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New Synthesis of Propargylic Amines from 2-(Bromomethyl)aziridines. Intermediacy of 3-Bromoazetidinium Salts

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A new, efficient, and straightforward synthesis provides propargylamines in high overall yields (64−77%) by transformation of 1-(arylmethyl)-2-(bromomethyl)aziridines into *N*,*N*-di(arylmethyl)-*N*-(2-propynyl)amines via *N*-(2,3-dibromopropyl)amines and *N*-(2-bromo-2-propenyl)amines. The conversion of *N*-(2,3-dibromopropyl)amines into *N*-(2-bromo-2-propenyl)amines is based on a novel analogue of the Hofmann elimination. A Yamaguchi−Hirao alkylation, a Sonogashira coupling, or a hydroarylation reaction further functionalized these propargylamines toward potentially interesting compounds for medicinal and agrochemical use.

Introduction

Propargylamines are very much in demand in medicinal chemistry, due to the pronounced physiological activities of these compounds and their derivatives.[1−27] A very generally occurring mode of action of propargylamines concerns the inhibition of the enzyme monoamine oxidase (MAO, EC 1.4.3.4),[1−3,27] which makes them potential drugs for treatment of neurotic, psychiatric, and other disorders, such as depression, panic disorder, social phobia,[5,6,27] Parkinson's disease,[7,27] and Alzheimer's disease.[8,9] The biochemical role of the enzyme MAO concerns the oxidation of many monoamines, including important neurotransmitter amines.[27] Other biological activities of propargylamines are for example related to treatment of diabetics,[4] blood lipid lowering activity,[22] and use as fibrin-stabilizing factor inhibitors.[26] In the literature, a variety of synthetic methods toward propargylamines is found. A very common method consists of the alkylation of primary or secundary amines with propargyl halides,[28−35] although the latter compounds are rather

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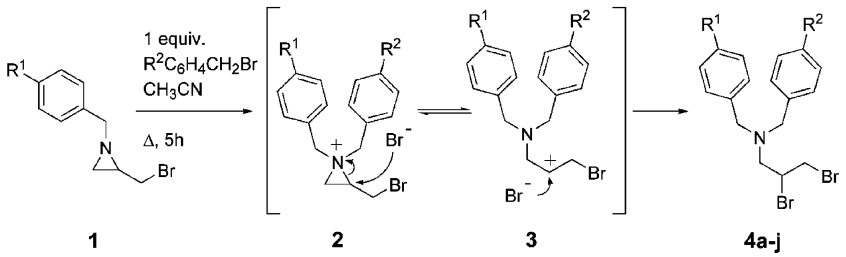
SCHEME 1



expensive. The Mannich reaction, in which an acetylene, formaldehyde, and a primary or secundary amine are reacted, is also a well-established and general procedure for the preparation of propargylamines.[36] Furthermore, some methods in which 1-(dialkylaminomethyl)benzotriazoles,[37,38] arylimines,[39] propargyl phosphates[40] or 1,1-dibromo-1-alkenes[41] are used for the synthesis of propargylamines are known. Except for the last example, all these procedures and methods are based on the use of a commercially available alkyne moiety.

In the present report a new and efficient synthesis of *N*,*N*-di(arylmethyl)propargylamines, based on three innovating steps and starting from 1-(arylmethyl)-2-(bromomethyl)aziridines, is presented. The chemistry of 2-(bromomethyl)aziridines is for the major part yet unexplored. The possibility of ring-opening reactions at the aziridine moiety and substitution and elimination reactions due to the bromomethyl unit explains the great synthetic potential of 2-(bromomethyl)aziridines as building blocks in organic synthesis.

Results and Discussion

1-(Arylmethyl)-2-(bromomethyl)aziridines **1** were treated with 1 equiv of a benzyl bromide in acetonitrile under reflux for 5 h to afford *N*-(2,3-dibromopropyl)amines **4** in a quantitative way. A nucleophilic attack of bromide at the least hindered position of the intermediate aziridinium salt **2**, which could not be isolated, would have given rise to 2-(di(arylmethyl)amino)-1,3-dibromopropanes, but instead only 1-(di(arylmethyl)amino)-2,3-dibromopropanes **4** were formed. The synthesis of a large number of analogues in excellent yields, starting from different aryl-substituted aziridines **1**[42] and/or different benzyl bromides, illustrates the general character of this reaction (Scheme 1, Table 1). The high purity of these compounds allowed us to use them as such in the next step. To provide analytically pure samples for elemental analysis, compounds **4** were purified by means of column chromatography in 50−62% yield. These lower yields illustrate the reactive nature of these β,γ-dibromoamines **4**.

TABLE 1. Reaction of 1-(Arylmethyl)-2-(bromomethyl)aziridines 1 with Different Benzyl Bromides

entry	product	R^1	R^2	crude yield (%)[a]
1	**4a**	H	H	100
2	**4b**	Me	H	100
3	**4c**	MeO	H	100
4	**4d**	Br	H	100
5	**4e**	Me	Me	100
6	**4f**	MeO	Me	100
7	**4g**	Br	Me	100
8	**4g**	Me	Br	100
9	**4h**	MeO	Br	100
10	**4i**	Cl	H	100
11	**4j**	Br	Br	100

[a] Purity (NMR) >97%.

In addition, these results confirm the observation that 2-substituted aziridinium salts are preferably opened at the more hindered position, when bromide acts as a nucleophile. The reactivity of *N*-functionalized aziridines, with respect to alkyl halides, has been investigated in the past.[43−50] In most cases, the formation of an intermediate aziridinium salt is described. Generally, this electrophilic species is then further attacked by a nucleophilic counterion, resulting in an acyclic aminopropane derivative. As recently demonstrated, the regioselectivity of the ring opening of the aziridinium ion depends on the nucleophile: the opening of a 1,1-di(arylmethyl)-2-benzylaziridinium ion occurs at the less hindered position with cyanide, but at the more hindered position with chloride or bromide.[51−53] In a similar example in the literature, a 2-cyano-1,1-dimethylaziridinium salt was treated with LiCl. After reaction, 2-chloro-3-(dimethylamino)propanenitrile was isolated, indicating

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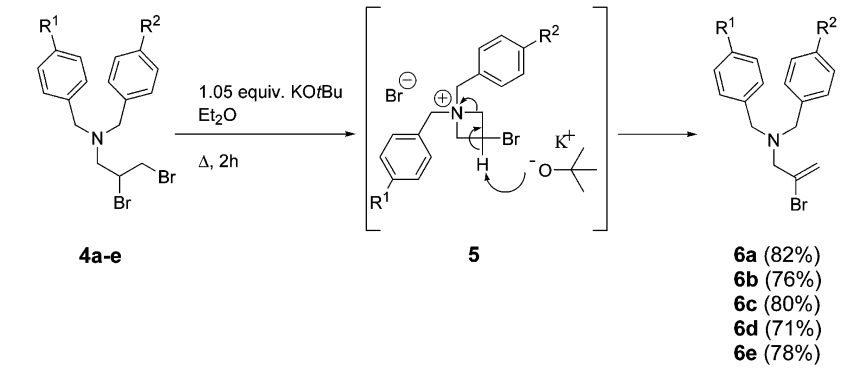
SCHEME 2



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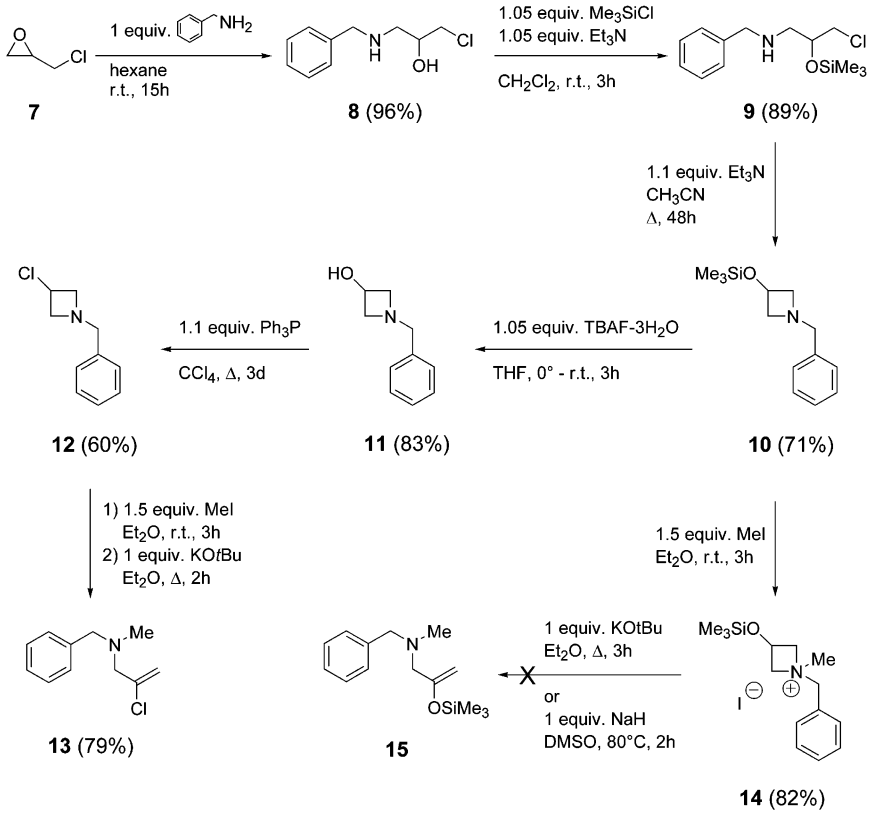

that the aziridinium salt opened up spontaneously to form a secondary carbenium ion, which was then trapped by chloride.[44]

The *N*,*N*-di(arylmethyl)-*N*-(2,3-dibromopropyl)amines **4**, prepared from 1-(arylmethyl)-2-(bromomethyl)aziridines **1**, were used for the synthesis of *N*,*N*-di(arylmethyl)-*N*-(2-bromo-2-propenyl)amines **6** in a straightforward reaction with KO*t*Bu in diethyl ether under reflux for 2 h. The underlying mechanism can be explained considering a neighboring group participation of the *N*,*N*-dibenzylamino function. KO*t*Bu is then responsible for the deprotonation of the intermediate 3-bromoazetidinium salt **5**, resulting in the desired vinyl bromides **6** (Scheme 2). This reaction can be listed as a variant of the well-known Hofmann elimination.

To support the suggested mechanism of this unusual transformation, a halo-analogue of the presumptive intermediate azetidinium salt **5**, i.e. 1-benzyl-3-chloroazetidine **12**, was synthesized via an alternative procedure (Scheme 3). Treatment of epichlorohydrine **7** with benzylamine in hexane resulted in amino alcohol **8**,[54] which was silylated by using trimethylsilyl chloride in CH_2Cl_2 to afford the silyl ether **9** in good yield. Ring closure of the protected alcohol **9** toward 3-(trimethylsilyloxy)azetidine **10** was performed with triethylamine in acetonitrile upon reflux for 48 h. The spectral data of 1-benzyl-3-(trimethylsilyloxy)azetidine **10** correspond well with those mentioned in the literature.[54] Subsequently, 3-hydroxyazetidine **11**, prepared from the silyl ether **10** by treatment with TBAF in THF, was transformed into the corresponding 3-chloroazetidine **12** upon reaction with triphenylphosphine in tetrachloromethane and reflux for 3 days.[55a] As mentioned in the literature, 1-benzyl-2-(chloromethyl)aziridine was formed as a side product in a ratio of 3/2 (major/minor).[55a] Finally, the 3-chloroazetidine **12** was precipitated as an azetidinium

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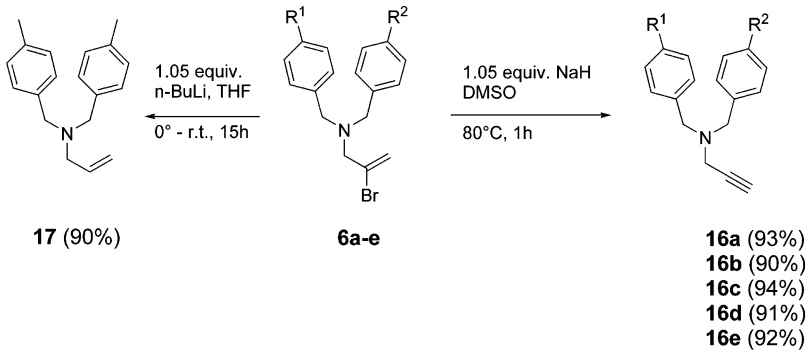
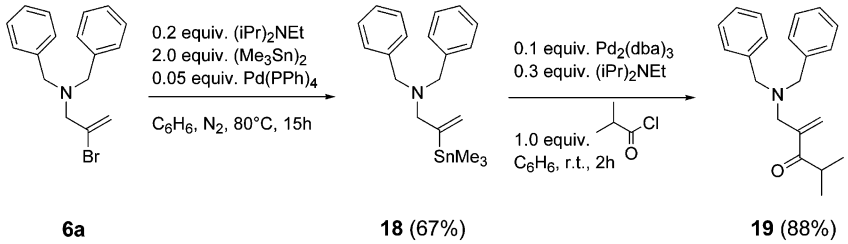
SCHEME 4



SCHEME 5



salt upon quaternization with iodomethane in diethyl ether (colorless precipitate) and this salt was immediately treated with 1 equiv of a base (KO*t*Bu) in ether furnishing the desired vinyl chloride **13** in 79% yield. When the trimethylsilyl ether **10** was alkylated with iodomethane, the corresponding azetidinium salt **14** was isolated as a colorless solid and subsequently treated with both KO*t*Bu in ether (reflux, 3 h) and sodium hydride in DMSO (80 °C, 2 h). However, in both cases only complex reaction mixtures were formed without any trace of the allylamine **15**. The structural identity of allylamine **13** was confirmed by comparison with spectral data found in the literature.[56] Consequently, the peculiar mechanism responsible for the dehydrohalogenation of *N*-(2,3-dibromopropyl)amines **4** in the synthesis of the vinyl bromides **6** can be explained considering the intermediacy of azetidinium salts **5**. This novel transformation, in which a 3-haloazetidine suffers ring opening to furnish a *N*-(2-halo-2-propenyl)amine, clearly extends the present knowledge of azetidine chemistry.

The synthesis of propargylamines **16** could be established in excellent yields (90−94%) by treatment of *N*,*N*-di(arylmethyl)-*N*-(2-bromo-2-propenyl)amines **6** with NaH in DMSO. The dimsyl anion, resulting from the reaction of NaH and dimethyl sulfoxide, appeared to be a suitable base for the deprotonation of *N*,*N*-di(arylmethyl)-*N*-(2-bromo-2-propenyl)amines **6** (Scheme 4). Also other bases were evaluated, but in those cases no alkynes were isolated. With $NaNH_2$ in NH_3/Et_2O (−78 °C for 3 h, or r.t. for 1 h, or Δ for 15 h), no reaction occurred, and the starting material was recovered. When *n*-BuLi (2.5 M in hexane) in THF at room temperature was used, debromination of **6e** instead of dehydrobromination occurred resulting in allylamine **17** in 90% yield (Scheme 4).[57]

Although the conversion of (2-bromo-2-propenyl)-amines into propargylamines had been described in the literature, only $NaNH_2$ in NH_3,[58−62] KO*t*Bu in THF,[63] PhLi in THF,[64] and NaOH[65] were evaluated as bases resulting in the desired propargylamines in moderate to good yields. The presented method with NaH in DMSO offers an easy and very efficient alternative for the dehydrobromination of (2-bromo-2-propenyl)amines into propargylamines in high yields.

Vinyl bromides are known to be good substrates for Stille coupling reactions.[66,67] The presence of an aminomethyl functionality in the vinyl bromides **6** allows a new approach toward α-(aminomethyl)-substituted α,*β*-unsaturated ketones, which have an interest as antimicrobial agents and for the treatment of pain, fever, and inflammation.[68,69] To reach this objective, *N*,*N*-dibenzyl-*N*-(2-bromo-2-propenyl)amine **6a** was transformed in the corresponding trimethylstannyl derivative **18** by reaction with bis(trimethyltin) in the presence of a catalytic amount of Hünig's base and tetrakis(triphenylphosphine)-palladium in benzene at 80 °C for 15 h.[66,67] This stannane **18** was then further reacted with 2-methylpropanoyl

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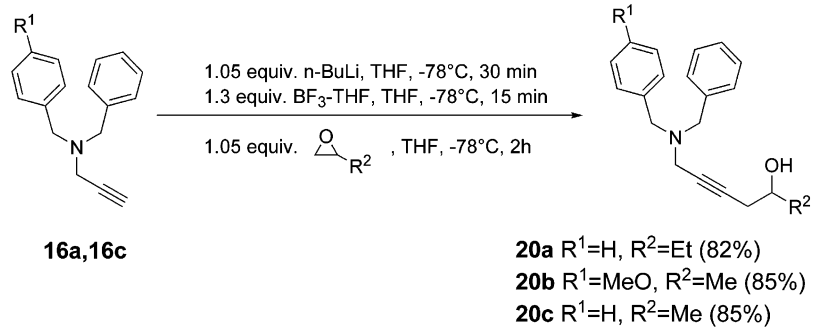
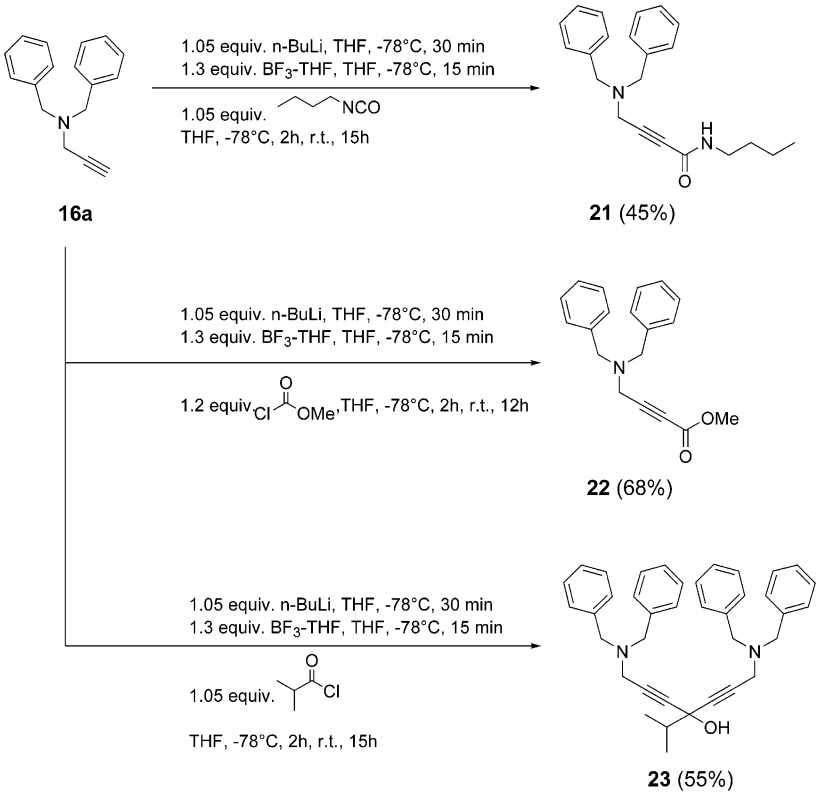
SCHEME 6



SCHEME 7



chloride in a palladium-based Stille coupling reaction with Hünig's base and tris(dibenzylideneacetone)dipalladium in benzene at room temperature for 2 h,[66,67] resulting in 2-[(dibenzylamino)methyl]-4-methyl-1-penten-3-one **19** in 88% yield (Scheme 5). This reaction proves that the conditions for a Stille coupling can be successfully applied for nitrogen-containing vinyl bromides, pointing to the conclusion that vinyl bromides **6** can be applied as useful synthetic intermediates in different synthetic pathways.

Since many functionalized propargylamines are known to possess various physiological activities,[1−27] derivatization of *N*,*N*-di(arylmethyl)-*N*-(2-propynyl)amines **16** was further investigated. To serve this purpose, the Yamaguchi−Hirao alkylation of lithio-acetylides by epoxides with 1.05 equiv of *n*-BuLi (2.5M in hexane) in the presence of 1.3 equiv of a BF_3·THF complex was evaluated.[70] The applicability of this method on the acetylides of propargylamines appeared to be very successful (Scheme 6) and offers a feasible alternative for the use of $NaNH_2$ in NH_3.[71] However, when 2-methylthiirane was used instead of an epoxide, no reaction occurred and the starting material was recovered, even after reflux for 15 h. Other types of electrophiles, such as carbonyl compounds, were also evaluated. The reaction of *N*,*N*-dibenzyl-*N*-(2-propynyl)amine **16a** with *n*-butylisocyanate, using Yamaguchi−Hirao conditions, i.e. *n*-BuLi and BF_3·THF, resulted in the corresponding amide **21** (Scheme 7). In the same way, γ-amino esters can be synthesized, using methyl chloroformate as the electrophile (Scheme 7). The resulting methyl 4-(dibenzylamino)-2-butynoate **22** is the precursor of the corresponding γ-amino acid. The use of β- and γ-amino acids in peptide chemistry has become an important field of investigation during the last decennium.[72] When an acid chloride was used, e.g. isobutyryl chloride, another type of compound could be

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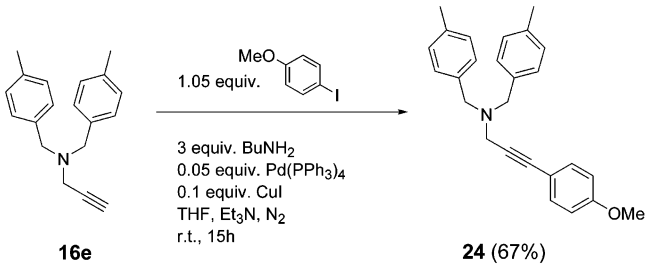
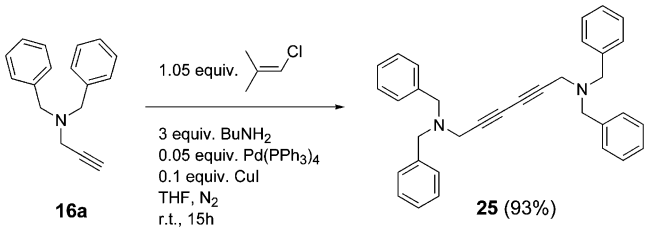
SCHEME 8



SCHEME 9

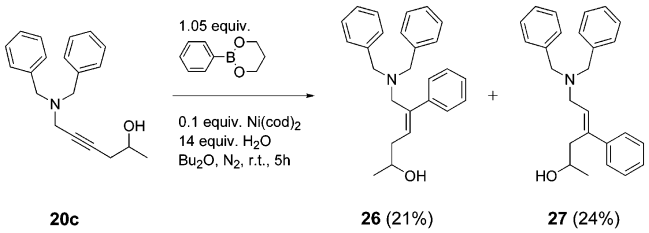


synthesized. The main compound in the reaction mixture appeared to be the tertiary alcohol **23** (Scheme 7). This can be rationalized considering a second nucleophilic addition of the lithiated alkyne across the carbonyl group.

A second type of derivatization of *N*,*N*-di(arylmethyl)-*N*-(2-propynyl)amines **16** concerned the Sonogashira coupling.[73,74] By means of a catalytic amount of $Pd(PPh_3)_4$ and CuI as cocatalyst, coupling of *N*,*N*-di((4-methylphenyl)methyl)-*N*-(2-propynyl)amine **16e** and 4-iodoanisole was realized in THF at room temperature for 15 h (Scheme 8). *N*-(3-Phenyl-2-propynyl)-*N*,*N*-dialkylamines are known to exhibit inhibition of MAO, which makes propargylamine **24** an interesting target with potential biological activity.[22,23] When the iodoarene was replaced by a vinyl chloride, based on a known coupling between an alkyne and a vinyl chloride,[74] the expected coupling reaction did not occur although similar conditions, i.e. a catalytic amount of $Pd(PPh_3)_4$ and CuI in THF, were applied. Instead, the diyne **25** was isolated in a high yield (Scheme 9). The formation of this diamine **25** under these conditions is justified by some literature references, in which for example the oxidative coupling of terminal alkynes in the presence of $Pd(PPh_3)_4$, CuI, and $BuNH_2$ in benzene is described.[75] Similar diyne compounds are used as pesticides to protect grain from various infections caused by for instance the rice weevil (*Sitophilus oryzae*) and the pulse beetle (*Callosobruchus chinensis*).[76]

Driven by the numerous biological activities of *N*,*N*-di(arylmethyl)allylamines, such as fungicidal,[77−79] antiviral, and antitumor activity,[80,81] attempts were made to hydrogenate the functionalized propargylamines **20**. Hydrogenation of the homopropargylic alcohol **20a** in pentane in the presence of a Lindlar catalyst (0.1 equiv or an excess)[82] under 5 bar of H_2 pressure and 0 °C for 20 min to 15 h was not successful, even when the catalyst was poisened with 0.05 equiv of quinoline, all resulting in recovery of the starting material. On the basis of a nickel-catalyzed hydroarylation of 4-octyne and diphenylethyne, described in the literature,[83] the reactivity of propargylamine **20c** and 2-phenyl-1,3,2-dioxaborinane was evaluated. With 10 mol % of bis(1,5-cyclooctadiene)-nickel, two isomeric allylamines **26** and **27** were isolated and separated by flash chromatography (Scheme 10).

SCHEME 10



Conclusions

A new and straightforward synthesis of *N*,*N*-di(arylmethyl)-*N*-(2-propynyl)amines, compounds with a broad applicability, was developed in high overall yields (64−77%), starting from 1-(arylmethyl)-2-(bromomethyl)aziridines. This method for the synthesis of propargylamines offers an excellent alternative for the double alkylation of propargylamine since the latter is extremely expensive. A novel and very interesting analogue of the Hofmann elimination, in which *N*-(2,3-dibromopropyl)amines are converted into *N*-(2-bromo-2-propenyl)amines via intermediate azetidinium salts, was described and a general method for the conversion of (2-bromo-2-propenyl)amines into propargylamines is disclosed. Extension of the Yamaguchi−Hirao alkylation and a known hydroarylation reaction to nitrogen-containing compounds was discussed. Furthermore, a new approach for the synthesis of α-((dibenzylamino)methyl)-α,β-unsaturated ketones, based on a Stille coupling, was presented.

Experimental Section

1. General Procedure for the Synthesis of *N*,*N*-Di(arylmethyl)-*N*-(2,3-dibromopropyl)amines 4. As an example, the synthesis of *N*-benzyl-*N*-(2,3-dibromopropyl)-*N*-((4-methylphenyl)methyl)amine **4b** is described. To a solution of 2-(bromomethyl)-1-((4-methylphenyl)methyl)aziridine[42] (3.60 g, 15 mmol) in acetonitrile (50 mL) was added benzyl bromide (2.56 g, 15 mmol). After the solution was heated 5 h under reflux, the solvent was removed in vacuo, resulting in *N*-benzyl-*N*-(2,3-dibromopropyl)-*N*-((4-methylphenyl)methyl)amine **4b** (6.15 g, 100%). *N*,*N*-Di(arylmethyl)-*N*-(2,3-dibromopropyl)-amines **4** were purified by means of column chromatography

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on silica gel (SiO_2) utilizing a mixture of hexane and ethyl acetate as an eluent.

***N,N*-Dibenzyl-*N*-(2,3-dibromopropyl)amine 4a:** Colorless oil, 51% yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.88 and 3.08 (2H, 2 × d × d, J = 13.9 Hz, J = 7.3, 6.6 Hz, N(*HCH*)-CHBr), 3.63 and 3.67 (4H, 2 × d, J = 13.9 Hz, 2 × N(HCH)C), 3.60−3.77 (2H, m, CH_2Br), 4.01 (1H, quint, J = 6.3 Hz, CHBr), 7.22−7.44 (10H, m, 2 × C_6H_5). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 35.7, 50.8, 59.1, 59.2, 127.2, 128.2, 128.9, 138.5. IR (NaCl, cm^{-1}): ν_{max} 3085, 3062, 3028, 2929, 2804, 1494, 1453, 748, 699. MS (70 eV): *m*/*z* (%) 395/7/9 (M^+, 7), 316/8 (9), 302/4 (8), 212 (18), 211 (54), 210 (100), 181 (25), 146 (12), 127 (11), 125 (25), 120 (12), 92 (23), 91 (58), 89 (14), 84 (11), 65 (20), 51 (13), 49 (11). Anal. Calcd for $C_{17}H_{19}Br_2N$: C 51.41; H 4.82; N 3.53. Found: C 51.62; H 4.90; N 3.40.

2. General Procedure for the Synthesis of *N,N*-Di(arylmethyl)-*N*-(2-bromo-2-propenyl)amines 6. As a representative example, the synthesis of *N*-(2-bromo-2-propenyl)-*N*,*N*-di((4-methylphenyl)methyl)amine **6e** is described. To a solution of *N*-(2,3-dibromopropyl)-*N*,*N*-di((4-methylphenyl)-methyl)amine **4e** (4.25 g, 10 mmol) in dry diethyl ether (50 mL) was added KO*t*Bu (1.12 g, 10 mmol). After the mixture was heated for 2 h under reflux, the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent yielded *N*-(2-bromo-2-propenyl)-*N*,*N*-di((4-methylphenyl)methyl)amine **6e** (2.67 g, 78%). *N*,*N*-Di(arylmethyl)-*N*-(2-bromo-2-propenyl)amines **6** were purified by distillation under reduced pressure.

***N,N*-Dibenzyl-*N*-(2-bromo-2-propenyl)amine 6a:** Colorless oil, 82% yield, bp 115 °C/0.02 mmHg. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.26 (2H, s), 3.62 (4H, s), 5.60 (1H, s(broad)), 5.96 (1H, d, J = 1.3 Hz), 7.21−7.43 (10H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 57.2, 61.3, 118.4, 126.9, 128.2, 128.6, 132.0, 138.7. IR (NaCl, cm^{-1}): ν_{max} 3085, 3062, 3028, 2924, 2800, 1629, 1494, 1454, 746, 698. MS (70 eV): *m*/*z* (%) 315/7 (M^+, 4), 210 (14), 91 (100), 65 (13). Anal. Calcd for $C_{17}H_{18}BrN$: C 64.57; H 5.74; N 4.43. Found: C 64.44; H 5.80; N 4.48.

3. Synthesis of 1-Benzyl-3-chloroazetidine 12, Subsequent Quaternization, and Ring Opening. 1-Benzyl-3-hydroxyazetidine 11: To an ice-cooled solution of 1-benzyl-3-(trimethylsilyl)azetidine **10**[54] (1.17 g, 5 mmol) in THF (15 mL) was added TBAF·$3H_2O$ (1.65 g, 1.05 equiv) and the resulting mixture was stirred for 3 h at room temperature. Afterward, the reaction mixture was poured in water (15 mL), extracted with diethyl ether (3 × 10 mL), and dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent in vacuo afforded 1-benzyl-3-hydroxyazetidine **11** (0.68 g, 83%). Purity (GC) >97%. The spectral data correspond well with those published in the literature, where the deprotection was realized in 73% yield with use of NaOMe in methanol.[84]

1-Benzyl-3-chloroazetidine 12: To a solution of 1-benzyl-3-hydroxyazetidine **11** (0.82 g, 5 mmol) in CCl_4 (10 mL) at room temperature was added triphenylphosphine (1.44 g, 1.1 equiv) and the mixture was heated under reflux for 3 days upon which a solid separated. The cooled reaction mixture was filtered and the filtrate was extracted with dilute sulfuric acid (2 × 10 mL, 1 N in H_2O) and washed with water (2 × 20 mL). The combined aqueous extracts were made strongly alkaline with a 4 N NaOH solution (30 mL) and extracted with diethyl ether (3 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 1-benzyl-3-chloroazetidine **12** and 1-benzyl-2-(chloromethyl)aziridine (ratio 3/2 based on GC).[55a] The compound was purified by distillation. Only ^{1}H NMR data for 1-benzyl-3-chloroazetidine **12** were found in the literature.[55b]

Colorless liquid, 60% yield, bp 51 °C/0.02 mbar; TLC R_f 0.37 (hexane/EtOAc 6/4). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.20−3.25 (2H, m), 3.63 (2H, s), 3.72−3.82 (2H, m), 4.12−4.20 (1H, m), 7.21−7.32 (5H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 60.8, 63.8, 64.7, 127.4, 128.6, 137.6. IR (NaCl, cm^{-1}): ν_{max} 3086, 3063, 3029, 2958, 2837, 909, 733, 698. MS (70 eV): *m*/*z* (%) 181/3 (M^+, 4), 180/2 (10), 146 (4), 145 (4), 119 (7), 104 (12), 91 (100), 65 (9).

3-(*N*-Benzyl-*N*-methyl)amino-2-chloro-1-propene 13: To a solution of 1-benzyl-3-chloroazetidine **12** (0.36 g, 2 mmol) in diethyl ether (10 mL) was added iodomethane (0.43 g, 1.5 equiv) and the solution was stirred for 3 h at room temperature upon which a colorless solid separated. Subsequently, KO*t*Bu (0.22 g, 1.0 equiv) was added and the suspension was refluxed for 2 h. Extraction with diethyl ether (3 × 10 mL), drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 3-(*N*-benzyl-*N*-methyl)amino-2-chloro-1-propene **13** (0.31 g, 79%). The spectral data obtained here are in accordance with those mentioned in the literature.[56]

4. Stille Coupling. *N,N*-Dibenzyl-2-(trimethylstannyl)-2-propen-1-amine 18: This compound was prepared applying Stille coupling conditions.[58,59] To a solution of *N*,*N*-dibenzyl-*N*-(2-bromo-2-propenyl)amine **6a** (1.58 g, 5 mmol) in benzene (40 mL) at room temperature and under nitrogen atmosphere were added Hünig's base (0.17 g, 0.2 equiv) and hexamethylditin (2.72 mL, 2.0 equiv) via a syringe, followed by tetrakis(triphenylphosphine)palladium (0.27 g, 0.05 equiv). The yellow solution was heated for 1 h at 80 °C, gradually darkening from yellow to black, and additionally stirred for 1 h at room temperature. The reaction mixture was quenched by the addition of a saturated aqueous solution of $CuSO_4$ (40 mL). Extraction with hexane (2 × 30 mL), washing with brine (1 × 30 mL), drying over $MgSO_4$, filtration through Celite, and purification by column chromatography (SiO_2, hexane/EtOAc 95/5) afforded *N*,*N*-dibenzyl-2-(trimethylstannyl)-2-propen-1-amine **18** (1.34 g, 67%).

Light yellow oil, 67% yield; TLC R_f 0.64 (hexane/EtOAc 95/5). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.08 (9H, t, J = 26.7 Hz), 3.18 (2H, s), 3.50 (4H, s), 5.33 and 5.91 (2H, 2 × d, J = 1.5 Hz), 7.27−7.36 (10H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ −9.2, 57.8, 63.7, 126.8, 127.1, 128.1, 129.2, 138.8, 154.7. IR (NaCl, cm^{-1}): ν_{max} 3086, 3063, 3029, 2977, 2911, 2793, 1602, 1495, 1454, 748, 698, 521. MS (70 eV): *m*/*z* (%) 394/396/397/398/399/400/401/402/404/405 (M^+ + 1, 100), 300 (25) 270 (20), 268 (44), 250 (14), 239 (19), 238 (94), 236 (15), 198 (12). Anal. Calcd for $C_{20}H_{27}NSn$: N 3.50. Found: N 3.41.

2-[(Dibenzylamino)methyl]-4-methyl-1-penten-3-one 19: This compound was prepared applying Stille coupling conditions.[66,67] 2-Methylpropanoyl chloride (0.21 g, 1.0 equiv) was dissolved in benzene (10 mL) and treated with tris(dibenzylideneacetone)dipalladium (0.10 g, 0.05 equiv), followed by Hünig's base (0.08 g, 0.3 equiv). To the resultant purple solution was added vinylstannane **18** (0.80 g, 2 mmol) and the mixture was stirred for 30 min at room temperature. An additional amount of palladium (0.10 g, 0.05 equiv) was added to the black solution, regenerating the purple color. After an additional 2 h at room temperature, the reaction mixture was filtered through a pad of SiO_2 with EtOAc (40 mL) and concentrated in vacuo, affording 2-[(dibenzylamino)-methyl]-4-methyl-1-penten-3-one **19** (0.54 g, 88%).

Yellow oil, 88% yield, filtration (SiO_2) with EtOAc. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.04 (6H, d, J = 6.8 Hz), 3.14 (1H, sept, J = 6.8 Hz), 3.28 (2H, s), 3.54 (4H, s), 6.06−6.08 (2H, m), 7.20−7.42 (10H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 19.0, 35.0, 53.8, 58.1, 124.3, 126.9, 128.2, 128.6, 139.2, 145.2, 206.3. IR (NaCl, cm^{-1}): ν_{max} 3085, 3062, 3028, 2972, 2931, 2873, 2798, 1738, 1673, 1623, 1495, 1451, 698. MS (30 V): *m*/*z* (%) 308 (M^+ + 1, 100), (70 V), 308 (M^+ + 1, 2), 181 (11), 166 (7), 91 (100). Anal. Calcd for $C_{21}H_{25}NO$: C 82.04; H 8.20; N 4.56. Found: C 82.18; H 8.35; N 4.46.

5. General Procedure for the Synthesis of *N,N*-Di(arylmethyl)-*N*-(2-propynyl)amines 16. As a representative example, the synthesis of *N*,*N*-dibenzyl-*N*-(2-propynyl)amine **16a** is described. To DMSO (20 mL) was added sodium hydride (0.25 g, 10.5 mmol) and the solution was stirred for 30 min at

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80 °C. *N*,*N*-Dibenzyl-*N*-(2-bromo-2-propenyl)amine **6a** (3.15 g, 10 mmol) was added and the mixture was further stirred for 3 h at 80 °C. After addition of water and extraction with diethyl ether (3 × 20 mL), the organic phase was washed with water (3 × 50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to yield *N*,*N*-dibenzyl-*N*-(2-propynyl)amine **16a** (2.18 g, 93%). The *N*,*N*-di(arylmethyl)-*N*-(2-propynyl)amines **16** were purified by means of column chromatography on silica gel utilizing a mixture of hexane and ethyl acetate as eluent.

***N*,*N*-Dibenzyl-*N*-(2-propynyl)amine 16a:** Yellow crystals, 93% yield; TLC R_f 0.38 (hexane/EtOAc 16/1); mp 42 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.28 (1H, t, J = 2.3 Hz), 3.26 (2H, d, J = 2.3 Hz), 3.69 (4H, s), 7.22−7.42 (10H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 41.1, 57.4, 73.4, 78.5, 127.1, 128.3, 129.0, 138.7. IR (NaCl, cm^{-1}): $\nu_{\equiv C-H}$ 3297, ν_{max} 3062, 3028, 2923, 2805, 1495, 1454. MS (70 eV): *m*/*z* (%) 236 (M^+ + 1, 100), 198 (27), 91 (12). Anal. Calcd for $C_{17}H_{17}N$: C 86.77; H 7.28; N 5.95. Found: C 86.86; H 7.38; N 5.90.

***N*,*N*-Di((4-methylphenyl)methyl)-*N*-(2-propenyl)-amine 17:** To a solution of *N*-(2-bromo-2-propenyl)-*N*,*N*-di((4-methylphenyl)methyl)amine **6e** (0.35 g, 1 mmol) in THF (50 mL) at 0 °C and under nitrogen atmosphere was added n-BuLi (0.43 mL, 2.5 M in hexane, 1.05 equiv) via a syringe and the resulting solution was stirred for 15 h at room temperature. The reaction mixture was poured out in water (50 mL), extracted with diethyl ether (3 × 30 mL), and washed with water (3 × 30 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded *N*,*N*-di((4-methylphenyl)methyl)-*N*-(2-propenyl)amine **17** (0.24 g, 90%). Purity (GC) >95%.

Colorless oil, 90% yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.34 (6H, s), 3.03 (2H, d, J = 6.3 Hz), 3.52 (4H, s), 5.11−5.23 (2H, m), 5.82−5.95 (1H, m), 6.96−7.41 (8H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 21.1, 56.2, 57.3, 117.2, 128.7, 128.8, 136.1, 136.5. IR (NaCl, cm^{-1}): ν_{max} 3048, 3021, 2924, 2859, 2804, 1642, 1514, 1452, 806. MS (70 eV): *m*/*z* (%) 265 (M^+, 2), 160 (11), 105 (100), 91 (18), 77 (26). Anal. Calcd for $C_{19}H_{23}N$: C 85.99; H 8.74; N 5.28. Found: C 86.13; H 8.83; N 5.17.

6. Functionalization of Propargylamines 16. The compounds **20**, **21**, **22**, and **23** were prepared in accordance with a procedure adapted from the literature.[70] General procedure for the synthesis of propargylamines **20**, **21**, **22**, and **23**: To a solution of a *N*,*N*-di(arylmethyl)-*N*-(2-propynyl)amine **16** (10 mmol) in THF (40 mL) at −78 °C and under nitrogen atmosphere was added *n*-BuLi (2.5M in hexane, 1.05 equiv) via a syringe, and the solution was stirred for 30 min at −78 °C. To this reaction mixture was added a solution of BF_3−THF (1.3 equiv) at −78 °C via a syringe in THF (10 mL) and, after 15 min of stirring, a solution of the electrophile (1.05 equiv) in THF (10 mL). After an additional 2 h at −78 °C the mixture was heated to ambient temperature, quenched with a saturated NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 20 mL), washed with water (3 × 20 mL), and dried over $MgSO_4$. Filtration of the drying agent, removal of the solvent in vacuo, and purification by column chromatography (SiO_2) afforded the propargylamines **20**, **21**, **22**, and **23** in high yields.

7-(*N*,*N*-Dibenzylamino)-5-heptyn-3-ol 20a: Colorless oil, 82% yield; TLC R_f 0.17 (CH_2Cl_2/methanol 100/1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.01 (3H, t, J = 7.4 Hz), 1.58−1.69 (2H, m), 1.96 (1H, s(broad)), 2.37−2.58 (2H, m), 3.26 (2H, t, J = 2.2 Hz), 3.66 (4H, s), 3.66−3.71 (1H, m), 7.21−7.41 (10H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 10.0, 27.2, 29.1, 41.6, 57.6, 71.5, 77.1, 81.9, 127.1, 128.3, 129.0, 138.8. IR (NaCl, cm^{-1}): ν_{OH} 3397, ν_{max} 3029, 2963, 2927, 2877, 2824, 1495, 1454. MS (70 eV): *m*/*z* (%) 308 (M^+ + 1, 100). Anal. Calcd for $C_{21}H_{25}NO$: C 82.04; H 8.20; N 4.56. Found: C 82.15; H 8.32; N 4.50.

7. Reduction of Functionalized Propargylamines. Compounds **26** and **27** were prepared according to a method known in the literature for alkynes without heteroatoms present.[83] To a solution of 6-(*N*,*N*-dibenzylamino)-4-hexyn-2-ol **20c** (1.18 g, 4 mmol) in dibutyl ether (40 mL) was added under nitrogen atmosphere 2-phenyl-1,3,2-dioxaborinane (0.69 g, 1.05 equiv), bis(1,5-cyclooctadiene)nickel (0.11 g, 0.1 equiv), and water (1.03 g, 14 equiv), and the resulting solution was stirred for 5 h at room temperature. The reaction mixture was poured into water (100 mL), extracted with diethyl ether (3 × 20 mL), and dried over $MgSO_4$. Filtration of the drying agent, removal of the solvent in vacuo, and separation by means of column chromatography (SiO_2) afforded (4*E*)-6-[di(phenylmethyl)amino]-5-phenyl-4-hexen-2-ol **26** (0.33 g, 21%) and (4*Z*)-6-[di(phenylmethyl)amino]-5-phenyl-4-hexen-2-ol **27** (0.38 g, 24%).

(4*E*)-6-[Di(phenylmethyl)amino]-5-phenyl-4-hexen-2-ol 26: Colorless oil, 21% yield; TLC R_f 0.40 (hexane/EtOAc 4/1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.11 (3H, d, J = 6.3 Hz), 2.44 and 2.50 (2H, 2 × d × d, J = 14.1 Hz, J = 8.4, 4.9 Hz), 2.95 and 3.30 (2H, 2 × d × d, J = 13.5, 7.1 Hz), 3.48 and 3.82 (4H, 2 × d, J = 13.2 Hz), 3.65−3.72 (1H, m), 6.01 (1H, t, J = 7.1 Hz), 7.15−7.45 (15H, m). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 23.8, 39.8, 50.8, 58.7, 65.8, 126.5, 127.4, 127.6, 128.3, 129.4, 129.5, 127.2, 133.6, 138.3, 142.4. IR (NaCl, cm^{-1}): ν_{OH} 3388, ν_{max} 3084, 3061, 3028, 2964, 2926, 2801, 1601, 1495, 1453, 1372, 1313. MS (70 eV): *m*/*z* (%) 372 (M^+ + 1, 100). Anal. Calcd for $C_{26}H_{29}NO$: C 84.06; H 7.87; N 3.77. Found: C 84.17; H 7.96; N 3.69.

Acknowledgment. The authors are indebted to the Fund for Scientific Research−Flanders (Belgium) (F.W.O.-Vlaanderen) and Ghent University (GOA) for financial support.

Supporting Information Available: General information and all spectroscopic data of compounds **4b**−**j**, **6b**−**e**, **16b**−**e**, **20b**, **21**, **22**, **23**, **24**, **25**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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