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Aza-[2,3]-Wittig Sigmatropic Rearrangement of Allylic Tertiary Amines: A Successful Example with High Chirality Transfer

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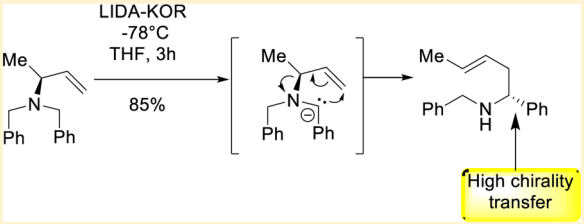
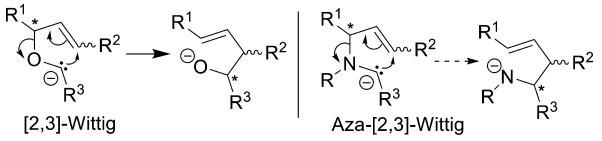
Supporting Information

ABSTRACT: We report herein a successful example of an aza-[2,3]-Wittig rearrangement in an allylic tertiary *N*,*N*-dibenzyl amine derived from (*S*)-alaninol or (*S*)-isoleucinol. This reaction occurs upon metalation at the benzylic position with a mixture of butyllithium/diisopropylamine/potassium *t*-butoxide and proceeds with a high 1,3 transfer of chirality.



The [2,3]-Wittig rearrangement has become a very useful synthetic tool in organic synthesis[1] due to its often efficient outcome for chirality transfer coupled with the availability of the enantiomerically pure allylic alcohols required as starting materials for the preparation of reactants. Conversely, its aza analogue is known to be reluctant to proceed in the acyclic series and competes with [1,2] rearrangement.[2] This can be explained by the lower electronegativity of the nitrogen atom compared to oxygen, which, as a result, increases the energy of the transition state where significant anionic charge is developed at the heteroatom (Scheme 1).

Scheme 1. [2,3]-Wittig and Aza-[2,3]-Wittig Rearrangements

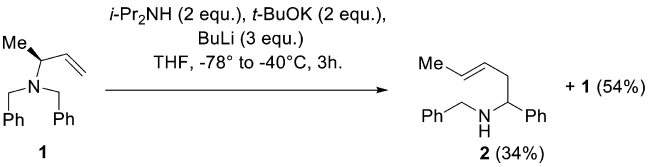


Therefore, it is now accepted that such aza-Wittig rearrangements can only proceed if additional structural features in the reacting allylic amine help to "pass the hill" of the energetic transition state, such as ring-strain release,[3] acylation of the nitrogen atom,[4] a silicon atom on the alkene,[5] or a combination of these features. Within these restrictions, good chirality transfer can be achieved however, and Anderson notably demonstrated the power of this reaction in the total synthesis of kainic acid.[6] To the best of our knowledge, the use of simple tertiary amines in the acyclic series still remains elusive, and as a consequence, chirality transfer in these kinds of substrates has never been studied.

We report herein a successful example of such a reaction and demonstrate that it proceeds with high transfer of chirality.

With the initial goal of promoting a carbometalation reaction leading to an azetidine, allylic amine **1**, readily prepared from (*S*)-alaninol, was treated with a 2/2/3 mixture of potassium *t*-butoxide/diisopropylamine/butyllithium (LIDA-KOR) at −78 °C to generate the benzylic anion. The deep red color of the reacting medium demonstrated the formation, at least to some extent, of the metalated intermediate, which underwent an unexpected smooth aza-[2,3]-Wittig rearrangement below −40 °C, yielding homoallylic amine **2** (Scheme 2) together with unreacted starting material.

Scheme 2. LIDA-KOR Promotes the Aza-[2,3]-Wittig Rearrangement of 1



Particularly striking here is the total absence of [1,2]-rearrangement and the high level of stereocontrol in the produced alkene because only the (*E*) isomer is detectable. Furthermore, this homoallylic amine was produced with some level of chirality transfer as testified by the positive value of its optical rotatory power, suggesting the absence of competitive metalation at the chiral center that would lead to racemization. Encouraged by this result, we began to optimize this reaction by varying some parameters, including the amount of base, its nature, and the temperature. Some key results are reported in Table 1.

These results highlight the extreme sensitivity of this reaction toward the experimental conditions. The amounts of base, together with a precise control of the temperature, are key parameters for the success of this reaction. The best conditions involved a molar ratio of tBuOK/iPr$_2$NH/BuLi of 4/4/6 with respect to the starting amine and low temperature (−78 °C),

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J. Org. Chem. XXXX, XXX, XXX−XXX

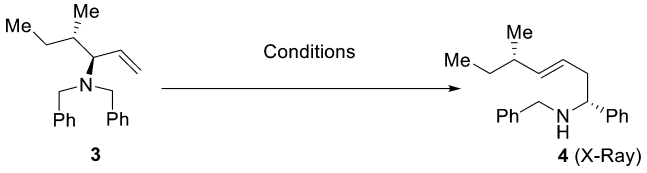
Table 1. Optimization of the Aza-[2,3]-Wittig Reaction with 1

entry	tBuOK/iPr_2NH/BuLi	conditions	conversion[a]	yield[b]
1	2/2/3	−78 to −40 °C, 3 h	40	34 (52)
2	2/2/3	−78 °C, 3 h	43	26
3	2/2/3	−78 to −10 °C, 2 h	>90	24
4	2/2/3	0 °C, 5 m	0	
5	4/0/4	−78 °C, 3 h	35	16 (45)
6	4/4/6	−78 °C, 3 h	100	85
7	4/4/6	−78 °C, 2 h	40	32
8	4/4/6	−40 °C, 3 h	100	20
9	4/4/6	0 °C, 5 m	0	
10	4/4/6	−78 °C, 6 h	90	36

[a]Determined by NMR on the crude reaction mixture. [b]Yields in brackets refer to recovered starting material. All reactions were run on 0.4−0.6 mmol scale except entries 7 and 10 (3.3 mmol scale).

which allowed total conversion and high yield (85%, entry 6), but scale-up of this reaction (entries 7, 10) led to a severe erosion of the yield. The use of other bases, such as *s*-BuLi/TMEDA, or additives (HMPA) did not lead to the formation of any product. It is noteworthy that there was no detectable incorporation of deuterium at the benzylic carbon in either starting material or rearranged product when the reaction was quenched with methanol-d_4, although this quenching led to an immediate fading of the deep-red color. This suggests that the concentration of the intermediate benzylic anion is very low in the reaction medium, and that the deprotonation step is probably rate-determining. Gratifyingly, the optical rotatory power of different samples of **2** displayed a constant value of +40 (*c* 1, DCM) ± 2. To estimate more precisely the degree of chirality transfer in this reaction, it was performed starting with the (L)-isoleucine-derived allylic amine **3**. Though at first glance the structural change between **1** and **3** seems only minor, this compound failed to produce rearranged **4** using the optimized conditions for **1** and required a higher molar ratio of base to achieve a reasonable yield, thus reflecting again the sensitivity of this reaction (Table 2). To our delight, compound **4** was

Table 2. Optimization of the Aza-[2,3]-Wittig Reaction with 3



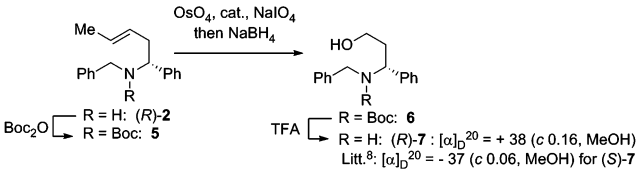
3 **4** (X-Ray)

entry	tBuOK/iPr_2NH/BuLi	conditions	yield
1	4/4/6	−78 °C, 3 h	no conversion
2	4/4/6	−50 °C, 2 h	25
3	6/6/9	−60 °C, 15 h	34
4	6/6/9	−78 °C, 1 h; then −65 °C, 6.5 h	61

produced as a single detectable isomer by ^{1}H NMR examination of the crude reaction mixture, and its structure was confirmed by X-ray diffraction analysis (see the Supporting Information (SI))[7] with the (*R*) configuration at the newly produced stereocenter and a high transfer of chirality.

In order to determine the absolute configuration of compound **2**, it was transformed into the known[8] amino alcohol **7** through the sequence depicted in Scheme 3, which confirmed the (*R*) configuration in **7** and a high level of enantiomeric purity (Scheme 3).

Scheme 3. (*R*) Configuration in 2 Determined by Chemical Correlation with 7



We next briefly evaluated the scope of this reaction starting with allylic amines **12**−**14** and **16** (Scheme 4) following the optimized conditions for the production of compound **2** (Table 1, entry 6). However, it was again found to be extremely substrate dependent, and none of these substrates rearranged in the same way as **2** except for **14**, which yielded 25% of rearranged **15** together with 25% of isolated starting material. Interestingly, when proline-derived **16** was engaged in this reaction, pure 2,3-*trans*-piperidine **17**[9] was isolated, albeit in low yield (13%), which arises from a diastereoselective [1,2] rearrangement. Clearly, this reaction proceeds only when strict parameters are respected, and compounds **12** and **13**, selected for a hypothetical beneficial Thorpe−Ingold effect, remained essentially unchanged.

It is well established that transition states for [2,3]-Wittig sigmatropic rearrangements pass via an envelope-form 5-membered ring[10] and proceed predominantly with inversion of the configuration at the anionic center.[2c] Assuming that this reaction proceeds through a similar cyclic transition state, and allowing for both invertomers at the nitrogen atom, then eight possibilities can be considered, as depicted in Figure 1. From the experimental results, regarding the stereochemistry of the produced alkene as well as the sense of asymmetric induction, this reaction should then go through transition states **D** and **D′**. In these states, the benzyl substituent at the nitrogen atom can be either *endo* (**D**), or *exo* (**D′**) to the envelope, and it is not possible to choose between them from the experimental results. Nonetheless, the sp^3 hybridization of the nitrogen atom is surely a crucial parameter, allowing for selection between all eight possible transition states. Anderson[5c] reported that when similar substrates with an *N*-Boc group instead of an *N*-Bn group react, then the reaction proceeds via all four possible transition states (now the nitrogen atom is sp^2), leading to poor alkene *Z*/*E* stereoselectivity and low chirality transfer. Between **D** and **D′**, the position of the benzyl group should at first sight favor **D**, thus avoiding a *gauche* interaction with the adjacent phenyl group, and the ultimate selection, if any, between **D** and **D′** could be guided by computational chemistry. However, many unknown parameters, such as the real nature of the metal cation (Li^+ or K^+) and its degree of solvation, for the moment preclude any reasonable attempt at calculation. One point seems to be established however: the nature of the "super-base" popularized by Schlosser[11] and used herein seems to be the key point for the success of this reaction.

In conclusion, we have demonstrated that aza-[2,3]-Wittig rearrangements can proceed in the acyclic series, starting with "unactivated" tertiary amines when deprotonated with a superbase. In addition, we have demonstrated that this reaction allows for a high 1,3 chirality transfer. Though its scope seems

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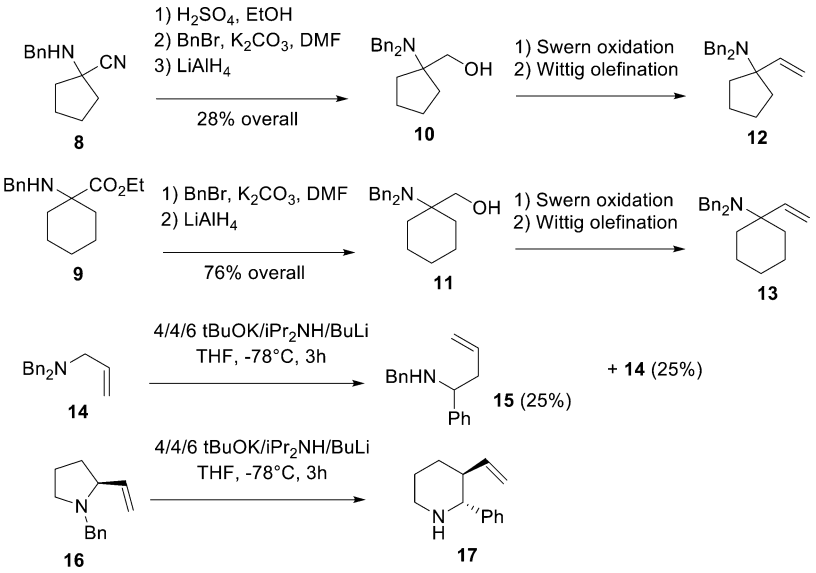
Scheme 4. Synthesis of Allylic Amines 12 and 13 and Attempted Aza-[2,3]-Wittig Reaction with 14 and 16



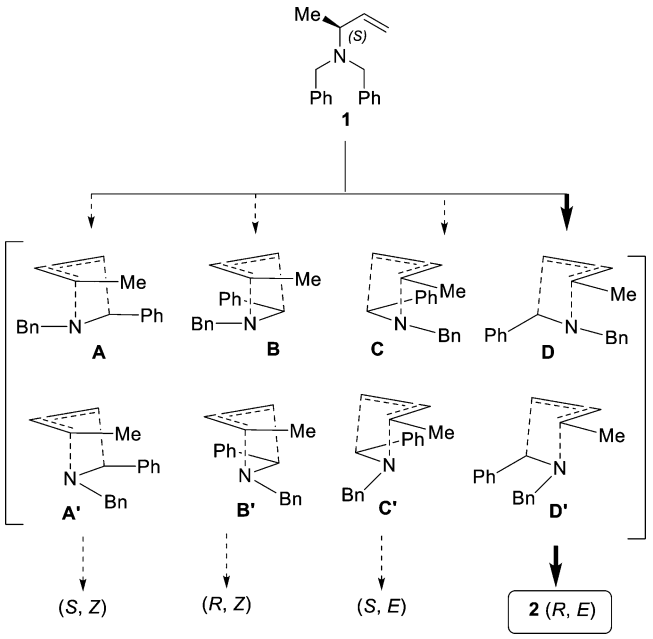


Figure 1. Proposed structure of transition states for aza-[2,3]-Wittig rearrangement.

narrow at present, its feasibility and efficiency in terms of stereocontrol has been established.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 and 75 or 50 MHz, respectively. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are reported in hertz and and rounded 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 the internal standard when assigning NMR 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). All reactions were carried out under argon. Column chromatography was performed on silica gel (230−400 mesh) with use of various mixtures of Et_2O, AcOEt, pentane, and cyclohexane (CyH). TLCs was run on Merck Kieselgel 60 F254 plates. Melting points are uncorrected. THF was distilled under argon from sodium using benzophenone as the indicator. Dichloromethane was distilled from calcium hydride. Isomeric ratios were determined by NMR analysis of crude reaction mixtures before purification. Compounds **1**,[12] **14**,[13] and **16**[14] were prepared following reported procedures.

General Procedure for the Synthesis of the Starting Allyl Amines 3, 12, and 13 from the Corresponding Alcohols through Swern Oxidation/Wittig Olefination. A solution of DMSO (2 equiv) in dichloromethane (1 mL/mmol) at −78 °C was treated with oxalyl chloride (1.5 equiv). After the solution was stirred for 15 min, a solution of the requisite alcohol (1.0 equiv) in dichloromethane (1.5 mL/mmol) was added. This reaction mixture was stirred at −78 °C for 0.5 h before adding triethylamine (4 equiv) and subsequent being warmed to 25 °C. Brine was added to the reaction mixture, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the corresponding aldehyde; the crude product of which was used for the next step. To a suspension of phosphonium ylide in THF (3.5 mL/mmol), prepared by the reaction of methyltriphenylphosphonium bromide (1.5 equiv) with BuLi (1.6 M in THF, 1.5 equiv) at 0 °C, was added a solution of the required aldehyde (1 equiv) in THF (1 mL/mmol). The reaction mixture was stirred at 0 °C for 0.5 and 1 h at 25 °C before adding water. The aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the corresponding allylic amine, which was purified by flash chromatography.

(1*R*,2*S*)-Dibenzyl-(2-methyl-1-vinyl-butyl)-amine 3 (from (*S*)-*N*,*N*-Dibenzyl Isoleucinol[15]). Overall yield: 42%, as a colorless oil, $[\alpha]_D^{20}$ +23 (c 1.01, $CHCl_3$). R_f = 0.9 (pentane/EtOAc: 90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.22 (m, 10H, 2Ph), 5.76−5.64 (m, 1H, NC*H*CH_2), 5.37 (dd, J = 10 Hz and J = 2 Hz, 1H, NCHC*H*H), 5.00 (dd, J = 17 Hz and J = 2 Hz, 1H, NCHCH*H*), 3.87 (d, AB syst., J = 11 Hz, 1H, NC*H*HPh), 3.30 (d, AB syst., J = 11 Hz, 1H, NCH*H*Ph), 2.63−2.56 (m, 1H, NCHα), 2.15−2.00 (m, 1H, CH_3C*H*H), 1.72−1.65 (m, 1H, CH_3C*H*), 1.15−1.06 (m, 1H, CH_3CH*H*), 0.81 (t, J = 7 Hz, 3H, CH_3), 0.74 (d, J = 7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5 (Cq Ar), 135.2 (CH), 128.9, 128.1, 126.6 (CHAr), 118.8 (CH_2), 66.6 (CH), 53.7 (CH_2), 35.0 (CH), 25.4 (CH_2), 16.7, 10.9 (CH_3). IR ν_{max}: 3063, 3026, 2961, 2928, 2873, 2802, 1603, 1494, 1453, 1372, 1236, 1068, 962, 741 cm^{-1}. HRMS (TOF MSES positive mode) m/z: calcd for $C_{21}H_{28}N$, 294.2222; found, 294.2219.

Dibenzyl-(1-vinyl-cyclopentyl)-amine 12. Overall yield: 53%, as a colorless oil. R_f = 0.3 (pentane/EtOAc: 99/1). ^{1}H NMR (300 MHz,

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J. Org. Chem. XXXX, XXX, XXX−XXX

$CDCl_3$): δ 7.30−7.11 (m, 10H, 2Ph), 6.13−6.04 (m, 1H, C*H*═CH_2), 5.34 (dd, *J* = 11 Hz and *J* = 1 Hz, 1H, CH═C *H*H), 5.15 (dd, *J* = 17 Hz and *J* = 1 Hz, 1H, CH═CH*H*), 3.73 (s, 4H, NCH_2Ph), 1.78−1.50 (m, 8H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1 (Cq Ar), 140.4 (CH), 128.5, 127.8, 126.2 (CHAr), 114.3 (CH_2), 72.0 (Cq), 56.0, 36.3, 22.8 (CH_2). IR ν_{max}: 3061, 3025, 2956, 2872, 1602, 1493, 1452, 1409, 1372, 1243, 1118, 1027, 914, 739, 695 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{21}H_{26}N$, 292.2065; found, 292.2062.

Dibenzyl-(1-vinyl-cyclohexyl)-amine 13. Overall yield: 69%, as a colorless solid; mp 28 °C. R_f = 0.7 (pentane/EtOAc: 90/10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.10 (m, 10H, 2Ph), 5.90−5.80 (m, 1H, C*H*═CH_2), 5.38 (dd, *J* = 12 Hz and *J* = 1 Hz, 1H, CH═C*H*H), 5.20 (dd, *J* = 18 Hz and *J* = 1 Hz, 1H, CH═CH*H*), 3.75 (s, 4H, NCH_2Ph), 1.83−1.80 (m, 2H, CH_2), 1.86−1.52 (m, 6H, CH_2), 1.39−1.24 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5 (CH), 141.0 (Cq Ar), 128.4, 127.7, 126.0 (CHAr), 115.4 (CH_2), 61.9 (Cq), 53.6, 34.4, 26.1, 22.7 (CH_2). IR ν_{max}: 3083, 3061, 3025, 2932, 2853, 1601, 1493, 1451, 1409, 1120, 1069, 916, 739, 691 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{22}H_{28}N$, 306.2222; found, 306.2217.

(1*R*)-Benzyl-(1-phenyl-pent-3-enyl)-amine 2 (Following the Conditions of Table 1, entry 6). To a solution of sublimed *t*-BuOK (179 mg, 1.6 mmol) and diisopropylamine (0.22 mL, 1.6 mmol) in dry THF (5 mL) at −78 °C was added butyllithium (1.4 M solution in hexanes, 1.7 mL, 2.4 mmol) dropwise. The reaction mixture was stirred for 0.5 h at −78 °C before adding a solution of allylamine **1** (100 mg, 0.4 mmol) in THF (3 mL) dropwise. After the solution was stirred at −78 °C for 3 h (dark red solution), the reaction was quenched with methanol-d_4 (0.5 mL) and allowed to reach rt. Brine was added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by using flash chromatography (pentane/ethyl acetate 95/5 + 1% NEt_3) gave (*R*)-**2** as a colorless oil (85 mg, 0.34 mmol, 85%). R_f = 0.24 (pentane/EtOAc: 95/5). $[\alpha]_D^{20}$ +42 (*c* 1.9, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.24 (m, 10H, 2Ph), 5.59−5.48 (m, 1H, CH═C*H*-CH_3), 5.41−5.31 (m, 1H, CH_2−C*H*═CH), 3.73−3.53 (m, 3H, NCHPh, NCH_2Ph), 2.39−2.34 (m, 2H, CH_2-CH═CH), 1.67 (d, *J* = 6.3 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1, 140.7 (Cq Ar), 128.3, 128.3, 128.1, 127.9, 127.3, 126.9, 126.8 (CH Ar, CH═), 62.1 (CH), 51.5, 41.9 (CH_2), 17.9 (CH_3). IR ν_{max}: 3061, 3024, 2914, 2840, 2797, 1601, 1493, 1452, 1114, 1027, 967, 731, 696, 618 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{18}H_{22}N$, 252.1752; found, 252.1752.

(1*R*,5*S*)-Benzyl-(5-methyl-1-phenyl-hept-3-enyl)-amine 4. Following the procedure reported above for **2** but with a 6/6/9 tBuOK/iPr_2NH/BuLi molar ratio with respect to starting **3** (0.4 mmol) and a reaction time of 1 h at −78 °C, and 6.5 h at −65 °C, the title compound was obtained as an oil that crystallized upon standing (72 mg, 61%). Mp 35 °C. R_f = 0.2 (pentane/EtOAc: 90/10). $[\alpha]_D^{20}$ +54 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.24 (m, 10H, 2Ph), 5.38−5.20 (m, 2H, C*H*═C*H trans*), 3.72−3.63 (m, 2H, NCHα, NC*H*HPh), 3.52 (d, AB syst., *J* = 13 Hz, 1H, NCH*HPh*), 2.39−2.35 (m, 2H, NCHαCH_2), 2.01−1.92 (m, 1H, C*H*CH_3), 1.33−1.17 (m, 2H, CH_3CH_2), 0.93 (d, 3H, *J* = 7 Hz, 3H, CH_3), 0.81 (t, *J* = 7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.9 (CH), 128.7, 128.3, 128.2, 127.4, 126.9, 126.8 (CHAr), 124.9, 62.0 (CH), 51.4, 42.0 (CH_2), 38.5 (CH), 29.7 (CH_2), 20.3, 11.9 (CH_3). IR ν_{max}: 3026, 2966, 2950, 2922, 2896, 2866, 1492, 1452, 1437, 1372, 1104, 1070, 962, 752, 729 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{21}H_{28}N$, 294.2222; found, 294.2210. Data have been deposited at the Cambridge Crystallographic Data Centre and have been allocated the deposition number CCDC 1052073.

Procedure for the Chemical Correlation of Homoallylamine 2 to (*R*)-7. *(1R)-Benzyl-(1-phenyl-pent-3-enyl)-carbamic Acid tert-Butyl Ester **5**.* Compound **2** (200 mg, 0.8 mmol) was dissolved in MeCN (5 mL), and Boc_2O (347 mg, 1.6 mmol) was added. The mixture was stirred at rt for 3 days, and then concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate: 99/1) gave **5** as a colorless oil (248 mg, 0.71 mmol, 88%). R_f = 0.52 (pentane/EtOAc: 95/5). $[\alpha]_D^{20}$ +55 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.08 (m, 10H, ArH), 5.37 (b, 3H, NCHPh, *CH*═*CH*), 4.32 (b, 1H, NCH_2Ph), 4.12 (d, *J* = 15.4 Hz, 1H, NCH_2Ph), 2.60 (bs, 2H, CH_2-CH═CH) 1.61 (d, *J* = 4.9 Hz, 3H, CH_3), 1.42 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2 (C═O), 140.4, 139.7 (Cq Ar), 128.3, 128.1, 127.9, 127.6, 127.3, 126.5 (CH Ar, CH═), 79.8 ((CH_3)$_3$C), 58.9 (CH), 47.6, 34.8 (CH_2), 28.3 ((CH_3)$_3$C), 18.0 (CH_3). IR ν_{max}: 3028, 2973, 2930, 2852, 1685, 1495, 1451, 1401, 1364, 1247, 1159, 1073, 963, 868, 735, 696, 610 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{23}H_{29}NO_2Na$, 374.2094; found, 374.2094.

*(1R)-Benzyl-(3-hydroxy-1-phenyl-propyl)-carbamic Acid tert-Butyl Ester **6**.* Compound **5** (70 mg, 0.2 mmol) was dissolved in 3/1 dioxane/H_2O (2 mL). 2,6-Lutidine (0.05 mL, 0.4 mmol), OsO_4 (0.157 M in H_2O, 0.025 mL, 0.004 mmol), and $NaIO_4$ (171 mg, 0.8 mmol) were added to the solution. The mixture was stirred at rt for 45 min and then diluted with CH_2Cl_2 and H_2O. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was dissolved in MeOH (2 mL), and $NaBH_4$ (19 mg, 0.5 mmol) was added. The mixture was stirred at rt for 15 min and then diluted with CH_2Cl_2. The solution was washed with 0.25 N aqueous HCl solution and then with a saturated aqueous NaCl solution. The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate: 75/25) gave **6** as a colorless oil (40 mg, 0.12 mmol, 58%). R_f = 0.22 (pentane/EtOAc: 75/25). $[\alpha]_D^{20}$ +61 (*c* 1.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25−6.92 (m, 10H, ArH), 5.57 (b, 1H, NC*H*Ph), 4.23 (d, *J* = 14.6 Hz, 1H, NCH_2Ph), 3.79 (d, *J* = 14.6 Hz, 1H, NCH_2Ph), 3.50−3.42 (m, 2H, CH_2OH), 2.85 (bs, 1H, OH), 2.05−1.93 (m, 1H, CHCH_2), 1.86−1.79 (m, 1H, CHCH_2), 1.37 (s, 9H, 3CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4 (Cq Ar), 128.7, 128.6, 128.5, 128.1, 127.7, 127.4, 126.8 (CH Ar), 80.8 ((CH_3)$_3$*C*), 58.8 (CH_2OH), 54.7 (CH), 46.9 (NCH_2), 33.5 (CH_2), 28.3 (CH_3). IR ν_{max}: 3438, 3060, 3030, 2974, 2925, 2876, 1683, 1661, 1495, 1452, 1404, 1365, 1248, 1157, 1121, 1028, 871, 735, 697 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{21}H_{27}NO_3Na$, 364.1889; found, 364.1890.

*(1R)-3-Benzylamino-3-phenyl-propan-1-ol (R)-**7**.* Compound **6** (35 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (2.7 mL), and the solution was cooled in an ice bath. Trifluoroacetic acid (0.3 mL) was added, and the mixture was stirred at 0 °C for 30 min and then at rt for 2 h. The mixture was diluted with toluene and concentrated under reduced pressure. The residue was taken up in EtOAc and washed with a saturated aqueous $NaHCO_3$ solution. The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification via flash chromatography (CH_2Cl_2/MeOH 95/5) gave (*R*)-**7** as a colorless oil (21 mg, 0.08 mmol, 87%). R_f = 0.33 (CH_2Cl_2/MeOH: 95/5). $[\alpha]_D^{20}$ +38 (*c* 0.16 MeOH) (lit.[8] $[\alpha]_D^{20}$ −37 (*c* 0.06 MeOH) for (*S*)-**7**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.16 (m, 10H, ArH), 3.81 (dd, *J* = 3.2, 9.6 Hz, 1H, NC*H*Ph), 3.74−3.72 (m, 2H, CH_2OH), 3.59 (d, *J* = 12.8 Hz, 1H, NCH_2Ph), 3.52 (d, *J* = 12.8 Hz, 1H, NCH_2Ph), 3.27 (bs, 2H, OH, NH), 1.98−1.86 (m, 1H, CHCH_2) 1.78−1.72 (m, 1H, CHCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 134.1 (Cq Ar), 129.3, 129.0, 128.9, 128.7, 128.5, 127.4 (CH Ar), 62.9 (CH), 61.1 (CH_2OH), 49.9 (NCH_2), 36.9 (CH_2). IR ν_{max}: 3287, 3064, 3026, 2923, 2848, 1674, 1602, 1493, 1452, 1360, 1200, 1063, 1027, 743, 696, 617 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{16}H_{20}NO$, 242.1545; found, 242.1550.

Procedures for the Preparation of Compounds 10 and 11. *(1-Dibenzylamino-cyclopentyl)methanol **10**.* A solution of compound **8**[16] (2 g, 10 mmol) in a mixture of ethanol (46 mL) and sulfuric acid (23 mL) was refluxed overnight. After cooling to 0 °C, the reaction mixture was poured very slowly onto an ice cold saturated hydrogen carbonate aqueous solution with stirring. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/ethyl acetate: 90/10) gave the corresponding ethyl ester as a colorless oil (1.023 g, 4.14 mmol, 41%). A suspension of potassium carbonate (2.09 g, 15.15 mmol) in DMF (10 mL) containing the above ester (0.75 g, 10 mmol)

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J. Org. Chem. XXXX, XXX, XXX−XXX

and benzyl bromide (1.1 mL, 9.11 mmol) was heated at 90 °C for 48 h. After cooling to ambient temperature, DMF was evaporated, and the residue was taken up in diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether: 90/10) gave the *N*,*N*-dibenzyl derivative as a colorless oil (0.804 g, 2.38 mmol, 79%). To a suspension of $LiAlH_4$ (68 mg, 1.8 mmol) in THF (2 mL) was added a solution of the above compound (0.6 g, 1.8 mmol) in THF (1 mL). The suspension was refluxed for 2 h. To the suspension cooled to 0 °C were added water (68 μL), 2 M sodium hydroxide aqueous solution (68 μL), and more water (204 μL). The solid was filtered and washed with diethyl ether. The filtrate was concentrated under reduced pressure. Purification by flash chromatography (pentane/diethyl ether: 80/20) gave **10** as a colorless oil (0.460 g, 1.6 mmol, 87%). Overall yield: 28%. R_f = 0.8 (pentane/Et_2O: 75/25). ^1H NMR (300 MHz, $CDCl_3$): δ 7.28−7.15 (m, 10H, 2Ph), 3.80 (s, 4H, NCH_2Ph), 3.55 (s, 2H, OCH_2), 2.95 (s, 1H, OH), 1.94−1.80 (m, 2H, CH_2), 1.78−1.68 (m, 2H, CH_2), 1.66−1.50 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 141.3 (Cq Ar), 128.3, 128.0, 126.8 (CHAr), 72.4 (Cq), 65.6, 54.5, 31.7, 24.3 (CH_2). IR ν_{max}: 3411, 3061, 3025, 2948, 2868, 1601, 1492, 1452, 1330, 1048, 1027, 941, 741, 695 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{20}H_{26}NO$, 296.2014; found, 296.2010.

(1-Dibenzylamino-cyclohexyl)-methanol ***11***. A suspension of potassium carbonate (0.69 g, 5 mmol) in acetonitrile (10 mL) containing compound **9**[17] (0.52 g, 2 mmol), potassium iodide (33 mg, 0.2 mmol), and benzyl bromide (0.47 mL, 4 mmol) was heated at 80 °C for 24 h. After cooling to ambient temperature, acetonitrile was evaporated, and the residue was taken up in diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/ethyl acetate: 95/5) gave an *N*,*N*-dibenzyl derivative as a colorless oil (0.611 g, 1.74 mmol, 87%). To a suspension of $LiAlH_4$ (63 mg, 1.65 mmol) in THF (3 mL) was added a solution of the above compound (0.58 g, 1.65 mmol) in THF (3 mL). The suspension was refluxed overnight. To the suspension cooled to 0 °C were added water (63 μL), 2 M sodium hydroxide aqueous solution (63 μL), and more water (189 μL). The solid was filtered and washed with diethyl ether. The filtrate was concentrated under reduced pressure. Purification by flash chromatography (pentane/ethyl acetate: 75/25) gave **11** as a colorless solid (0.448 g, 1.45 mmol, 88%). Overall yield 76%; mp 104 °C. R_f = 0.5 (pentane/EtOAc: 75/25). ^1H NMR (300 MHz, $CDCl_3$): δ 7.27−7.16 (m, 10H, 2Ph), 3.79 (s, 4H, NCH_2Ph), 3.72 (s, 2H, OCH_2), 3.42 (s, 1H, OH), 1.67−1.48 (m, 7H, CH_2), 1.40−1.10 (m, 3H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5 (Cq Ar), 128.3, 128.2, 126.6 (CHAr), 62.5 (Cq), 61.0, 52.1, 29.6, 25.8, 22.7 (CH_2). IR ν_{max}: 3350, 3025, 2945, 2916, 2861, 1491, 1449, 1412, 1050, 1028, 955, 744, 708, 698 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{21}H_{28}NO$, 310.2171; found: 310.2173.

Benzyl-(1-phenyl-but-3-enyl)-amine ***15***. Following the procedure reported for the preparation of **2**, and starting with allyl-dibenzyl-amine **14**[13] (119 mg, 0.5 mmol), we obtained title compound **15** as an oil (30 mg, 25%) that matched ^1H and ^{13}C NMR literature data.[18] Thirty milligrams of recovered **14** were also isolated upon purification by flash chromatography.

trans-2-Phenyl-3-vinyl-piperidine ***17***. Following the procedure reported for the preparation of **2**, and starting with **16**[14] (100 mg, 0.53 mmol), we obtained title compound **17** as an oil (13 mg, 13%). R_f = 0.3 (CH_2Cl_2/MeOH: 80/20). ^1H NMR (300 MHz, $CDCl_3$): δ 7.34−7.22 (m, 5H, Ph), 5.55−5.43 (m, 1H, C*H*═CH_2), 4.84−4.78 (m, 2H, CH═CH_2), 3.32 (d, *J* = 10 Hz, 1H, 2-H), 3.17 (d, *J* = 11 Hz, 1H, 6-H), 2.81−2.72 (m, 1H, 6′-H), 2.50−2.28 (m, 2H, NH and 3-H), 1.95 (d, *J* = 13 Hz, 1H, 4-H), (1.79−1.69 (m, 2H, 5-H), 1.49−1.37 (m, 1H, 4′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0 (Cq Ar), 140.3 (CH), 128.2, 128.0, 127.4 (CHAr), 114.6 (CH_2), 67.5 (CH), 47.4 (CH_2), 46.9 (CH), 31.2, 25.7 (CH_2). IR ν_{max}: 3063, 3027, 2927, 2850, 2782, 1639, 1491, 1453, 1437, 1319, 1125, 991, 911, 751, 698 cm^{-1}. HRMS (TOF MSES positive mode) *m*/*z*: calcd for $C_{13}H_{18}N$, 188.1439; found, 188.1440.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds and X-ray data for **4**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01230.

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Notes

The authors declare no competing financial interest.

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J. Org. Chem. XXXX, XXX, XXX−XXX