), 114.8 (C_{Ar}), 109.5 (C_q), 61.1 (CH_2OH), 46.1 (NCH_2) ppm. IR: ν_{max} =3301, 3176 (b), 2936, 2850, 1590, 1494, 1268, 1210, 1059, 899, 807, 681, 608, 510 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_8H_{11}BrNO$ $[MH]^+$: 216.0024, found 216.0031.

General Procedure for the *N*-Arylation of Other Amino Alcohols.[9] In a dried, round-bottomed flask were mixed the required iodoaryl coumpound (1.2 equiv), the required amino alcohol (10 mmol, 1 equiv), copper iodide (0.05 equiv), and freshly crushed sodium hydroxide (2 equiv). 2-Propanol was added (10 mL/10 mmol of starting amino alcohol), and the mixture was stirred overnight at 90 °C for 12 h. To the resulting suspension was added water (40 mL for 10 mmol of starting amino alcohol). The layer was extracted with CH_2Cl_2, washed with aqueous 1 N NaOH and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography.

*(1R,2S)-1-Phenyl-2-(phenylamino)propan-1-ol (**11**).* Yield: 1.48 g, 65%. White solid. Mp: 73−75 °C, R_f: 0.3 (PE/EtOAc/MeOH: 85/15/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47−7.19 (m, 7H, Ar), 6.87−6.65 (m, 3H, Ar), 5.03 (d, J = 3.1 Hz, 1H, CHOH), 3.88−3.76 (m, 1H, CHMe), 1.05 (d, J = 6.6 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9 (C_q), 141.4 (C_q), 129.5 (C_{Ar}), 128.4 (C_{Ar}), 127.4 (C_{Ar}), 125.9 (C_{Ar}), 118.2 (C_{Ar}), 114.1 (C_{Ar}), 74.2 (CHOH), 54.6 (CHMe), 13.9 (Me) ppm. IR: ν_{max} = 3173, 1600, 1498, 1141, 998, 895, 867, 751, 693, 501 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{15}H_{18}NO$ $[MH]^+$: 228.1388, found 228.1382.

*(R)-2-(Phenylamino)butan-1-ol (**12**).* Yield: 1.57 g, 95%. Clear oil. R_f: 0.3 (PE/EtOAc/MeOH: 70/30/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (t, J = 7.8 Hz, 2H, Ar), 6.77 (t, J = 7.5 Hz, 1H, Ar), 6.69 (d, J = 8.4 Hz, 2H, Ar), 3.75 (dd, J = 10.9, 4.2 Hz, 1H, CHHOH), 3.54 (dd, J = 10.9, 5.8 Hz, 1H, CHHOH), 3.48−3.35 (m, 1H, CHCH$_2$Me), 3.08 (bs, 2H, OH and NH), 1.74−1.41 (m, 2H, CHCH_2Me), 0.99 (t, J = 7.5 Hz, 3H, CHCH$_2$*Me*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9 (C_q), 129.4 (C_{Ar}), 117.8 (C_{Ar}), 113.8 (C_{Ar}), 64.0 (CH$_2$OH), 56.7 (CHCH$_2$Me), 24.8 (CHCH$_2$Me), 10.7 (Me) ppm. IR: ν_{max} = 3392 (b), 2961, 2929, 2876, 1726, 1600, 1497, 1315, 1246, 1042, 747, 691 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{10}H_{16}NO$ $[MH]^+$: 166.1232, found 166.1225.

*(S)-2-Phenyl-2-(phenylamino)ethanol (**13**).* Yield: 1.79 g, 84%. Clear oil. R_f: 0.5 (PE/EtOAc/MeOH: 70/30/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47−7.24 (m, 5H, Ar), 7.15 (t, J = 8.0 Hz, 2H, Ar), 6.74 (t, J = 7.3 Hz, 1H, Ar), 6.62 (d, J = 8.1 Hz, 2H, Ar), 4.52 (dd, J = 7.1 and 4.2 Hz, 1H, CHPh), 3.95 (dd, J = 11.2 and 4.2 Hz, 1H, CHHOH), 3.76 (dd, J = 11.1 and 7.1 Hz, 1H, CHHOH), 3.29 (s, 2H, OH and NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.2 (C_q), 140.1 (C_q), 129.2 (C_{Ar}), 128.9 (C_{Ar}), 127.7 (C_{Ar}), 126.8 (C_{Ar}), 118.0 (C_{Ar}), 114.0 (C_{Ar}), 67.3 (CH_2OH), 60.0 (CHPh) ppm. IR: ν_{max} =3398 (b), 3050, 3024, 2926, 1600, 1502, 1264, 1064, 1027, 732, 692 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{14}H_{16}NO$ $[MH]^+$: 214.1232, found 214.1235.

General Procedures for the *N*-Cyanomethylation of *N*-Arylamino Alcohols. *Method A/1 (One-Pot, Two-Step Procedure).* A solution of the starting amino alcohol (5 mmol) and paraformaldehyde (10 mmol) in MeCN (30 mL) was refluxed for 12 h. After the solution was cooled to room temperature, TMSCN (10 mmol) was added, followed by AcOH (10 mmol), and the reaction mixture was further refluxed for 12 h. After the solution was cooled to room temperature, water (50 mL) was added, and extraction by EtOAc followed by usual workup gave a residue that was further purified by flash chromatography.

*[(2-Hydroxyethyl)phenylamino]acetonitrile (**14**).* Yield: 720 mg, 82%. Colorless oil. R_f: 0.2 (PE/EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (t, J = 7.9 Hz, 2H, Ph), 6.94 (t, J = 7.6 Hz, 1H, Ph), 6.88 (d, J = 8.1 Hz, 2H, Ph), 4.21 (s, 2H, CH_2CN), 3.82 (t, J = 5.3 Hz, 2H, CH_2OH), 3.51 (t, J = 5.3 Hz, 2H, NCH_2). 2.73 (bs, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.0 (C_q), 129.6 (C_{Ar}), 120.2 (C_{Ar}), 116.4 (CH$_2$CN), 114.8 (C_{Ar}), 60.2 (CH$_2$OH), 54.0 (NCH$_2$), 40.8 (CH$_2$CN) ppm. IR: ν_{max} = 3250 (b), 1592, 1493, 1422, 1369, 1215, 1169, 1048, 1035, 931, 875, 749, 690, 462 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{10}H_{13}N_2O$ $[MH]^+$: 177.1028 , found 177.1032.

*[(2-Hydroxyethyl)-(4-methoxyphenyl)amino]acetonitrile (**15**).* Yield: 870 mg, 84%. Colorless oil. R_f: 0.4 (PE/EtOAc 1/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.95 (d, J = 9.2 Hz, 2H, Ar), 6.87 (d, J = 9.2 Hz, 2H, Ar), 4.09 (s, 2H, CH_2CN), 3.77 (s, 3H, OMe), 3.74 (t, J = 5.3 Hz, 2H, CH_2OH), 3.37 (t, J = 5.3 Hz, 2H, CH_2N), 2.44 (s, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0 (C_q), 141.4 (C_q), 119.5 and 119.4 (C_{Ar}), 116.2 (CH$_2$CN), 114.9 (C_{Ar}), 59.8 (CH$_2$OH), 55.6 (OMe), 54.7 (CH$_2$N), 42.71 and 42.67 (CH$_2$CN) ppm. IR: ν_{max} = 3290 (b), 2945, 2920, 2831, 1511, 1252, 1180, 1034, 881, 815, 526 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{11}H_{15}N_2O_2$ $[MH]^+$: 207.1134, found 207.1136.

*[(3,5-Dimethylphenyl)-(2-hydroxyethyl)amino]acetonitrile (**16**).* Yield: 820 mg, 80%. White solid. Mp: 71−73 °C. R_f: 0.6 (PE/EtOAc 1/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.62 (s, 1H, Ar), 6.54 (s, 2H, Ar), 4.21 (s, 2H, CH_2CN), 3.85 (t, 2H, J = 5.4 Hz, CH_2OH), 3.51 (t, 2H, J = 5.4 Hz, NCH_2), 2.32 (s, 6H, Me), 2.11 (s, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.2 (C_q), 139.3 (C_q), 122.5 (C_{Ar}), 116.4 (CH$_2$CN), 113.2 (C_{Ar}), 60.2 (CH$_2$OH), 54.0 (NCH$_2$), 41.0 (CH$_2$CN), 21.7 (Me) ppm. IR: ν_{max} = 3297 (b), 2968, 2923, 1595, 1475, 1357, 1185, 1040, 978, 814, 693 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{12}H_{17}N_2O$ $[MH]^+$: 205.1341, found 205.1350.

*[(2-Hydroxyethyl)naphthalen-1-ylamino]acetonitrile (**17**).* Yield: 925 mg, 82%. White solid. Mp: 71−73 °C. R_f: 0.3 (PE/EtOAc 7/3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23−8.13 (m, 1H, Ar), 7.97−7.85 (m, 1H, Ar), 7.74 (d, J = 7.7 Hz, 1H, Ar), 7.62−7.40 (m, 4H, Ar), 4.16 (s, 2H, CH_2CN), 3.77 (t, J = 5.1 Hz, 2H, CH_2OH), 3.52 (t, J = 5.1 Hz, 2H, NCH_2), 2.02 (bs, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3 (C_q), 134.9 (C_q), 129.7 (C_q), 128.9 (C_{Ar}), 126.7 (C_{Ar}), 126.4 (C_{Ar}), 125.7 (C_{Ar}), 122.1 (C_{Ar}), 119.6 (C_{Ar}), 115.5 (CH$_2$CN), 59.9 (CH$_2$OH), 54.9 (NCH$_2$), 44.9 (CH$_2$CN) ppm. IR: ν_{max} = 3441, 3054, 2962, 2886, 2813, 1579, 1394, 1060, 869, 770, 571, 429 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{14}H_{15}N_2O$ $[MH]^+$: 227.1184 , found 227.1180.

Method B/3 (Two-Step Procedure). To a solution of the starting amino alcohol (2 mmol) and 37% aqueous formaldehyde (175 μL, 2.4 mmol) in CH_2Cl_2 (10 mL) were added 4 Å molecular sieves (1 g), and the reaction mixture was allowed to sit for 12 h without stirring. Filtration and washing (CH_2Cl_2) gave the crude oxazolidine after concentration under reduced pressure. This crude compound was taken

DOI: 10.1021/acs.joc.6b00169
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up in AcOH (5 mL), and TMSCN (504 μL, 4 mmol) was added. The reaction mixture was stirred for 1 h at rt. Addition of water was followed by extraction with EtOAc, and the combined organic phases were neutralized by several washings with saturated aqueous Na_2CO_3. Drying over $MgSO_4$ of the organic layer and concentration under reduced pressure gave a residue that was purified by flash chromatography.

*[(4-Chlorophenyl)(2-hydroxyethyl)amino]acetonitrile (**18**).* Yield: 850 mg, 81%. White solid. Mp: 60−62 °C. R_f: 0.3 (PE/EtOAc 6/4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, J = 9.1 Hz, 2H, Ar), 6.79 (d, J = 9.1 Hz, 2H, Ar), 4.21 (s, 2H, CH_2CN), 3.82 (t, J = 5.2 Hz, 2H, CH_2OH), 3.48 (t, J = 5.2 Hz, 2H, NCH_2), 2.26 (bs, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.6 (C_q), 129.5 (C_{Ar}), 125.1 (C_q), 116.1 (CH_2CN), 115.9 (C_{Ar}), 60.1 (CH_2OH), 54.1 (NCH_2), 40.8 (CH_2CN) ppm. IR: ν_{max} = 3414 (b), 3341 (b), 1591, 1494, 1356, 1207, 1062, 803, 504 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{10}H_{12}ClN_2O$ $[MH]^+$: 211.0638, found 211.0643.

Method B/4 (Two-Step Procedure). To a solution of the starting amino alcohol (2 mmol) and 37% aqueous formaldehyde (175 μL, 2.4 mmol) in CH_2Cl_2 (10 mL) were added 4 Å molecular sieves (1 g), and the reaction mixture was allowed to sit for 12 h without stirring. Filtration and washing (CH_2Cl_2) gave the crude oxazolidine after concentration under reduced pressure. This crude compound was taken up in MeCN (15 mL), and BF_3·OEt_2 was added dropwise (250 μL, 4 mmol) at 0 °C, followed by TMSCN (500 μL, 4 mmol). The reaction mixture was stirred for 10 min and then quenched by addition of water (20 mL). The reaction mixture was extracted with EtOAc, and the combined organic phases were neutralized by several washings with saturated aqueous Na_2CO_3. Drying over $MgSO_4$ of the organic layer and concentration under reduced pressure gave a residue that was purified by flash chromatography.

*[(4-Bromophenyl)(2-hydroxyethyl)amino]acetonitrile (**19**).* Yield: 800 mg, 64%. White solid. Mp: 66−68 °C. R_f: 0.3 (PE/EtOAc 6/4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, J = 9.1 Hz, 2H, Ar), 6.74 (d, J = 9.1 Hz, 2H, Ar), 4.22 (s, 2H, CH_2CN), 3.83 (t, J = 5.2 Hz, 2H, CH_2OH), 3.49 (t, J = 5.2 Hz, 2H, NCH_2), 2.12 (bs, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0 (C_q), 132.4 (C_{Ar}), 116.3 (C_{Ar}), 116.1 (CH_2CN), 112.4 (C_q), 60.1 (CH_2OH), 54.0 (NCH_2), 40.7 (CH_2CN) ppm. IR: ν_{max} = 3414 (b), 3332 (b), 2923, 2872, 1584, 1491, 1355, 1208, 1062, 801 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{10}H_{12}BrN_2O$ $[MH]^+$: 255.0133, found 255.0141.

Method A/4 (One-Pot, Two-Step Procedure). A solution of the starting amino alcohol (5 mmol) and paraformaldehyde (10 mmol) in MeCN (30 mL) was refluxed for 12 h. After the solution was cooled to room temperature, BF_3·OEt_2 was added dropwise (250 μL, 4 mmol), followed by TMSCN (500 μL, 4 mmol). The reaction mixture was stirred for 10 min and then quenched by addition of water (20 mL). The reaction mixture was extracted with EtOAc, and the combined organic phases were neutralized by several washings with saturated aqueous Na_2CO_3. Drying over $MgSO_4$ of the organic layer and concentration under reduced pressure gave a residue that was purified by flash chromatography.

*(1R,2S)-[(2-Hydroxy-1-methyl-2-phenylethyl)phenylamino]-acetonitrile (**20**).* Yield: 1.08 g, 81%. Oil. R_f: 0.5 (PE/EtOAc 75/25). $[\alpha]_D^{20}$ −23 (c 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46−7.26 (m, 7H, Ar), 7.03−6.87 (m, 3H, Ar), 5.05 (d, J = 2.5 Hz, 1H, CHOH), 4.37 and 4.24 (two d, J = 18 Hz, 2H, CH_2CN), 4.09 (qd, J = 6.9 and 2.8 Hz, 1H, CHMe), 2.42 (s, 1H, OH), 1.24 (d, J = 6.9 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.0 (C_q), 142.1 (C_q), 129.7 (C_{Ar}), 128.6 (C_{Ar}), 127.7 (C_{Ar}), 125.7 (C_{Ar}), 119.7 (C_{Ar}), 117.9 (CH_2CN), 114.6 (C_{Ar}), 75.5 (CHOH), 58.9 (CHMe), 35.6 (CH_2CN), 10.6 (Me) ppm. IR: ν_{max} = 3449 (b), 3059, 3024, 2981, 1596, 1501, 1246, 1174, 1026, 742, 690 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{17}H_{19}N_2O$ $[MH]^+$: 267.1497, found 267.1500.

*(R)-[(1-Hydroxymethylpropyl)phenylamino]acetonitrile (**21**).* Yield: 870 mg, 85%. Oil. R_f: 0.3 (PE/EtOAc/MeOH 75/25/1). $[\alpha]_D^{20}$ + 47 (c 1.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (dd, J = 8.7 and 7.4 Hz, 2H, Ph), 6.98−6.87 (m, 3H, Ph), 4.19 and 4.12 (two d, J = 18.0 Hz, 2H, CH_2CN), 3.90−3.66 (m, 3H, CH_2OH and CHCH$_2$Me), 2.22 (bs, 1H, OH), 1.66 (q, J = 7.3 Hz, 2H, CHCH_2Me), 0.97 (t, J = 7.4 Hz, 3H, CHCH$_2$*Me*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9 (C_q), 129.6 (C_{Ar}), 119.7 (C_{Ar}), 117.7 (CH_2CN), 114.7 (C_{Ar}), 62.7 (CH_2OH), 62.0 (CHCH$_2$Me), 34.0 (CH_2CN), 21.9 (CHCH$_2$Me), 11.3 (Me) ppm. IR: ν_{max} = 3420 (b), 2964, 2932, 2869, 1597, 1502, 1039, 748, 690 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{12}H_{17}N_2O$ $[MH]^+$: 205.1341, found 205.1337

Method C/2 (Two-Step Procedure). A solution of the starting amino alcohol (5 mmol), p-TsOH (2 mol %), and paraformaldehyde (300 mg, 10 mmol) in benzene (100 mL) was azetropically refluxed for 12 h. After being cooled to room temperature, the mixture was neutralized by washing with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained crude oxazolidine was rapidly passed through a short pad of silica gel, eluting with EP/EtOAc 80/20 to remove small quantities of unreacted amino alcohol. The oxazolidine was then dissolved in AcOH (50 mL), and solid KCN (2.6 g, 40 mmol, 8 equiv) was added cautiously portionwise (Caution: evolved HCN was trapped in an aqueous solution of 1 M NaOH). The reaction mixture was heated to 70−80 °C until complete conversion of the oxazolidine was observed by TLC (1−2 h). After the mixture was cooled to room temperature, water was added (150 mL), and the resulting mixture was extracted with EtOAc. The combined layers were neutralized by several washings with saturated aqueous K_2CO_3 solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was further purified by flash chromatography.

*(S)-[(2-Hydroxy-1-phenylethyl)phenylamino]acetonitrile (**22**).* Yield: 1.03 g, 82%. White solid. Mp: 90−92 °C. R_f: 0.3 (PE/EtOAc 75/25). $[\alpha]_D^{20}$ −108 (c 1.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46−7.29 (m, 7H, Ph), 7.07 (d, J = 7.8 Hz, 2H, Ph), 7.01(t, J = 7.4 Hz, 1H, Ph), 4.97 (t, J = 5.8 Hz, 1H, CHPh), 4.21−3.98 (m, 4H, CH_2CN and CH_2OH), 1.97 (dd, J = 6.6, 5.4 Hz, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.0 (C_q), 142.1 (C_q), 129.7 (C_{Ar}), 128.6 (C_{Ar}), 127.7 (C_{Ar}), 125.7 (C_{Ar}), 119.7 (C_{Ar}), 117.9 (CH_2CN), 114.6 (C_{Ar}), 75.5 (CHOH), 58.9 (CHMe), 35.6 (CH_2CN), 10.6 (Me) ppm. IR: ν_{max} = 3474 (b), 2936, 1594, 1500, 1365, 1245, 1161, 1065, 958, 745, 690, 511 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{16}H_{17}N_2O$ $[MH]^+$: 253.1341, found 253.1353.

Method D/2 (Two-Step Procedure). A solution of the starting amino alcohol (5 mmol), p-TsOH (2 mol %), and the required aromatic aldehyde (5 mmol) in benzene (100 mL) was azeotropically refluxed for 12 h. After being cooled to room temperature, the mixture was neutralized by washing with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained crude oxazolidine was recrystallized from i-PrOH (20 mL) to remove small quantities of unreacted amino alcohol. The oxazolidine was then treated with KCN in AcOH, following method 2 above.

*(4-Bromophenyl)[(2-hydroxyethyl)phenylamino]acetonitrile (**23**).* Yield: 1.31 g, 79%. Oil. R_f: 0.3 (PE/EtOAc 75/25). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.6 Hz, 2H, Ar), 7.42 (d, J = 8.2 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.11−7.02 (m, 3H, Ar), 5.62 (s, 1H, CHCN), 3.70−3.56 (m, 2H, CH_2OH), 3.49 (dt, J = 14.2, 5.0 Hz, 1H, NCHH), 3.28 (ddd, J = 14.2, 6.8, 5.5 Hz, 1H, NCHH), 1.92 (bs, 1H, OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4 (C_q), 132.5 (C_q), 132.3 (C_{Ar}), 129.6 (C_{Ar}), 129.1 (C_{Ar}), 123.4 (C_q), 123.1 (C_{Ar}), 120.0 (C_{Ar}), 116.6 (CHCN), 59.7 (CH_2OH), 59.3 (CHCN), 51.5 (NCH_2) ppm. IR: ν_{max} = 3395 (b), 1596, 1486, 1071, 1009, 747, 693 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{16}H_{16}BrN_2O$ $[MH]^+$: 331.0446, found 331.0443.

Azetidine Synthesis. *Two-Step Procedure via an Intermediate Mesylate.* To a solution of the starting amino alcohol (2 mmol) and triethylamine (0.7 mL, 5 mmol) in CH_2Cl_2 (6 mL) cooled to 0 °C was added dropwise methanesulfonyl chloride (186 μL, 2.4 mmol). The reaction mixture was stirred at 0 °C for 30 min, warmed to rt, and stirred for an additional 30 min. The mixture was quenched by addition of water (15 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with 2% aqueous HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained mesylate was next dissolved in dry THF (15 mL), and t-BuOK (270 mg, 2.4 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and then quenched with water, followed by usual workup (EtOAc). The crude azetidine was purified by flash chromatography.

*1-Phenylazetidine-2-carbonitrile (**25**).* Yield: 295 mg, 92%. White solid. Mp: 78−80 °C. R_f: 0.6 (PE/EtOAc 85/15). ^{1}H NMR (300 MHz,

DOI: 10.1021/acs.joc.6b00169
J. Org. Chem. 2016, 81, 2899−2910

$CDCl_3$): δ = 7.31 (t, J = 8.0 Hz, 2H, Ph), 6.92 (t, J = 7.4 Hz, 1H, Ph), 6.61 (d, J = 7.8 Hz, 2H, Ph), 4.58 (dd, J = 8.1 and 6.6 Hz, 1H, C*H*CN), 4.09−3.98 (m, 1H, NCH*H*), 3.79 (q, J = 7.4 Hz, 1H, NC*H*H). 2.90−2.60 (m, 2H, NCH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.1 (C_q), 129.2 (C_{Ar}), 119.7 (C_{Ar}), 118.8 (CHCN), 112.0 (C_{Ar}), 50.6 (NCH_2), 50.4 (*C*HCN), 22.5 (NCH_2CH_2) ppm. IR: ν_{max} =3031, 2967, 2872, 1701, 1598, 1500, 1323, 755, 692, 515 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{10}H_{11}N_2$ $[MH]^+$: 159.0922, found 159.0923.

*1-(4-Methoxyphenyl)azetidine-2-carbonitrile (**26**).* Yield: 350 mg, 94%. White solid. Mp: 49−51 °C. R_f: 0.4 (PE/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.87 (d, J = 9.0 Hz, 2H, Ar), 6.56 (d, J = 9.0 Hz, 2H, Ar), 4.52 (dd, J = 8.3, 6.7 Hz, 1H, C*H*CN), 4.03−3.95 (m, 1H, NCH*H*), 3.86−3.68 (m, 4H, NC*H*H and OMe), 2.87−2.59 (m, 2H, NCH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6 (C_q), 143.5 (C_q), 118.9 (CHCN), 114.8 (C_{Ar}), 113.3 (C_{Ar}), 55.7 (OMe), 50.9 (CHCN and NCH_2), 22.5 (NCH_2CH_2) ppm. IR: ν_{max} = 2955, 2869, 2831, 1504, 1440, 1237, 1028, 827, 619 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{11}H_{13}N_2O$ $[MH]^+$: 189.1028, found 189.1026.

*1-(3,5-Dimethylphenyl)azetidine-2-carbonitrile (**27**).* Yield: 325 mg, 87%. White solid. Mp: 99−101 °C. R_f: 0.3 (PE/EtOAc 95/5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.56 (s, 1H, Ar), 6.23 (s, 2H, Ar), 4.56 (dd, J = 8.4, 6.8 Hz, 1H, C*H*CN), 4.07−3.98 (m, 1H, NCH*H*), 3.77 (q, J = 7.5 Hz, 1H, NC*H*H), 2.89−2.75 (m, 1H, NCH_2CHH), 2.74−2.60 (m, 1H, NCH_2CHH), 2.31 (s, 6H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.4 (C_q), 139.1 (C_q), 121.8 (C_{Ar}), 118.9 (CHCN), 109.8 (C_{Ar}), 50.6 (NCH_2), 50.4 (*C*HCN), 22.6 (NCH_2CH_2), 21.5 (Me) ppm. IR: ν_{max} = 2961, 2910, 2875, 1594, 1473, 1350, 1204, 823 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{12}H_{15}N_2$ $[MH]^+$: 187.1235, found 187.1237.

*1-(Naphthalen-1-yl)azetidine-2-carbonitrile (**28**).* Yield: 340 mg, 82%. White solid. Mp: 130−132 °C. R_f: 0.4 (PE/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03−7.77 (m, 2H, Ar), 7.56−7.38 (m, 4H, Ar), 6.76 (d, J = 7.4 Hz, 1H, Ar), 4.93 (dd, J = 8.3 and 6.8 Hz, 1H, C*H*CN), 4.55−4.46 (m, 1H, NCH*H*), 3.87 (q, J = 5.1 Hz, 1H, NC*H*H), 2.92−2.78 (m, 1H, NCH_2CHH), 2.78−2.64 (m, 1H, NCH_2CHH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.1 (C_q), 134.8 (C_q), 128.7 (C_q), 126.2 (C_{Ar}), 125.6 (C_{Ar}), 125.3 (C_{Ar}), 125.2 (C_{Ar}), 123.0 (C_{Ar}), 122.5 (C_{Ar}), 118.5 (CHCN), 109.6 (C_{Ar}), 54.4 (NCH_2), 51.0 (*C*HCN), 22.8 (NCH_2CH_2) ppm. IR: ν_{max} = 3053, 2993, 2958, 2910, 2888, 2239, 1573, 1397, 1285, 1070, 1022, 799, 770 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{14}H_{13}N_2$ $[MH]^+$ 209.1079, found 209.1074.

*1-(4-Chlorophenyl)azetidine-2-carbonitrile (**29**).* Yield: 285 mg, 74%. White solid. Mp: 64−66 °C. R_f: 0.3 (PE/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.8 Hz, 2H, Ar), 6.50 (d, J = 8.8 Hz, 2H, Ar), 4.57 (dd, J = 8.2, 6.7 Hz, 1H, C*H*CN), 4.08−3.93 (m, 1H, NCH*H*), 3.77 (q, J = 7.4 Hz, 1H, NC*H*H), 2.90−2.62 (m, 2H, NCH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.5 (C_q), 129.2 (C_{Ar}), 124.8 (C_q), 118.4 (CHCN), 113.2 (C_{Ar}), 50.6 (NCH_2), 50.5 (CHCN), 22.4 (NCH_2CH_2) ppm. IR: ν_{max} = 2983, 2879, 1597, 1492, 1326, 1092, 812, 506 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{10}H_{10}ClN_2$ $[MH]^+$: 193.0533, found 193.0525.

*1-(4-Bromophenyl)azetidine-2-carbonitrile (**30**).* Yield: 340 mg, 72%. White solid. Mp: 82−84 °C. R_f: 0.2 (PE/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.9 Hz, 2H, Ar), 6.45 (d, J = 8.9 Hz, 2H, Ar), 4.57 (dd, J = 8.3, 6.6 Hz, 1H, C*H*CN), 4.08−3.95 (m, 1H, NCH*H*), 3.77 (q, J = 7.4 Hz, 1H, NC*H*H), 2.90−2.62 (m, 2H, NCH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9 (C_q), 132.0 (C_{Ar}), 118.3 (CHCN), 113.7 (C_{Ar}), 112.0 (C_q), 50.6 (NCH_2), 50.4 (CHCN), 22.4 (NCH_2CH_2) ppm. IR: ν_{max} = 2980, 2872, 1591, 1489, 1329, 808, 500 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{10}H_{10}BrN_2$ $[MH]^+$: 237.0027, found 237.0032.

*(2S,4R)-4-Ethyl-1-phenylazetidine-2-carbonitrile (**31a** and **31b**).* Yield: 310 mg, 83%. Crude ratio: 60:40 for **31a**:**31b**. These epimers were separated by preparative TLC. Major epimer **31a**. Oil. R_f: 0.55 (PE/EtOAc 95/5). $[\alpha]_D^{20}$ +136 (c 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29 (t, J = 7.8 Hz, 2H, Ph), 6.91 (t, J = 7.4 Hz, 1H, Ph), 6.68 (d, J = 7.9 Hz, 2H, Ph), 4.36 (dd, J = 8.7 and 7.5 Hz, 1H, C*H*CN), 3.98 (qd, J = 7.9 and 3.9 Hz, 1H, C*H*CH_2Me), 2.76 (dt, J = 11.1 and 8.4 Hz, 1H, CH_2CHCN), 2.47 (dt, J = 11.2 and 7.3 Hz, 1H, CH_2CHCN), 2.09−1.93 (m, 1H, CHCH_2Me), 1.95−1.78 (m, 1H, CHCH_2Me), 1.01 (t, J = 7.5 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0 (C_q), 129.3 (C_{Ar}), 120.0 (C_{Ar}), 119.4 (CHCN), 112.3 (C_{Ar}), 64.3 (*C*HCH_2Me), 47.9 (CHCN), 29.3 (CHCH_2Me), 27.9 (*C*H_2CHCN), 8.3 (Me) ppm. IR: ν_{max} = 2972, 2930, 2875, 1652, 1576, 1405, 750 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{12}H_{15}N_2$ $[MH]^+$: 187.1235, found 187.1240. Minor epimer **31b**. Oil. R_f: 0.45 (PE/EtOAc 95/5). $[\alpha]_D^{20}$ −381 (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (t, J = 7.8 Hz, 2H, Ar), 6.90 (t, J = 7.4 Hz, 1H, Ar), 6.61 (d, J = 8.3 Hz, 2H, Ar), 4.79 (dd, J = 8.3 and 3.5 Hz, 1H, C*H*CN), 4.31 (qd, J = 7.8 and 3.6 Hz, 1H, C*H*CH_2Me), 2.71−2.59 (m, 1H, CH_2CHCN), 2.49 (dt, J = 11.1 and 7.7 Hz, 1H, CH_2CHCN), 2.10−1.94 (m, 1H, CHCH_2Me), 1.78−1.59 (m, 1H, CHCH_2Me), 0.94 (t, J = 7.5 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.7 (C_q), 129.2 (C_{Ar}), 119.7 (C_{Ar}), 118.3 (CHCN), 112.9 (C_{Ar}), 63.6 (*C*HCH_2Me), 48.3 (*C*HCN), 27.9 (*C*HCH_2Me), 27.5 (*C*H_2CHCN), 8.2 (Me) ppm. IR: ν_{max} = 3317 (b), 2964, 2929, 2877, 1651, 1600, 1577, 1406, 1041, 752, 639 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{12}H_{15}N_2$ $[MH]^+$ 187.1235, found 187.1237.

*(1R,2S)-((2-Chloro-1-methyl-2-phenylethyl)phenylamino)-acetonitrile (**32**).* This compound was prepared following the above procedure for **25** starting from **20**. The expected intermediate mesylate was completely transformed into the corresponding chloride. However, **32** is unstable on silica gel, and after purification by flash chromatography, a 1/1 mixture of chloride **32** and alcohol **20** was obtained. R_f: 0.6 (PE/EtOAc 95/5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48−7.28 (m, 7H^{OH} and 7H^{Cl}, Ph), 6.96 (m, 3H^{OH} and 3H^{Cl}, Ph), 5.21 (d, J = 5.1 Hz, 1H^{Cl}), 5.09 (d, J = 2.7 Hz, 1H^{OH}, C*H*OH), 4.43−4.24 (m, 2H^{OH} and 2H^{Cl}, CH_2^{OH}CN CH*H*^{Cl}CN and C*H*^{Cl}Me), 4.16−4.00 (m, 1H^{OH} and 1H^{Cl}, C*H*^{Cl}HCN and C*H*^{OH}Me), 2.23 (s, 1H ^{OH}, OH), 1.50 (d, J = 6.7 Hz, 3H^{Cl}, Me), 1.26 (d, J = 6.9 Hz, 3H^{OH}, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.2 (C_q), 138.6 (C_q), 128.7 (C_{Ar}), 127.2 (C_{Ar}), 120.4 (C_{Ar}), 117.1 (CH_2CN), 115.2 (C_{Ar}), 66.4 (CHCl), 60.1 (CHMe), 35.4 (CH_2CN), 13.3 (Me) ppm of HRMS (TOF MSES positive mode) m/z calcd for $C_{17}H_{18}ClN_2$ $[MH]^+$: 285.1159, found 285.1150.

One-Pot, Two-Step Procedure via an Intermediate Chloride or Mesylate. To a solution of the starting amino alcohol (2 mmol) and triethylamine (0.7 mL, 5 mmol) in THF (6 mL) cooled to 0 °C was added dropwise methanesulfonyl chloride (186 μL, 2.4 mmol). The reaction mixture was stirred to 0 °C for 30 min, warmed to rt, and stirred for an additional 30 min. It was then cooled to 0 °C, and *t*-BuOK (900 mg, 8 mmol) was added portionwise at 0 °C. The reaction mixture was allowed to warm to room temperature, and addition of water was followed by usual workup (EtOAc). The crude azetidine was purified by flash chromatography.

*(2S,3S,4S)-4-Methyl-1,3-diphenylazetidine-2-carbonitrile (**33a**) and (2R,3S,4S)-4-Methyl-1,3-diphenylazetidine-2-carbonitrile (**33b**).* Yield: 380 mg, 76%, Crude ratio: 60:40 for **33a**:**33b**. These epimers were separated by flash chromatography. Major epimer **33a** (68%). White solid. Mp: 100−102 °C. R_f: 0.45 (PE/EtOAc 95/5). $[\alpha]_D^{20}$ +50 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45−7.23 (m, 7H, Ph), 6.97 (t, J = 7.4 Hz, 1H, Ph), 6.79 (d, J = 7.9 Hz, 2H, Ph), 4.38 (d, J = 7.4 Hz, 1H, C*H*CN), 4.16 (q, J = 6.2 Hz, 1H, C*H*Me), 3.83 (t, J = 7.3 Hz, 1H, C*H*Ph), 1.70 (d, J = 6.0 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.2 (C_q), 137.1 (C_q), 129.5 (C_{Ar}), 129.0 (C_{Ar}), 128.2 (C_{Ar}), 127.1 (C_{Ar}), 120.6 (C_{Ar}), 118.9 (CHCN), 112.8 (C_{Ar}), 66.6 (CHMe), 55.2 (CHCN), 49.6 (CHPh), 22.7 (Me) ppm. IR: ν_{max} = 2958, 2876, 1596, 1493, 1321, 1129, 755, 659 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{17}H_{17}N_2$ $[MH]^+$: 249.1392, found 249.1393. Suitable crystals of **33a** for X-ray crystallography were obtained by slow evaporation of an *i*-PrOH solution. Minor epimer **33b** (8%). Oil. R_f: 0.25 (PE/EtOAc 95/5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.55−7.10 (m, 7H, Ph), 6.94 (t, J = 7.4 Hz, 1H, Ph), 6.70 (d, J = 7.2 Hz, 2H, Ph), 5.21 (d, J = 8.2 Hz, 1H, C*H*CN), 4.61 (p, J = 6.2 Hz, 1H, C*H*Me), 3.84 (t, J = 7.7 Hz, 1H, C*H*Ph), 1.58 (d, J = 6.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4 (C_q), 135.3 (C_q), 129.3 (C_{Ar}), 128.8 (C_{Ar}), 128.3 (C_{Ar}), 120.2 (C_{Ar}), 115.9 (CHCN), 113.6 (C_{Ar}), 64.0 (CHMe), 55.9 (CHCN), 46.8 (CHPh), 20.6 (Me) ppm. HRMS (TOF MSES positive mode) m/z calcd for $C_{17}H_{17}N_2$ $[MH]^+$: 249.1392, found 249.1390

DOI: 10.1021/acs.joc.6b00169
J. Org. Chem. 2016, 81, 2899−2910

*(2S,4R)-1,4-Diphenylazetidine-2-carbonitrile (**34a**) and (2R,4R)-1,4-Diphenylazetidine-2-carbonitrile (**34b**).* Yield: 330 mg, 70%. Crude ratio: 82:18 for **34a**:**34b**. Pasty solid. R_f: 0.5 (PE/EtOAc 9/1). These isomers could not be separated by chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 7.0 Hz, 2H^M, Ar), 7.39−7.21 (m, 3H^M and 5H^m, Ar), 7.12 (t, J = 7.8 Hz, 2H^M and 2H^m, Ar), 6.79 (t, J = 7.3 Hz, 1H^M and 1H^m, Ar), 6.50 (d, J = 8.0 Hz, 2H^M, Ar), 6.42 (d, J = 8.0 Hz, 2H^m, Ar), 5.14 (t, J = 7.8 Hz, 1H^m, C*H*^{m}CN), 4.88−4.71 (m, 1H^M and 1H^m, C*H*^{M}CN and C*H*^{m}Ph), 4.42 (t, J = 8.0 Hz, 1H^M, C*H*^{M}Ph), 2.96 (dt, J = 11.0, 8.2 Hz, 1H^M, CH*H*^{M}CHCN), 2.82 (ddd, J = 10.5, 7.7, 2.6 Hz, 1H^m, CH*H*^{m}CHCN), 2.67−2.48 (m, 1H^M and 1H^m, C*H*^{M}HCHCN and C*H*^{m}HCHCN) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.5 (C_q^M), 146.4 (C_q^m), 141.3 (C_q^M), 140.9 (C_q^m), 129.3 (C_{Ar}^M), 129.2 (C_{Ar}^m), 129.1 (C_{Ar}^M), 129.0 (C_{Ar}^m), 128.43 (C_{Ar}^M), 128.37 (C_{Ar}^m), 126.1 (C_{Ar}^M), 126.0 (C_{Ar}^m), 120.5 (C_{Ar}^M), 120.2 (C_{Ar}^m), 119.1 (CH*C*^{M}N), 118.0 (CH*C*^{m}N), 113.3 (C_{Ar}^m), 112.7 (C_{Ar}^M), 65.8 (*C*^{M}HPh), 65.5 (*C*^{m}HPh), 48.5 (*C*^{m}HCN), 47.4 (*C*^{M}HCN), 33.0 (*C*^{m}H$_2$), 32.8 (*C*^{M}H$_2$) ppm. IR: ν_{max} = 3062, 3031, 2968, 2913, 2876, 1598, 1498, 1322, 751, 693, 1041, 752, 639 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{16}H_{15}N_2$ [MH]$^+$: 235.1235, found 235.1240. Suitable crystals of **34a** for X-ray crystallography were obtained by slow evaporation of a $CHCl_3$ solution of the mixture.

*2-(4-Bromophenyl)-1-phenylazetidine-2-carbonitrile (**35**).* Yield: 500 mg, 80%. White solid. Mp: 90−92 °C. R_f: 0.6 (PE/EtOAc 95/5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (s, 4H, Ar), 7.24 (dd, J = 8.7, 7.5 Hz, 2H, Ph), 6.91 (t, J = 7.4 Hz, 1H, Ph), 6.47 (d, J = 7.7 Hz, 2H, Ph), 4.11−4.00 (m, 2H, NC*H*$_2$), 2.99 (ddd, J = 10.9, 6.8, 3.9 Hz, 1H, NCH$_2$CH*H*), 2.71 (dt, J = 11.0, 8.6 Hz, 1H, NCH$_2$C*H*H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.5 (C_q), 137.4 (C_q), 132.4 (C_{Ar}), 129.1 (C_{Ar}), 127.0 (C_{Ar}), 123.4 (C_q), 120.3 (C_{Ar}), 118.5 (*C*CN), 112.9 (C_{Ar}), 66.7 (*C*CN), 47.5 (NCH$_2$), 35.0 (NCH$_2$CH$_2$) ppm. IR: ν_{max} =2974, 2948, 2875, 1599, 1484, 1315, 822, 761, 695 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{16}H_{14}BrN_2$ [MH]$^+$: 313.0340, found 313.0347.

*(2R)-[(2-Chloro-2-phenylethyl)phenylamino]acetonitrile (**36**).* This compound was obtained after refluxing a solution of the intermediate mesylate obtained from **22** (2 mmol) prepared without isolation as reported above for **20**, but using as solvent acetonitrile instead of THF. It was purified by flash chromatography. Yield: 495 mg, 92%. Oil. R_f: 0.4 (PE/EtOAc 9/1). $[\alpha]_D^{20}$ −8 (c 1.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50−7.29 (m, 7H, Ph), 6.97 (t, J = 7.4 Hz, 1H, Ph), 6.83 (d, J = 7.9 Hz, 2H, Ph), 5.13 (t, J = 7.0 Hz, 1H, C*H*Cl), 4.20−3.76 (m, 4H, C*H*$_2$CN and C*H*$_2$CHCl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.9 (C_q), 138.8 (C_q), 129.8 (C_{Ar}), 129.2 (C_{Ar}), 129.1 (C_{Ar}), 127.3 (C_{Ar}), 120.2 (C_{Ar}), 115.8 (CH$_2$*C*N), 113.8 (C_{Ar}), 60.5 (*C*H$_2$CHCl), 60.1 (*C*HCl), 40.6 (CH$_2$*C*N) ppm. IR: ν_{max} = 3031, 1598, 1503, 1348, 1208, 1174, 748, 693 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{16}H_{16}ClN_2$ [MH]$^+$: 271.1002, found 271.1013

*(2R,3R)-1,3-Diphenylazetidine-2-carbonitrile (**37a**) and (2S,3R)-1,3-Diphenylazetidine-2-carbonitrile (**37b**).* To a solution of the above chloride **36** (100 mg, 0.37 mmol) in THF (10 mL) was added portionwise at 0 °C *t*-BuOK (62 mg, 0.55 mmol, 1.5 equiv). The reaction mixture was stirred for 20 min and allowed to reach room temperature. Addition of water was followed by usual workup (EtOAc). The crude azetidines were purified by flash chromatography. Yield: 77 mg, 89%. Crude ratio: 73:27 for **37a**:**37b**. These epimers were separated by flash chromatography. Major epimer **37a** (65%). Oil. R_f: 0.6 (PE/EtOAc 9/1). $[\alpha]_D^{20}$ −126 (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46−7.30 (m, 7H, Ph), 6.97 (t, J = 7.4 Hz, 1H, Ph), 6.72 (d, J = 7.7 Hz, 2H, Ph), 4.56 (d, J = 6.6 Hz, 1H, C*H*CN), 4.44 (dd, J = 8.1, 6.6 Hz, 1H, NC*H*H), 4.34 (q, J = 7.2 Hz, 1H, C*H*Ph), 3.94 (t, J = 6.7 Hz, 1H, NCH*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.2 (C_q), 137.9 (C_q), 129.4 (C_{Ar}), 129.1 (C_{Ar}), 128.2 (C_{Ar}), 127.0 (C_{Ar}), 120.2 (C_{Ar}), 118.3 (CHCN), 112.4 (C_{Ar}), 57.6 (*C*HCN), 57.3 (NCH$_2$), 41.1 (*C*HPh) ppm. IR: ν_{max} = 3029, 2865, 1598, 1497, 1319, 748, 691 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{16}H_{15}N_2$ [MH]$^+$: 235.1235, found 235.1241. Minor epimer **37b** (24%). Oil. R_f: 0.4 (PE/EtOAc 9/1). $[\alpha]_D^{20}$ +92 (c 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62−7.18 (m, 7H, Ph), 6.95 (t, J = 7.2 Hz, 1H, Ph), 6.70 (d, J = 7.8 Hz, 1H, Ph), 5.02 (d, J = 8.1 Hz, 1H, C*H*CN), 4.27−4.03 (m, 3H, C*H*Ph and NC*H*$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.7 (C_q), 137.2 (C_q), 129.3 (C_{Ar}), 129.0 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 120.0 (C_{Ar}), 116.5 (CHCN), 112.4 (C_{Ar}), 57.1 (*C*HCN), 57.0 (NCH$_2$), 38.5 (CHPh) ppm. HRMS (TOF MSES positive mode) m/z calcd for $C_{16}H_{15}N_2$ [MH]$^+$: 235.1235, found 235.1230

Procedure for Azetidinium Salt Formation. Azetidine **25** (200 mg, 1.3 mmol) was dissolved in DCM (4 mL), and methyl trifluoromethanesulfonate (250 μL, 2.5 mmol) was added dropwise. The mixture was stirred under argon for 12 h and then poured into Et_2O (5 mL). The precipitate was filtered and washed with cold Et_2O (10 mL). The white solid was dried under vacuum.

*2-Cyano-1-methyl-1-phenylazetidin-1-ium Methanesulfonate **38**.* Yield: 360 mg, 89%. Ratio Major/minor: 1/0.22. ^{1}H NMR (300 MHz, acetone d_6): δ = 7.95 (d, J = 8.3 Hz, 2H^m, Ph), 7.80−7.60 (m, 5H^m and 3H^M, Ph), 6.64 (t, J = 9.6 Hz, 1H^M, *C*HCN), 6.34 (dt, J = 6.4, 2.8 Hz, 1H^m, *C*HCN), 5.78 (q, J = 10.1 Hz, 1H^m, NCH*H*), 5.40 (q, J = 9.8 Hz, 1H^M, NCH*H*), 5.07 (m, 1H^M and 1H^m, NC*H*H), 4.05 (s, 1H^m, Me), 4.04 (s, 1H^M, Me), 4.00−3.85 (m, 1H^m, NCH$_2$CH*H*), 3.85−3.67 (m, 1H^M, NCH$_2$CH*H*), 3.32−3.13 (m, 1H^M, NCH$_2$C*H*H), 3.10−2.96 (m, 1H^m, NCH$_2$C*H*H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.4 (C_q), 131.9 (C_{Ar}), 131.7 (C_{Ar}), 131.61 (C_{Ar}), 131.56 (C_{Ar}), 131.3 (C_{Ar}), 124.2 (CF_3), 123.0 (CF_3), 121.7 (C_{Ar}), 120.1 (C_{Ar}), 120.0 (CF_3), 114.3 (CH*C*^{m}N), 113.4 (CH*C*^{M}N), 68.7 (*C*^{m}HCN), 67.7 (NC^{M}H$_2$), 66.3 (NC^{m}H$_2$), 63.7 (*C*^{M}HCN), 57.9 (Me^m), 55.1 (Me^M), 22.5 (NCH$_2$C^{M}H$_2$), 22.2 (NCH$_2$C^{m}H$_2$) ppm. IR: ν_{max} = 2959, 1247, 1148, 1026, 759, 635, 515 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{11}H_{13}N_2$ [M]$^+$: 173.1079, found 173.1079

Procedure for Azetidinium Salt Ring Opening. Azetidinium salt **38** (161 mg, 0.5 mmol) was dissolved in freshly distilled DMF (2.5 mL), and NaN_3 (325 mg, 5 mmol) was added portionwise. The mixture was stirred for 12 h under argon and then quenched with water (15 mL) and EtOAc (15 mL). Extraction by EtOAc followed by usual workup gave a residue that was further purified by flash chromatography.

*2-Azido-4-(methyl(phenyl)amino)butanenitrile (**39**).* Yield: 47 mg, 44%. Oil. R_f: 0.4 (EP/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (t, 2H, Ph), 6.85−6.74 (m, 3H, Ph), 4.32 (dd, J = 7.4, 6.6 Hz, 1H, C*H*CN), 3.63−3.45 (m, 2H, C*H*$_2$NPh), 2.96 (s, 3H, Me), 2.24−2.01 (m, 2H, C*H*$_2$CHCN) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.8 (C_q), 129.5 (C_{Ar}), 117.7 (C_{Ar}), 116.2 (CHCN), 113.0 (C_{Ar}), 48.9 (*C*HCN), 48.4 (*C*H$_2$NPh), 38.9 (Me), 30.5 (*C*H$_2$CHCN) ppm. IR: ν_{max} = 2913, 2101, 1597, 1504, 1232, 747, 691 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{11}H_{14}N_5$ [MH]$^+$: 216.1249, found 216.1243

*4-Azido-4-(methyl(phenyl)amino)butanenitrile (**40**).* Yield: 8 mg, 7%, not totally separated from **39**, remaining as a 28% mixture with **40**. Oil. R_f: 0.55 (PE/EtOAc 75/25). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (t, 2H, Ph), 7.05−6.96 (m, 3H, Ph), 4.70 (dd, J = 8.5, 7.1 Hz, 1H, C*H*CN), 3.58 (t, J = 6.1 Hz, 2H, C*H*$_2$N$_3$), 2.90 (s, 3H, Me), 2.26−2.03 (m, 2H, C*H*$_2$CH$_2$N$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.2 (C_q), 129.5 (C_{Ar}), 121.6 (C_{Ar}), 117.4 (C_{Ar}), 117.1 (CHCN), 51.8 (*C*HCN), 47.0 (*C*H$_2$N$_3$), 34.5 (Me), 31.0. (*C*H$_2$CH$_2$N$_3$) ppm. HRMS (TOF MSES positive mode) m/z calcd for $C_{11}H_{14}N_5$ [MH]$^+$: 216.1249, found 216.1249

Procedure for the Preparation of Ketone (41). Azetidine **26** (50 mg, 0.32 mmol) was dissolved in dry THF, and the solution was cooled to 0 °C. A 2.5 M solution of BuLi in THF (252 μL, 0.64 mmol) was then added dropwise. The mixture was stirred at 0 °C for 30 min and then quenched with water. THF was removed under vacuum, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and then dried over $MgSO_4$. The residue was then rapidly purified by flash chromatography on a short silica gel column to provide **41** as a yellow oil.

*1-(1-Phenylazetidin-2-yl)pentan-1-one (**41**).* Yield: 49 mg, 71%. Oil. R_f: 0.65 (PE/EtOAc 95/5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (t, J = 8.0 Hz, 2H, Ph), 6.82 (t, J = 7.3 Hz, 1H, Ph), 6.44 (d, J = 8.2 Hz, 2H, Ph), 4.42 (t, J = 8.5 Hz, 1H, NC*H*CO), 4.08−3.94 (m, 1H, NCH*H*), 3.75 (q, J = 7.8 Hz, 1H, NC*H*H), 2.75 (dt, J = 17.5, 7.4 Hz, 1H, COCH*H*CH$_2$CH$_2$Me), 2.65−2.35 (m, 3H, COC*H*HCH$_2$CH$_2$Me and NCH$_2$C*H*$_2$), 1.64 (quint., J = 7.4 Hz, 2H, COCH$_2$C*H*$_2$CH$_2$Me), 1.36 (sext., J = 7.4 Hz, 2H, COCH$_2$CH$_2$C*H*$_2$Me), 0.93 (t, J = 7.3 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.5 (CO), 150.8 (C_q), 129.0

DOI: 10.1021/acs.joc.6b00169
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(C_{Ar}), 118.6 (C_{Ar}), 111.8 (C_{Ar}), 70.2 (NCHCO), 49.6 (NCH_2), 37.2 ($COCH_2CH_2CH_2Me$), 25.4 ($COCH_2CH_2CH_2Me$), 22.4 ($COCH_2CH_2CH_2Me$), 21.7 (NCH_2CH_2), 13.9 (Me) ppm. IR: ν_{max} = 2955, 2926, 2866, 1707, 1598, 1499, 1328, 749, 691 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{14}H_{20}NO$ $[MH]^+$: 218.1545, found 218.1540

Procedure for the Preparation of Alcohol 42. A solution of ketone **41** (320 mg, 1.5 mmol) and $ZnBr_2$ (364 mg, 1.6 mmol) in MeOH (7 mL) was stirred at room temperature for 30 min. $NaBH_4$ was then added (84 mg, 2.2 mmol), and after 10 h of stirring at room temperature, a further portion of $NaBH_4$ was added (84 mg, 2.2 mmol) to reach full conversion. Ethanolamine (350 μL, 5.9 mmol) was added, and after 30 min of stirring the mixture was quenched with water and extracted with EtOAc. The residue (de 88%) was purified by flash chromatography to provide pure **42** as a clear oil.

*(1S,2R)-1-(1-Phenylazetidin-2-yl)-pentan-1-ol (**42**).* Yield: 200 mg, 63%. Oil. R_f: 0.6 (PE/EtOAc 95/5). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (t, J = 7.9 Hz, 2H, Ph), 6.84 (t, J = 7.3 Hz, 1H, Ph), 6.60 (d, J = 8.0 Hz, 2H, Ph), 4.11 (td, J = 7.9, 2.3 Hz, 1H, NC*H*CHOH), 4.05−3.97 (m, 1H, NCHC*H*OH), 3.94−3.84 (m, 1H, NCH*H*), 3.64 (q, J = 8.0 Hz, 1H, NC*H*H), 2.95 (s, 1H, OH), 2.63−2.49 (m, 1H, NCH_2CHH), 2.16−2.01 (m, 1H, NCH_2CHH), 1.65−1.27 (m, 6H, $COHCH_2CH_2CH_2Me$), 0.97 (t, J = 6.9 Hz, 3H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2 (C_q), 129.0 (C_{Ar}), 118.7 (C_{Ar}), 112.5 (C_{Ar}), 70.4 (NCHCOH), 69.1 (NCHCOH), 50.1 (NCH_2), 31.1 ($COHCH_2CH_2CH_2Me$), 28.1 ($COHCH_2CH_2CH_2Me$), 22.9 ($COHCH_2CH_2CH_2Me$), 16.1 (NCH_2CH_2), 14.1 (Me) ppm. IR: ν_{max} = 3455 (b), 2955, 2926, 2860, 1598, 1498, 1314, 750, 691 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{14}H_{22}NO$ $[MH]^+$: 220.1701, found 220.1700

General Procedure for Suzuki Coupling. A solution of the azetidine (2 mmol) in toluene (13 mL), a solution of phenylboronic acid (488 mg, 4 mmol) in absolute EtOH (3 mL), and a 2 M aqueous solution of Na_2CO_3 (3 mL) were stirred together while argon was bubbled through the mixture for 15 min. $Pd(PPh_3)_4$ (36 mg, 5 mol %) was then added, and the mixture was stirred at 90 °C under argon in a sealed tube for 5 h, cooled to room temperature, and poured into EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and then dried over $MgSO_4$. The residue was then purified by flash chromatography.

*1-Biphenyl-4-yl-azetidine-2-carbonitrile (**43**).* Yield: 430 mg, 91%. White solid. Mp: 106−108 °C, R_f: 0.3 (PE/EtOAc 95/5). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60−7.50 (m, 4H, Ar), 7.43 (t, J = 7.5 Hz, 2H, Ar), 7.33 (d, J = 7.2 Hz, 1H, Ar), 6.68 (d, J = 8.7 Hz, 2H, Ar), 4.65 (dd, J = 8.4, 6.6 Hz, 1H, C*H*CN), 4.10 (ddd, J = 8.5, 6.8, 4.7 Hz, 1H, NCH*H*), 3.86 (dt, J = 8.3, 7.0 Hz, 1H, NC*H*H), 2.92−2.67 (m, 2H, NCH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.3 (C_q), 140.8 (C_q), 132.8 (C_{Ar}), 128.8 (C_{Ar}), 128.0 (C_{Ar}), 126.6 (C_{Ar}), 126.6 (C_{Ar}), 118.6 (CHCN), 112.4 (C_{Ar}), 50.6 (NCH_2), 50.5 (CHCN), 22.5 (NCH_2CH_2) ppm. IR: ν_{max} = 3031, 2977, 2856, 1604, 1521, 1485, 1318, 1066, 826, 762, 690 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{16}H_{15}N_2$ $[MH]^+$: 235.1235, found 235.1230

*2-Biphenyl-4-yl-1-phenylazetidine-2-carbonitrile (**44**).* Yield: 390 mg, 63%. Oil. R_f: 0.5 (PE/EtOAc 95/5). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.4 Hz, 2H, Ar), 7.71 (d, J = 8.3 Hz, 2H, Ar), 7.66 (d, J = 7.2 Hz, 2H, Ar), 7.51 (t, J = 7.4 Hz, 2H, Ar), 7.42 (t, J = 7.2 Hz, 1H, Ar), 7.27 (t, J = 7.9 Hz, 2H, Ar), 6.92 (t, J = 7.4 Hz, 1H, Ar), 6.56 (d, J = 7.9 Hz, 2H, Ar), 4.16−4.03 (m, 2H, NCH_2 CH_2), 3.04 (ddd, J = 10.8, 6.8, 3.9 Hz, 1H, NCH_2CHH), 2.80 (dt, J = 10.9, 8.6 Hz, 1H, NCH_2CHH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.8 (C_q), 142.2 (C_q), 140.2 (C_q), 137.3 (C_q), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.2 (C_{Ar}), 125.8 (C_{Ar}), 120.1 (C_{Ar}), 118.9 (CCN), 113.0 (C_{Ar}), 67.1 (CCN), 47.6, (NCH_2) 35.2 (NCH_2CH_2) ppm. IR: ν_{max} = 3031, 2967, 2886, 1598, 1498, 1320, 906, 726, 694 cm^{-1}. HRMS (TOF MSES positive mode) m/z calcd for $C_{22}H_{19}N_2$ $[MH]^+$: 311.1548, found 311.1155.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00169.

X-ray data for **33a** (CIF)
X-ray data for **34a** (CIF)
Computational details (PDF)
^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The University of Versailles St-Quentin-en-Yvelines and the CNRS are acknowledged for funding. P.Q. acknowledges l'École polytechnique for a Ph.D. grant.

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DOI: 10.1021/acs.joc.6b00169
J. Org. Chem. 2016, 81, 2899−2910