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Dimethylzinc-Mediated Alkynylation of Imines

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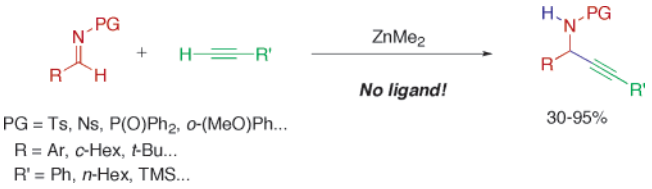

The treatment of various aromatic and aliphatic aldimines with a mixture of a terminal alkyne and a commercially available dimethylzinc solution in toluene yields the corresponding protected propargylic amines in moderate to excellent yields. The reaction proceeds in the absence of any activator. These observations led to the development of a three-component synthesis of propargylic amines in which the product was obtained upon mixing an aldehyde with *ortho*-methoxyaniline and phenylacetylene in the presence of dimethylzinc, through in situ formation of the corresponding imine.

Introduction

The addition of carbon nucleophiles to reactive electrophilic functions, such as C═O and C═N double bonds, is a process of fundamental importance in the development of a chemical synthesis.[1] Among the various nucleophilic species available, alkynes are excellent reagents for mild and selective C—C bond-forming reactions.[2]

While the addition of acetylenes to carbonyl compounds, in both a racemic and an enantioselective manner, has been the subject of a large number of publications,[3] 1,2 additions of alkynes to compounds with C═N double bonds by a direct nucleophilic reaction have been much less developed, mostly a result of the poor electrophilicity of the azomethine carbon.[4] Moreover, to overcome the general low reactivity of imines, often more activated substrates such as nitrones or iminium salts are used. Recent protocols commonly employ metal salts or complexes as promoters, used in either stoichiometric[5] or catalytic amounts.[6−12] An excellent example is Knochel's highly enantioselective copper-catalyzed addition of alkynes to enamines, further developed into a three-component reaction.[12] Despite these substantial advances in the direct addition of actylenes to C═N double bonds, a general and an easy-to-perform procedure for the alkynylation of simple imines is still desirable.

Recently, we found that mixtures of $ZnMe_2$ and acetylenes are able to promote the alkynylation of aldehydes and ketones to furnish propargylic alcohols in good to excellent yields at room temperature.[13] These results were surprising, because a mixture of phenylacetylene and dimethylzinc had previously been reported to be rather unreactive toward aldehydes[14] in the absence of a proper activator.[15] This suggested the possibility that the carbonyl oxygen could behave in a "ligand-like" fashion, activating $ZnMe_2$ by the coordination of its lone pairs.

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Prompted by these observations, we decided to investigate the reaction of N-substituted imines **1** with mixtures of alkylzinc reagents and acetylenes **2**. To our delight, we found that they exhibited here a similar behavior. Although zinc-mediated alkynylation reactions of C═N electrophiles have already been reported,[5b,c,e−g,6] our findings represent the first example of a $ZnMe_2$-promoted addition of acetylenes to activated imines. The results obtained in these experiments, as well as the development of an unprecedented Zn-mediated one-pot synthesis of propargylic imines, are reported herein.

Results and Discussion

First, the reaction of *N*-tosylphenylimine (**1a**) with 3 equiv of phenylacetylene (**2a**) in the presence of dimethylzinc (3.0 equiv, as a commercially available 2.0 M solution in toluene) in anhydrous toluene at room temperature was examined. Under those conditions, the conversion of **1a** was limited to about 65% after 48 h (as determined by the NMR analysis of the crude reaction mixture).[16] However, the reaction could easily be accelerated by raising the temperature, and after a brief optimization, we found that a mixture of **2a** and $ZnMe_2$ (1.5 equiv each) in toluene at 50 °C was able to convert **1a** quantitatively, affording the corresponding protected propargylamine **3aa** in 80% yield (Scheme 1 and Table 1, entry 1).

SCHEME 1. Alkynylation of *N*-Tosylphenylimine (1a) with Two Different Alkylzinc Reagents

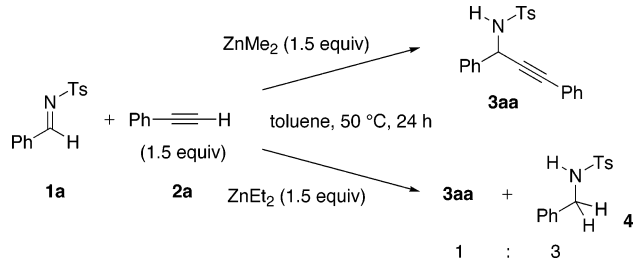
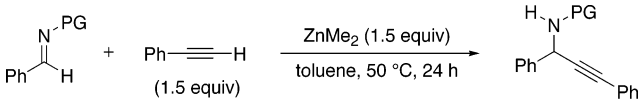


TABLE 1. Alkynylation of Different N-Substituted Phenylimines in the Presence of $ZnMe_2$



entry	substrate	PG	product	yield[a] (%)
1	**1a**	Ts	**3aa**	80
2	**1b**	Ms	**3ba**	78
3[b]	**1c**	SO_2Mes	**3ca**	(82)[c]
4	**1d**	Ns	**3da**	91
5	**1e**	$P(O)Ph_2$	**3ea**	69
6	**1f**	Bn	**3fa**	0
7	**1g**	4-(MeO)Ph	**3ga**	0
8	**1h**	2-(MeO)Ph	**3ha**	76[d]

[a] After flash column chromatography (see Supporting Information for details). [b] The reaction was carried out at 70 °C. [c] The product was only about 90% pure (as determined by NMR). [d] The amount of 2.5 equiv each of dimethylzinc and phenylacetylene was used.

Surprisingly, when $ZnEt_2$ (as a commercially available 1.0 M solution in heptane) was used instead of $ZnMe_2$ under the same conditions, the substrate was completely transformed, but benzylamine **4**, stemming from the reduction of **1a**, was found to be the major product, in a ratio of 3:1 to **3aa** (Scheme 1). Compound **4** is probably formed directly by the reaction of substrate **1a** with diethylzinc through a β-hydride transfer accompanied by the elimination of ethylene. This is in agreement with the observations recently reported by Qian and co-workers, who found that, in noncoordinating solvents such as toluene or hexane, $ZnEt_2$ can be efficiently used to reduce *N*-sulfonylimines to the corresponding protected amines in high yields.[17] It is noteworthy that in none of these experiments, including those described below, any trace of the product resulting from the direct alkyl addition to the substrate was found.

Having established the optimal reaction conditions for the conversion of **1a**, the effect of the nature of the nitrogen atom protecting group was examined. Thus, various N-substituted

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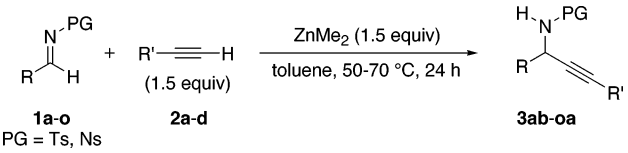
(16) This conversion value is based on the integration of the signals of the starting material (proton of the imino group, δ 8.98 ppm) and of the product (proton on the N-bearing carbon atom, δ 4.91 ppm) in the ^{1}H NMR spectrum of the crude reaction mixture. Signals of other compounds were not detected in the spectrum.

TABLE 2. Substrate Scope of the Alkynylation Reaction



1a-o PG = Ts, Ns **2a-d** **3ab-oa**

entry	substrate	PG	R	R′ (alkyne)	product	temp (°C)	yield[a] (%)
1	**1a**	Ts	Ph	*n*-hexyl (**2b**)	**3ab**	70	67
2[b]	**1a**	Ts	Ph	TMS (**2c**)	**3ac**	70	52
3[b,c]	**1a**	Ts	Ph	TMS (**2c**)	**3ac**	70	60
4	**1a**	Ts	Ph	4-CF_3-Ph (**2d**)	**3ad**	50	87
5	**1d**	Ns	Ph	*n*-hexyl (**2b**)	**3db**	70	79
6	**1i**	Ts	4-Me-Ph	Ph (**2a**)	**3ia**	60	77
7	**1i**	Ts	4-Me-Ph	*n*-hexyl (**2b**)	**3ib**	70	60
8	**1j**	Ts	4-MeO-Ph	Ph (**2a**)	**3ja**	60	85
9	**1k**	Ts	2-naph	Ph (**2a**)	**3ka**	50	85
10	**1l**	Ts	2-Br-Ph	Ph (**2a**)	**3la**	50	93
11	**1m**	Ts	2-furyl	Ph (**2a**)	**3ma**	50	80
12	**1m**	Ts	2-furyl	4-CF_3-Ph (**2d**)	**3md**	50	95
13	**1n**	Ts	*c*-hex	Ph (**2a**)	**3na**	70	84
14	**1o**	Ts	2-Me-propyl	Ph (**2a**)	**3oa**	70	15

[a] After flash column chromatography (see Supporting Information for details). [b] The amount of 2.5 equiv each of dimethylzinc and trimethylsilylethyne was used. [c] Commonly, the reaction was performed on a 0.5-mmol scale. In this case, however, 2.0 mmol of the imine were used.

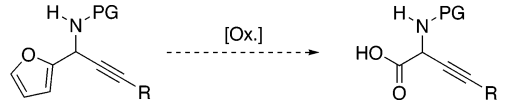
aromatic imines **1a**−**h** were treated with phenylacetylene in the presence of dimethylzinc. The results obtained are listed in Table 1.

Phenylimines bearing a sulfonyl group on the nitrogen atom proved to be excellent substrates for the reaction (Table 1, entries 1−4), the best being *N*-benzylidene 4-nitrobenzensulfonamide (**1d**). Probably the strong electron-withdrawing character of the nosyl group led to an activation of the imine moiety, resulting in a positive effect on the product yield (Table 1, entry 4). Only in the case of substrate **1c** bearing a mesitylsulfonyl (mesityl = 2,4,6-trimethylphenyl) substituent, was it necessary to increase the reaction temperature to 70 °C to obtain full conversion (Table 1, entry 3). Although the NMR signals of the desired product, **3ca**, could clearly be observed, its purification proved to be difficult, and an analytically pure sample could not be obtained.

N-benzylidene diphenylphosphinamide (**1e**) also gave full conversion to the corresponding product under the reaction conditions, but in this case the yield of **3ea** was slightly lower than that with the sulfonyl protecting groups (Table 1, entry 5). Non-electron-withdrawing groups such as benzyl and 4-methoxyphenyl failed to sufficiently activate the imine for the reaction with the alkynylating reagent (Table 1, entries 6 and 7). Surprisingly, however, the product could be obtained in good yield when *N*-benzylidene 2-methoxyaniline (**1h**) was used as the substrate (Table 1, entry 8). This result can be explained by considering the possibility of substrate **1h** acting as a ligand, thus activating the alkynylzinc species formed in the reaction mixture and facilitating the reaction. In contrast to para-substituted **1g**, the two donor atoms, N and O, present in **1h** are placed in a perfect position to form a chelate complex with a metal, in this case zinc. The strong activation furnished by chelation would then allow the reaction to proceed, even if **1h** is a far less reactive substrate than, for example, **1a**−**e**.

Next, the possibility of using alkynes other than phenylacetylene in the imine addition reaction and of varying the residue on the imines was examined (Table 2).

Acetylenes such as *n*-octyne (**2b**) and trimethylsilylethyne (**2c**) were also applicable (Table 2, entries 1 and 2), though they proved to be less reactive than **2a**, probably a result of their lower acidity. Consequently, a higher temperature was required and, in the case of **2c**, 2.5 equiv of the alkynylating mixture were needed to reach a reasonable yield of the product. In agreement with these observations, the yield of the corresponding product was superior when the more acidic 4-(trifluoromethyl)phenylacetylene (**2d**) was used in the addition to **1a** compared to the same reaction with **2a** (Table 2, entry 4 versus Table 1, entry 1, respectively). More electron-rich imines such as **1i**−**k** could also be easily converted into the corresponding propargylic amines (Table 2, entries 6−9), although the temperature had to be raised to 60 °C to obtain full conversion. A bulky halogen substituent in the ortho position was also tolerated (Table 2, entry 10), with the product being obtained in remarkably high yield (93%). Imines bearing heteroaryl substituents were also found to be viable substrates for the reaction (Table 2, entries 11 and 12). Thus, the combination of *N*-furfurylidene toluene-4-sulfonamide (**1m**) and alkyne **2d** furnished amine **3md** in the highest yield observed in this study (95%, entry 11). The latter transformation is particularly interesting, because the furane ring can be easily oxidized to the carboxylic acid,[18] thus opening the way for a possible synthesis of alkynyl-α-amino acids (eq 1).



(1)

Interestingly, when the reaction of **1a** with trimethylsilylethyne (**2c**) was performed on a 2.0 mmol (instead of the common 0.5 mmol) scale, the product yield was slightly higher (Table 2, entry 4). The treatment of amine **3ac** with tetrabutylammonium fluoride in THF for 30 min afforded the corresponding desilylated product **5** in good yield (eq 2).

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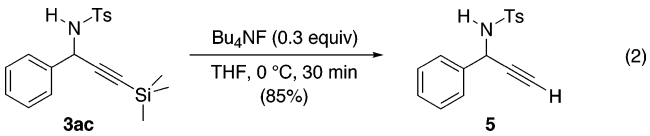
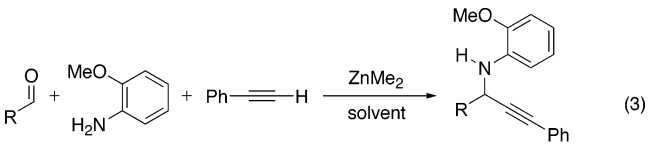


(2)

The results obtained with *N*-tosylimines derived from aliphatic aldehydes were more complex. Substrate **1n**, bearing a cyclohexyl group, reacted smoothly with **2a** at 70 °C, affording the corresponding product **3na** in remarkably high yield (84%, Table 2, entry 13). On the other hand, the reaction of compound **1o**, derived from isovaleraldehyde, with **2a** was sluggish, and several byproducts, probably stemming from enolization processes, were present in the crude reaction mixture together with the expected propargylic amine **3oa**. The latter compound could, therefore, be isolated only in very low yield (Table 2, entry 14). A lowering of the temperature and a shortening of the reaction time was not beneficial, and almost the same result was obtained at room temperature after only 12 h. These findings suggest that α-branched imines are suitable substrates for the present transformation, whereas more appropriate conditions have to be found for the efficient conversion of aliphatic aldehydes lacking the α branching.

The observation that imine **1h**, bearing an *ortho*-methoxyphenyl group on the nitrogen atom, gave rise to the expected product in the reaction with **2a**/$ZnMe_2$, coupled with the knowledge of already published protocols for the three-component synthesis of propargylic amines,[10−12] prompted us to explore the possibility of preparing compounds **3** by means of a three-component reaction of 2-methoxyaniline (**6**), an aldehyde (**7**), and phenylacetylene (**2a**) in the presence of dimethylzinc (eq 3).[19]



7 **6** **2a** **3** (3)

First, the reaction of 4-chlorobenzaldehyde (**7b**) with **6** and **2a** was examined. After optimization,[20] we found that the treatment of a mixture of **7b** and **6** with dimethylzinc (3.5 equiv, as a commercially available 2.0 M solution in toluene) and **2a** (2.5 equiv) in toluene at room temperature (method A) furnished the desired product **3pa** in 76% yield after 48 h. On the basis of this result, the substrate scope of the reaction was subsequently examined. The results are summarized in Table 3.

While the reactions with benzaldehyde (**7a**) and 4-phenylbenzaldehyde (**7f**) furnished the corresponding products **3ha** and **3ta**, respectively, in only moderate yields (Table 3, entries 1 and 6), benzaldehydes **7b**−**d** bearing halogen substituents on the ring proved to be better substrates (Table 3, entries 2−4). The best result, however, was obtained with 2-naphthaldehyde (**7e**), which gave the corresponding amine in 92% yield after 48 h (Table 3, entry 5). Aldehydes **7g**−**i**, having electron-withdrawing substituents on the ring, could also be transformed, although in one case a longer reaction time was necessary (Table 3, entries 7−9). Interestingly, perfluorinated compound **7j** and heterocyclic aldehyde **7k** were also suitable substrates for the reaction (Table 3, entries 10 and 11). In the latter case, the ligating properties of the pyridine ring, which are often a problem in organozinc-mediated reactions,[21] did not seem to compromise the efficiency of the protocol.

TABLE 3. Three-Component Synthesis of Propargylic Amines

entry	aldehyde	product	method[a]	time (h)	yield[b] (%)
1	benzaldehyde (**7a**)	**3ha**	A	48	48
2	4-chlorobenzaldehyde (**7b**)	**3pa**	A	48	76
3	3-bromobenzaldehyde (**7c**)	**3qa**	A	48	73
4	4-bromobenzaldehyde (**7d**)	**3ra**	A	48	73
5	2-naphthaldehyde (**7e**)	**3sa**	A	48	92
6	4-phenylbenzaldehyde (**7f**)	**3ta**	A	48	30
7	3-nitrobenzaldehyde (**7g**)	**3ua**	A	60	66
8	4-CF_3-benzaldehyde (**7h**)	**3va**	A	48	79
9	4-COOMe-benzaldehyde (**7i**)	**3wa**	A	48	65
10	pentafluorobenzaldehyde (**7j**)	**3xa**	A	48	63
11	3-carboxypyridine (**7k**)	**3ya**	A	48	65
12	cyclohexanecarbaldehyde (**7l**)	**3za**	A	48	22
13	cyclohexanecarbaldehyde (**7l**)	**3za**	B	48	85
14	pivalaldehyde (**7m**)	**3Aa**	B	96	67
15	octanal (**7n**)	**3Ba**	B	96	45

[a] Method A: reactions were carried out in toluene (ca. 0.1 M relative to the aldehyde) at room temperature, employing $ZnMe_2$ (2.0 M solution in toluene, 3.5 equiv) and phenylacetylene (**2a**, 2.5 equiv). Method B: no additional solvent was used (see Results and Discussion and Supporting Information for details). [b] After flash column chromatography (see Supporting Information for details).

Unfortunately, when cyclohexanecarbaldehyde (**7l**) was used as the substrate under the usual reaction conditions, only a very low yield of the product was obtained after 2 days (Table 3, entry 12).

Recently, Walsh demonstrated that the efficiency and selectivity of the enantioselective addition of alkylzinc reagents to ketones can be greatly enhanced under solvent-free or "highly concentrated" conditions.[22] Inspired by these observations, we performed the reaction using as the only solvent the toluene present in the commercial $ZnMe_2$ solution employed throughout this study (method B, corresponds to ca. a 0.6 M concentration relative to the aldehyde). Gratifingly, we found that propargylamine **3za** could now be obtained in a remarkable 85% yield after 48 h at room temperature (Table 3, entry 13). The application of the same conditions to pivaldehyde (**7m**) and octanal (**7n**) led to the isolation of the corresponding alkynylation products, albeit these reactions needed a longer time to reach completeness (Table 3, entries 14 and 15). Although in the latter case an α-unbranched substrate was used and side products (presumably derived from enolization processes) were detected, the desired product was isolated in an acceptable yield.

In conclusion, we have presented an efficient and facile addition of acetylenes to imines, mediated by commercially available $ZnMe_2$ solution in toluene, without the employment of specific ligands. The experimental procedure is easy and does not require special precautions, except for the use of anhydrous solvent under an inert atmosphere. Furthermore, a three-

(18) (a) Demir, A. S. *Pure Appl. Chem.* **1997**, *69*, 105. (b) Alvaro, G.; Martelli, G.; Savoia, D.; Zoffoli, A. *Synthesis* **1998**, 1773. (c) Borg, G.; Chino, M.; Ellman, J. A. *Tetrahedron Lett.* **2001**, *42*, 1433. (d) Demir, A. S.; Sesenoglu, Ö.; Ülkü, D.; Arici, C. *Helv. Chim. Acta* **2003**, *86*, 91.

(19) A related three-component, asymmetric, aza-Reformatzky reaction has recently been reported: Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600.

(20) See Supporting Information for details.

(21) For an example in the asymmetric phenylation of aldehydes, see: (a) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295. (b) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465.

(22) Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416.

component protocol has been developed that allows the preparation of protected propargylic amines in one step, thus circumventing a prior synthesis of the corresponding imines. Although aromatic aldehydes were superior substrates for this reaction, we demonstrated that simple modifications in the reaction protocol allowed the transformation of aliphatic substrates with a similar level of efficiency. Efforts to further expand the scope of this novel three-component procedure with regard to the alkyne moiety, as well as to develop an asymmetric version of the same transformation, are currently underway in our laboratories.

Experimental Section

N-sulfonyl imines **1a**−**d**,**i**−**m** were prepared using a modified version of the procedure described by Kim and co-workers,[23] employing 1,2-dichloroethane as the solvent instead of CH_2Cl_2 and heating at reflux for 48 h instead of 12 h. *N*-benzylidene diphenylphosphinamide (**1e**) was prepared following the procedure reported by Jennings and Lovely.[24] *N*-tosyl imines derived from aliphatic aldehydes (**1n**,**o**) were prepared following the procedure reported by Chemla and co-workers.[25]

Typical Procedure for the Alkynylation of N-Protected Imines. In an oven-dried Schlenk flask under an inert atmosphere of argon, alkynes **2a**−**d** (0.75−1.25 mmol, 1.5−2.5 equiv) were dissolved in anhydrous toluene (4.5 mL). A 2.0 M solution of dimethylzinc in toluene (0.38−0.63 mL, 0.75−1.25 mmol, 1.5−2.5 equiv) was then carefully added, and the resulting mixture was stirred at room temperature for 30 min. The appropriate imine **1** (0.5 mmol) was then added in one portion, and the temperature was increased to the desired value (50−70 °C). The resulting solution was stirred for 24 h, after which a white precipitate appeared in some cases. The reaction was quenched with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the organic phase was washed with brine (25 mL) and dried over $MgSO_4$. The evaporation of the solvent under reduced pressure furnished the crude product, typically as a solid, which was purified by flash column chromatography and/or by recrystallization (see Supporting Information for details).

***N*-(*p*-Toluenesulfonyl)-1,3-diphenyl-1-aminoprop-2-yne (3aa).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 4.91 (d, J = 9.2 Hz, 1H), 5.48 (d, J = 9.2 Hz, 1H), 7.01−7.08 (m, 2H), 7.11−7.34 (m, 8H), 7.44−7.52 (m, 2H), 7.70−7.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 49.8, 85.4, 86.7, 121.9, 127.3, 127.5, 128.1, 128.4, 128.6, 128.7, 129.5, 129.7, 131.5, 137.4, 143.5. Anal. Calcd. for $C_{22}H_{19}NO_2S$: C, 73.31; H, 5.03; N, 3.88. Found: C, 73.09; H, 5.17; N, 3.75.

(23) Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 1231.
(24) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5568.
(25) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75.

Typical Procedure for the Three-Component Synthesis of Propargylic Amines. Method A: In an oven-dried Schlenk flask under an inert atmosphere of argon were placed the appropriate aldehyde (**7**, 0.2 mmol) and 2-methoxyaniline (**6**, 0.2 mmol, 1.0 equiv), followed by anhydrous toluene (2.0 mL). After 30 min of stirring, a 2.0 M solution of dimethylzinc in toluene (0.35 mL, 0.7 mmol, 3.5 equiv) was added. The reaction mixture was then stirred for another 30 min before adding phenylacetylene (**2a**, 0.5 mmol, 2.5 equiv). The resulting solution was stirred at room temperature for 48−60 h. The reaction mixture was diluted with diethyl ether (5 mL) and quenched with water (10 mL). The resulting heterogeneous mixture was filtered over Celite. The aqueous phase was separated and washed with diethyl ether (2 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give the crude product, which was then purified by flash column chromatography (see Supporting Information for details).

Method B (Concentrated Conditions): In an oven-dried Schlenk flask under an inert atmosphere of argon were placed the appropriate aldehyde (**7**, 0.4 mmol) and 2-methoxyaniline (**6**, 0.4 mmol, 1.0 equiv). A 2.0 M solution of dimethylzinc in toluene (0.7 mL, 1.4 mmol, 3.5 equiv) was immediately added. The reaction mixture was then stirred for 15 min before the addition of phenylacetylene (**1a**, 1.0 mmol, 2.5 equiv). The resulting solution was stirred at room temperature for 48−96 h. Subsequently, the protocol followed the procedure reported above for method A.

***N*-(2-Methoxyphenyl)-1,3-diphenyl-1-aminoprop-2-yne (3ha).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H), 4.78 (s, 1H), 5.50 (s, 1H), 6.71−6.91 (m, 4H), 7.23−7.44 (m, 8H), 7.64−7.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.4, 55.5, 84.9, 88.7, 109.6, 111.7, 117.7, 121.1, 122.9, 127.4, 128.0, 128.16, 128.2, 128.7, 131.8, 136.4, 139.9, 147.1. Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.43; H, 6.22; N, 4.20.

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Supporting Information Available: General experimental information and procedures, complete analytical data of all the propargylic amines **3**, and copies of the ^{1}H and ^{13}C NMR spectra of these compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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