Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 10671–10683

Three-component one-pot process to propargylic amines and related amide and sulfonamide compounds: application to the construction of 2-(aminomethyl)benzofurans and indoles

Olivier Russo,[a] Samir Messaoudi,[a,b] Abdallah Hamze,[a,b] Nathanäel Olivi,[b] Jean-François Peyrat,[a,b] Jean-Daniel Brion,[a,b] Sames Sicsic,[a,b] Isabelle Berque-Bestel[a,c] and Mouâd Alami[a,b,*]

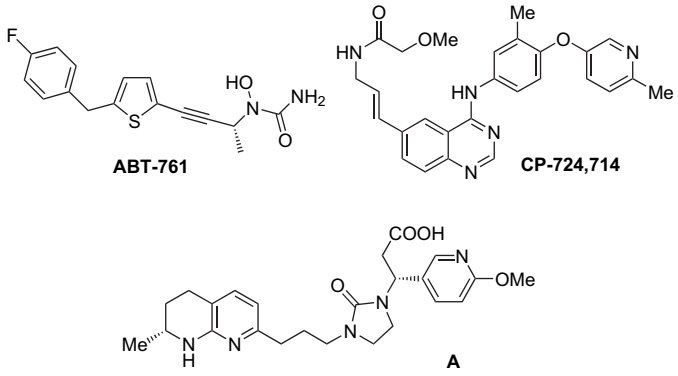
[a]*Univ Paris-Sud, BioCIS UMR 8076, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, rue J.B. Clément F-92296 Châtenay-Malabry, France*
[b]*CNRS, BioCIS UMR 8076, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, rue J.B. Clément F-92296 Châtenay-Malabry, France*
[c]*Inserm U869, Université Victor Segalen, 146 rue léo Saignat, F-33076 Bordeaux, France*

Received 21 June 2007; revised 24 July 2007; accepted 26 July 2007
Available online 1 August 2007

Abstract—An efficient palladium–copper-catalyzed three-component assembling of propargyl halides, aryl or heteroaryl halides, and secondary amines is described. A wide variety of tertiary propargylic amines were synthesized in good to excellent yields from easily accessible starting materials. This three-component assembling was also effective when using potassium phthalimide or di-*tert*-butyliminodicarbonate instead of secondary amines. Consequently, it provides a quick entry to *N*-protected propargylic amines suitable intermediates for the synthesis of primary and secondary propargylic amines. In a similar way, related compounds including propargylic amide, carbamate and sulfonamide derivatives were efficiently obtained. This catalytic domino three-component process has been applied successfully to the construction of functionalized 2-(aminomethyl)benzo[*b*]furan or indole derivatives of biological interest.

1. Introduction

Functionalized propargylic amines are important structural elements of natural products and therapeutic drug molecules. Many molecules bearing this original motif are well-known to exhibit strong inhibitory activities toward several enzymes[1] (e.g., **ABT-761**[2] is a selective 5-lipoxygenase inhibitor). These compounds are also versatile synthetic intermediates for the synthesis of various nitrogen heterocycles[3] and allyl- or alkylamines having highly potent biological activities (Scheme 1). For instance, **CP-724,714**[4] is a selective ErbB2 angiogenesis inhibitor currently being



Scheme 1.

* Corresponding author. E-mail: mouad.alami@u-psud.fr

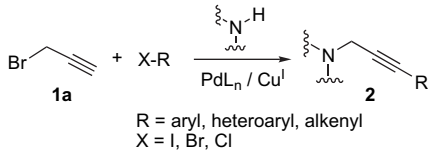
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.07.096

investigated for the treatment of breast, ovarian, and other types of cancer and compound **A**[5] is a $\alpha_v\beta_3$ integrin antagonist indicated in osteoporosis disease.

In recent years, great efforts have been made to find new routes to propargylic amines including amination of propargylic electrophiles (halides, triflates, or phosphates),[6] $TiCl_4$ mediated amination of propargyl ester,[7] addition of 1-alkynes to pre-formed imines,[8] or Sonogashira coupling of aryl halides with propargyl amines.[9] However, while these reactions are suitable methods, they require the preparation of either or both reagents. The obvious and certainly the most popular way to prepare propargylic amines is the Mannich three-component condensation of 1-alkynes, aldehydes, and amines.[10] While there are many commercially available amines and aldehydes, the number of terminal alkynes is limited (particularly functionalized terminal arylalkynes) and their preparation requires multistep sequence synthesis. Moreover, such terminal alkynes are sensitive substrates when bearing an electron-withdrawing substituent (NO_2, CN, CF_3, etc.) on the aromatic ring.[11] From the standpoint of flexibility, a method employing a common starting material as a precursor would have obvious advantages.

2. Results and discussion

We wish to detail herein our results, previously reported,[12] concerning a three-component nitrogen propargylation/alkynylation of organic halides leading to the synthesis of aryl- or heteroarylpropargylic amines as well as related amide and sulfonamide compounds. The basic concept of our process, illustrated in Scheme 2, is based on a tandem nitrogen propargylation/Sonogashira–Linstrumelle reaction using amines or potassium di-*tert*-butyliminodicarbonate, propargyl bromide, and aryl halides under palladium–copper catalysis. The commercial availability of such compounds makes this approach sufficiently diversity oriented, thus fulfilling the recent demand for the generation of large combinatorial chemical libraries.[13] Additionally, this novel domino three-component coupling reaction[14] provides a quick and efficient entry to functionalized 2-(aminomethyl)benzo[*b*]furan or indole derivatives of biological interest.[15]



Scheme 2.

2.1. Access to tertiary propargylic amines

In order to prepare highly functionalized tertiary propargylic amines **2**, we first carried out the reaction with secondary amines. As depicted in Table 1, a broad range of commercially available cyclic or acyclic secondary amines were studied in combination with functionalized aryl iodides or aryl bromides. In the following couplings, the amines were used as substrate and solvent of the reaction.[16] The reagents and catalysts are mixed together and experimental conditions are set up in such a way to promote the reaction cascade. Typically, the reaction was carried out by adding propargyl bromide **1a** (1.2 equiv) to a mixture containing aryl halide (1 equiv), secondary amine, $PdCl_2(PPh_3)_2$ (5 mol %), and CuI (10 mol %). As expected, aryl iodides underwent the three-component reaction without any heating and much more rapidly than aryl bromides. The reaction with these latter required a 60 °C heating during several hours for completion.

It is interesting to note that the presence of an electron-donating or electron-withdrawing substituent in *ortho* or *para* position of the aromatic ring did not interfere with the outcome of the coupling reaction. In all cases studied, propargylic amines **2a–h** were formed in good to excellent yields (Table 1, entries 1–8). Carrying out the three-component reaction with multiple halogenated aromatic substrates such as 1,4-diiodobenzene or 1,3,5-tribromobenzene furnished the corresponding bis-(**2i**)[17] or tris-coupling product (**2j**) in high yields (entries 9 and 10). Interestingly, this domino three-component coupling reaction was also effective with heteroaromatic halides and yielded the corresponding propargylic amines **2k–m** in good yields (entries 11–13).

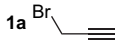
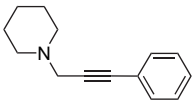
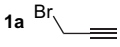
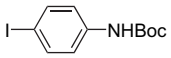
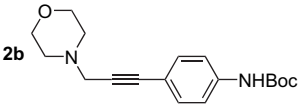
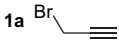
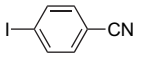
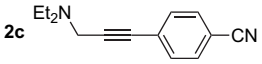
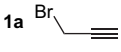
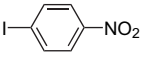
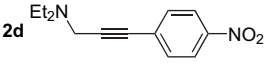
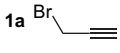
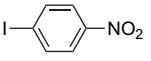
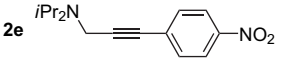
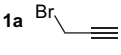
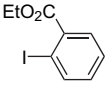
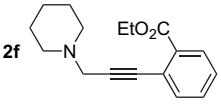
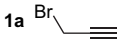
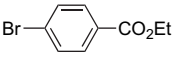
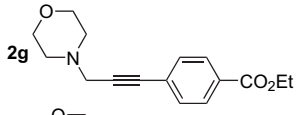
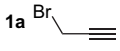
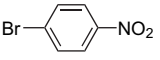
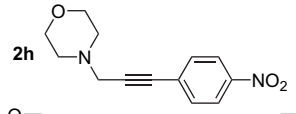
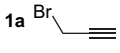
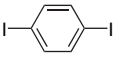
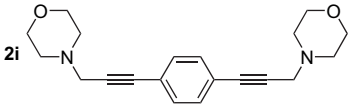
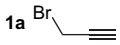
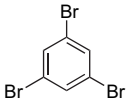
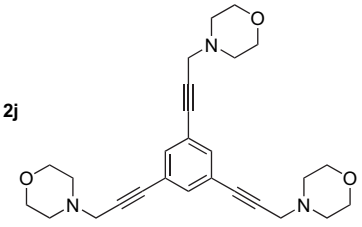
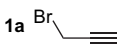
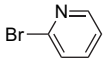
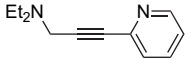
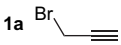
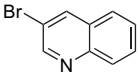
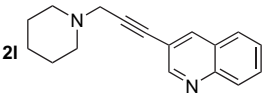
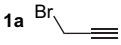
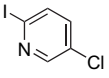
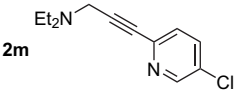
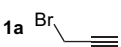
In the following examples, it is interesting to note that alkenyl chlorides[18] in spite of their poor reactivity were readily used in this domino process without any difficulty. In the case of chloroenynes, the reaction requires the use of $PdCl_2(PhCN)_2$[19] as catalyst instead of $PdCl_2(PPh_3)_2$ and afforded the enediyne product **2n** in an excellent yield (entry 14). Starting from a *E*/*Z* (1:1) mixture of 1,2-dichloroethylene,[20] the corresponding *E*-chloroenyne **2o** was selectively obtained in a good yield (*E*/*Z* 9:1, entry 15). Substituted propargyl chloride such as 3-chloro-oct-1-yne was also effective for the reaction and its coupling with methyl-4-iodobenzoate or 4-iodobenzonitrile, provided the desired propargylic amines **2p** and **2q** in excellent yields (entries 16 and 17).

2.2. Access to protected and unprotected propargylic amines

Besides the synthesis of tertiary propargylic amines **2**, our simple methodology could open an easy access to protected and unprotected functionalized aryl propargylic amines **3–5**. An access to primary propargylic amine can be envisaged through the direct coupling of propargylic amine with aryl halides. Nevertheless, this approach is uncertain,[21] yields being generally enhanced after protection of the propargylic amine.[22] Moreover, in the case of heteroaryl halides such as 2-bromopyridine, attempts coupling with commercially available prop-2-ynylamine at room temperature under various combinations of palladium catalyst and amines (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, Et_2NH, Et_3N, piperidine with or without CuI)[16] resulted in an unsatisfactory yield of **5c** certainly due to the instability of the resulting compound under the conditions used.

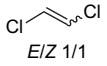
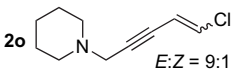
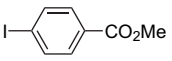
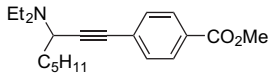
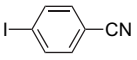
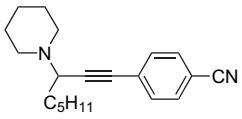
With regards to efficiency, instead of using previously synthesized protected propargylic amine, we were interested in forming the *N*-protected propargylic amine in situ. To this end, we planned to use a potassium salt of phthalimide or di-*tert*-butyliminodicarbonate during the reaction. Thus,

Table 1. Three-component assembling process of propargyl halides **1**, secondary amines, and aryl or heteroaryl halides under palladium–copper catalysis: synthesis of tertiary propargylic amines **2**

Entry	Amine	Propargylic halide **1**	RX	Propargylic amine **2**	Yield[a] (%)
1	Piperidine	**1a** 		**2a** 	92
2	Morpholine	**1a** 		**2b** 	83
3	Et_2NH	**1a** 		**2c** 	85
4	Et_2NH	**1a** 		**2d** 	94
5	*i*-Pr_2NH	**1a** 		**2e** 	69
6	Piperidine	**1a** 		**2f** 	82
7	Morpholine	**1a** 		**2g** 	93
8	Morpholine	**1a** 		**2h** 	86
9	Morpholine	**1a** 		**2i** 	98
10	Morpholine	**1a** 		**2j** 	62
11	Et_2NH	**1a** 		**2k** 	74
12	Piperidine	**1a** 		**2l** 	78
13	Et_2NH	**1a** 		**2m** 	79
14	Piperidine	**1a** 		**2n**	87[b]

(*continued*)

Table 1. (*continued*)

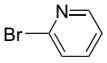
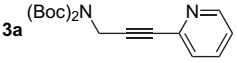
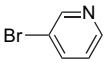
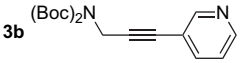
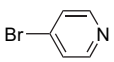
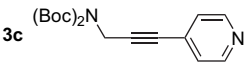
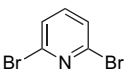
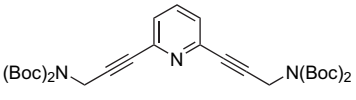
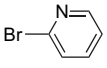
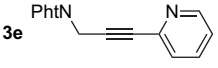
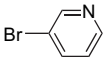
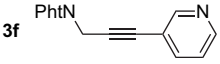
Entry	Amine	Propargylic halide **1**	RX	Propargylic amine **2**	Yield[a] (%)
15	Piperidine	**1a** 	 *E*/*Z* 1/1	**2o**  *E*:*Z* = 9:1	63[c]
16	Et_2NH	**1b** 		**2p** 	74
17	Piperidine	**1b** 		**2q** 	89

[a] Isolated yield based on RX. Unless otherwise stated, all reactions were conducted with RX (1 equiv), propargyl halide **1** (1.2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), and CuI (10 mol %) in secondary amine used as a solvent.
[b] $PdCl_2(PhCN)_2$ was used instead of $PdCl_2(PPh_3)_2$; see Ref. 19.
[c] Isolated yield based on propargyl bromide **1a** (1 equiv). The reaction was performed in the presence of an excess (10 equiv) of 1,2-dichloroethylene (*E*/*Z*=1:1); see Ref. 20; *E*/*Z* ratio was determined by ^1H NMR.

the three-component reaction was carried out in a sequential way by mixing in a first step in DMF propargyl bromide **1a** (2.0 equiv) and the potassium salt (2.0 equiv) then in a second step, by introducing heteroaryl halide (1 equiv), triethylamine, $PdCl_2(PPh_3)_2$ (5 mol %), and CuI (10 mol %). The results summarized in Table 2 show that this three-component coupling reaction worked very well with bromopyridine substrates but required heating at 80 °C for completion. Under these conditions, the use of potassium di-*tert*-butyliminodicarbonate in combination with 2-, 3- or 4-bromopyridine provided the *N*-protected primary propargylic amines **3a–c** in excellent yields (Table 2, entries 1–3). 2,6-Dibromopyridine also undergoes assembling reaction to give the dicoupling product **3d** in 53% yield (entry 4). This three-component coupling reaction was also effective when using potassium phthalimide instead of potassium di-*tert*-butyliminodicarbonate and afforded the corresponding protected propargylic amines **3e** and **3f** in moderate to good yields (entries 5 and 6).[23]

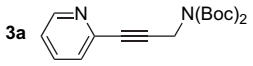
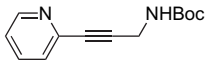
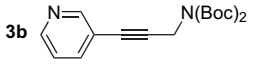
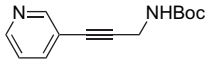
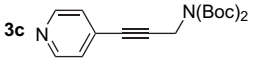
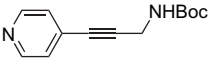
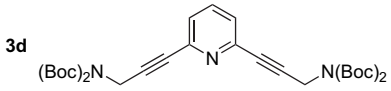
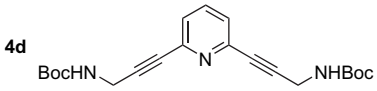
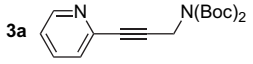
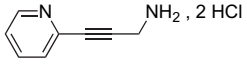
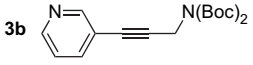
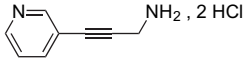
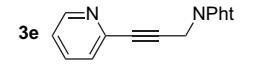
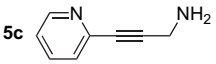
In order to demonstrate that compounds **3** are suitable intermediates for obtaining unprotected propargylic amines **4** and **5**, we then studied the deprotection of the amino function of compounds **3** (Table 3). According to the conditions used, it would be then possible to selectively obtain secondary propargyl amine derivatives **4** and their corresponding primary analogues **5**, which are unknown in the literature. Thus, selective monodeprotection of the amino function of compounds **3a–d** was accomplished according to Hernandez's procedure (LiBr/MeCN, condition A)[24] leading to the corresponding monoprotected propargylic amines **4a–d** in good yields (Table 3, entries 1–4). To obtain the corresponding

Table 2. Three-component coupling of propargyl bromide **1a**, potassium salts and bromopyridine substrates under palladium–copper catalysis: synthesis of protected propargylic amines **3**

Entry	Potassium salt	Propargylic halide **1**	ArX	Protected propargylic amines **3**	Yield of **3**[a] (%)
1	$(Boc)_2NK$	**1a**		**3a** 	93
2	$(Boc)_2NK$	**1a**		**3b** 	74
3	$(Boc)_2NK$	**1a**		**3c** 	82
4	$(Boc)_2NK$	**1a**		**3d** 	53
5	PthNK	**1a**		**3e** 	82
6	PthNK	**1a**		**3f** 	50

[a] Isolated yield based on ArX.

Table 3. Deprotection of the amino function of compounds **3**; synthesis of secondary and primary propargylic amines **4** and **5**

Entry	Propargylic amines **3**	Conditions[a]	Propargylic amines **4** and **5**	Yield[b] (%)
1		A		73
2		A		75
3		A		71
4		A		65
5		B		94
6		B		95
7		C		63

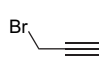
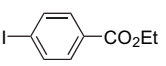
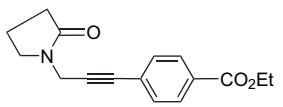
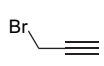
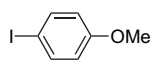
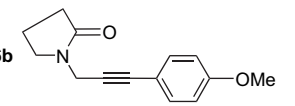
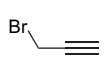
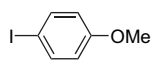
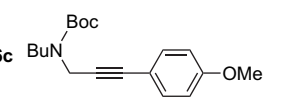
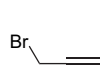
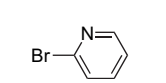
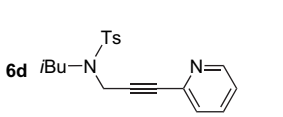
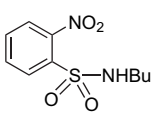
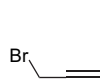
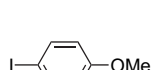
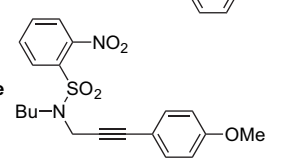
[a] Conditions A: LiBr (3 equiv), MeCN, 65 °C, 14 h; conditions B: HCl/MeOH 4 N, 20 °C, 1.5 h; conditions C: hydrazine hydrate (4 equiv), EtOH, 70 °C.
[b] Isolated yield based on starting material **3**.

primary propargylic amines, two conditions were examined. Thus, starting from phthalylpropargylamine **3e**, the use of hydrazine hydrate in EtOH (condition C)[23] provided **5c** in 63% yield (entry 7) whereas, the corresponding hydrochloride derivative **5a** was obtained in almost quantitative yield when the reaction was carried out from **3a** under acidic conditions (HCl/MeOH, condition B, entry 5).[25] In a similar way, analogue **5b** could be synthesized from **3b** (entry 6). It should be noted that **5a** and **5b** are sensitive compounds and should be stored under nitrogen at −15 °C in order to limit their decomposition.

2.3. Access to propargylic amides and related compounds

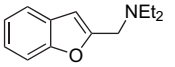
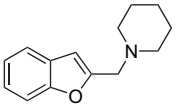
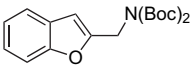
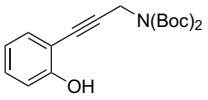
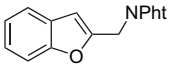
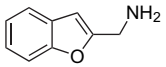
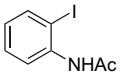
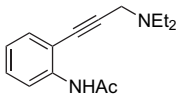
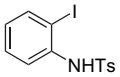
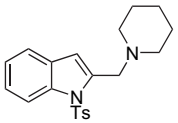
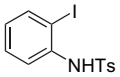
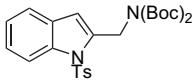
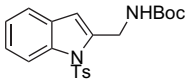
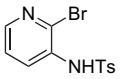
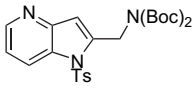
The high efficiency of this three-component coupling reaction prompted us to extend this methodology to amides, sulfonamides, and carbamates. In this case, the reaction

Table 4. Three-component coupling of sodium salts of amides, sulfonamides or carbamates formed in situ with propargyl bromide **1a**, aryl or heteroaryl halides under palladium–copper catalysis: synthesis of propargylic amides and related compounds **6**

Entry	'NH'	Propargylic halide **1**	ArX	Propargylic amine **6**	Yield[a] (%)
1		**1a** 		**6a** 	81
2		**1a** 		**6b** 	82
3		**1a** 		**6c** 	48
4		**1a** 		**6d** 	70
5		**1a** 		**6e** 	68

[a] Isolated yield based on ArX.

Table 5. Three-component coupling of propargyl bromide **1a**, secondary amine or potassium salt and *ortho*-substituted aryl halides under palladium–copper catalysis: synthesis of benzo[*b*]furan and indole derivatives **7** and **8**

Entry	ArX	Amine	Product (yield)[a]		Deprotected product (yield)[b]
1		Et_2NH	 **7a** (75%)	—	—
2		Piperidine	 **7b** (62%)	—	—
3		$K(NBoc)_2$	 **7c** (20%)	 **2r** (71%)	—
4		KNPht	 **7d** (66%)	—	 **8d** (77%)[c]
5		Piperidine	—	 **2s** (92%)	—
6		Piperidine	 **7e** (97%)	—	—
7		$K(NBoc)_2$	 **7f** (93%)	—	 **8f** (89%)[d]
8		$K(NBoc)_2$	 **7g** (80%)	—	—

[a] Isolated yield based on ArX.
[b] Isolated yield based on compounds **7**.
[c] The deprotection of the amino function of **7d** was performed according to conditions C (4 equiv of hydrazine hydrate, EtOH, 70 °C).
[d] The deprotection of the amino function of **7f** was performed according to conditions A (3 equiv of LiBr, MeCN, 65 °C).

requires in a preliminary stage the deprotonation of the nitrogen atom. The results are summarized in Table 4. Typically, the protocol implied treatment of amide, sulfonamide or carbamate by NaH in DMF for 30 min at room temperature followed by the addition of propargyl bromide **1a** (1.2 equiv) and subsequent reaction with aryl halide (1 equiv) in the presence of triethylamine, $PdCl_2(PPh_3)_2$ (5 mol %), and CuI (10 mol%). Firstly, we evaluated this methodology on cyclic amide such as pyrrolidin-2-one.[26] Thus under the protocol described above, this domino three-component coupling reaction provides efficiently the corresponding propargylic amides **6a** and **6b**; in addition the yields (81–82%, entries 1 and 2, Table 4) are independent of the electronic effect of substituents. Replacing the cyclic amide by a carbamate also provided the coupling product **6c**, although in a much lower yield (entry 3). Finally, the coupling process with sulfonamides was carried out in combination with 2-bromopyridine and 4-iodoanisole. As expected, this three-component one-pot process proceeded well and resulted in the formation of the corresponding propargylic sulfonamides **6d** and **6e** in 70 and 68% yields, respectively (entries 4 and 5). Altogether, these results demonstrated the efficiency of this three-component coupling reaction based on nitrogen propargylation/Sonogashira coupling to provide a broad variety of aryl propargylic amines and related amides, sulfonamide or carbamate derivatives.

2.4. Access to heterocycles

Being given the high flexibility of this catalytic domino three-component reactions, we expected that the newly developed procedure would serve as an extremely useful and quick synthetic route to obtain functionalized 2-(aminomethyl)benzo[*b*]furan or indole derivatives **7**. These classes of substituted heterocyclic compounds[27] offer a high degree of structural diversity and have proven to be broadly useful as biologically active compounds, including calindol.[15b] In this context, we were interested to investigate the construction of polycyclic furan and indole skeletons[28] by a tandem nitrogen propargylation/Sonogashira-cyclization sequence.

Starting from 2-iodophenol and secondary dialkylamine, the reagents and catalysts are mixed together and experimental conditions are set up in such a way to promote the reaction cascade. With diethylamine or piperidine, the cyclized benzofuran derivatives **7a** and **7b** were obtained in 75 and 62% yields, respectively (Table 5, entries 1 and 2). To obtain unprotected (aminomethyl)benzo[*b*]furan **8d**, this domino coupling–cyclization process was examined in the presence of potassium salts. Thus, the use of potassium di-*tert*-butyliminodicarbonate results, however, in partial cyclization of the coupling intermediate **2r** presumably for steric hindrance considerations and benzofuran derivative **7c** was isolated

in a low yield (20%, entry 3). Replacing potassium di-*tert*-butyliminodicarbonate by potassium phthalimide allows the cyclization step to occur in a highly effective way to provide the cyclized product **7d** in good overall yield (66%, entry 4). Further deprotection of the amino function of **7d** with hydrazine hydrate according to conditions C (cf.: Table 3) afforded the corresponding primary amine **8d** in 77% yield.

Based on this synthetic protocol, the coupling of 2-iodoacetalinide in the presence of piperidine and propargyl bromide **1a** provided the sp^2–sp coupling product **2s** in a quantitative yield (entry 5). No indole was formed, suggesting that the organopalladium intermediate is not reactive enough to cyclize to the indole. To activate the intermediate, we introduced a tolylsulfonyl group onto the aniline nitrogen.[28b] Thus, performing this domino coupling–cyclization process with *o*-iodo-*N*-tosylanilide in the presence of piperidine yielded the indole derivative **7e** very efficiently (entry 6). Interestingly, as well as piperidine, potassium di-*tert*-butyliminodicarbonate was also a good reactant in this assembling process and provided with *o*-iodo-*N*-tosylanilide and the parent bromopyridyl derivative the corresponding cyclized indoles **7f** and **7g** in 93 and 80% yields, respectively (entries 7 and 8). In both cases, the assembling process required heating at 100 °C for completion. Finally, subsequent selective deprotection of **7f** using Hernandez's procedure (LiBr/MeCN, condition A) afforded efficiently the indole **8f**, which could serve as efficient building-block for further N-functionalization (entry 7).

In conclusion we successfully developed an expeditious new three-component assembling of amines, organic halides, and propargyl halides for the synthesis of functionalized propargylic amines (including *N*-protected propargylic amines), amides, sulfonamides, carbamates in high yields. The procedure can be extended to the preparation of indole and benzofuran derivatives. Variation is allowed in each of the three-component, thus making a wide range of accessible products. This process is not only of interest for combinatorial synthesis of propargylic amines and heterocycles, but in many cases, also offers considerable synthetic advantages in term of yield, selectivity, and simplicity of the reaction procedure.

3. Experimental

3.1. Materials

All glasswares were oven-dried at 140 °C. THF was distilled from sodium–benzophenone ketyl and DMF from calcium hydride and usual solvents were purchased from SDS (Paris, France).

3.2. Instrumentation

The compounds were all identified by usual physical methods, i.e., ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ with a Bruker Avance 300. ^{1}H chemical shifts are reported in parts per million from the peak of residual chloroform (7.27 ppm). ^{13}C chemical shifts are reported in parts per million from the central peak of deuteriochloroform (77.14). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm^{-1}). Elemental analyses were performed with a Perkin–Elmer 240 analyser. Analytical TLC were performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Melting points (mp) were recorded on a Büchi B-450 apparatus and were uncorrected.

3.3. Typical procedure for the three-component formation of tertiary propargylic amines 2

Under an inert atmosphere, propargyl bromide (1.2 equiv) purchased from Aldrich was slowly added, at 0 °C, to a solution containing aryl iodide (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol %) and secondary amine (used as a solvent). The reaction mixture was stirred at room temperature (or heated at 80 °C when using an aryl bromide) and monitored by TLC until complete consumption of starting materials then concentrated in vacuo. Purification by chromatography on silica gel afforded pure propargylic amine **2**.

3.3.1. Compound 2a. Yield: 92%. IR (neat) ν_{max}/cm^{-1}: 2933, 1488, 1442; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.25 (m, 5H), 3.42 (s, 2H), 2.54 (t, J=4.8 Hz, 4H), 1.80–1.55 (m, 4H), 1.55–1.30 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 130.7 (2C), 127.2 (2C), 126.8, 122.5, 84.2, 84.1, 52.4 (2C), 47.5, 25.1 (2C), 23.1; MS (IE) *m*/*z* 199 ([M]$^+$ 14%), 115 (100%). Anal. Calcd for **2a** ($C_{14}H_{17}N$): C, 84.37; H, 8.60; N, 7.03. Found: C, 83.96; H, 8.79; N, 6.92.

3.3.2. Compound 2b. Yield: 83%. R_f (AcOEt)=0.32; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34 (s, 4H), 6.79 (br s, 1H), 3.78 (t, J=4.6 Hz, 4H), 3.49 (s, 2H), 2.64 (t, J=4.6 Hz, 4H), 1.52 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.4, 138.5, 132.0 (2C), 117.8 (2C), 116.6, 85.2, 82.6, 80.0, 66.4 (2C), 52.0 (2C), 47.7, 28.0 (3C). Anal. Calcd for **2b** ($C_{18}H_{24}N_2O_3$): C, 68.33; H, 7.65; N, 8.85. Found: C, 68.02; H, 7.79; N, 8.91.

3.3.3. Compound 2c. Yield: 85%. R_f (cyclohexane/AcOEt 1:1)=0.27; IR (neat) ν_{max}/cm^{-1}: 2971, 2227, 1604; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55–7.41 (m, 4H), 3.60 (s, 2H), 2.56 (q, J=7.2 Hz, 4H), 1.06 (t, J=7.2 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 132.1 (2C), 131.8 (2C), 128.2, 118.3, 111.2, 89.6, 83.4, 47.2 (2C), 41.4, 12.4 (2C); MS (IE) *m*/*z* 213 ([M+H]$^+$ 100%). Anal. Calcd for **2c** ($C_{14}H_{16}N_2$): C, 79.21; H, 7.60; N, 13.20. Found: C, 78.92; H, 7.82; N, 13.31.

3.3.4. Compound 2d. Yield: 94%. R_f (cyclohexane/AcOEt 1:1)=0.23; IR (neat) ν_{max}/cm^{-1}: 2971, 1593, 1516, 1339, 852; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.14 (d, J=8.5 Hz, 2H), 7.53 (d, J=8.5 Hz, 2H), 3.66 (s, 2H), 2.61 (q, J=7.1 Hz, 4H), 1.10 (t, J=7.1 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.5, 132.0 (2C), 129.9, 123.1 (2C), 90.5, 83.0, 47.0 (2C), 41.3, 12.2 (2C); MS (IE) *m*/*z* 232 ([M]$^+$ 14%), 217 (100%), 160 (47%). Anal. Calcd for **2d** ($C_{13}H_{16}N_2O_2$): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.01; H, 7.19; N, 11.92.

3.3.5. Compound 2e. Yield: 69%. R_f (cyclohexane/AcOEt 6:4)=0.17; IR (neat) ν_{max}/cm^{-1}: 2968, 1593, 1516, 1338,

852; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.11 (d, J=8.7 Hz, 2H), 7.48 (d, J=8.7 Hz, 2H), 3.68 (s, 2H), 3.25 (hept, J=6.6 Hz, 2H), 1.10 (d, J=6.6 Hz, 12H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.6, 131.9 (2C), 130.6, 123.1 (2C), 95.3, 81.7, 48.6 (2C), 34.8, 20.5 (4C); MS (IE) m/z 260 ([M]$^+$ 4%), 245 (100%). Anal. Calcd for **2e** ($C_{15}H_{20}N_2O_2$): C, 69.20; H, 7.74; N, 10.76. Found: C, 68.95; H, 7.95; N, 10.61.

3.3.6. Compound 2f. Yield: 82%. R_f (Et_2O)=0.5; IR (neat): 2971, 2935, 1727, 1453, 1133, 833 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (dd, J=7.7, 1.4 Hz, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.32 (td, J=7.5, 1.3 Hz, 1H), 7.22 (td, J=7.6, 1.3 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 3.46 (s, 2H), 2.55–2.51 (m, 4H), 1.59–1.52 (m, 4H), 1.37 (m, 2H), 1.29 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 134.2, 132.3, 131.3, 129.9, 127.5, 123.5, 90.3, 83.7, 60.9, 53.3 (2C), 48.6, 25.9 (2C), 23.8, 14.2; MS m/z (ES$^+$) 272.0 [M+H]$^+$. Anal. Calcd for **2f** ($C_{17}H_{21}NO_2$): C, 75.25; H, 7.80; N, 5.16. Found: C, 75.49; H, 8.01; N, 5.23.

3.3.7. Compound 2g. Yield: 93%. R_f (cyclohexane/AcOEt 1:1)=0.2; IR (neat) ν_{max}/cm^{-1}: 2961, 1714, 1606, 1268; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 (d, J=8.5 Hz, 2H), 7.37 (d, J=8.5 Hz, 2H), 4.25 (q, J=7.1 Hz, 2H), 3.64 (t, J=4.7 Hz, 4H), 3.40 (s, 2H), 2.51 (t, J=4.7 Hz, 4H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.5, 131.2 (2C), 129.6, 129.1 (2C), 127.2, 87.0, 84.6, 66.5 (2C), 60.7, 52.1(2C), 47.7, 14.0; MS (IE) m/z 274 ([M+H]$^+$ 100%), 296 [M+Na]$^+$. Anal. Calcd for **2g** ($C_{16}H_{19}NO_3$): C, 70.13; H, 7.01; N, 5.12. Found: C, 70.05; H, 7.41; N, 5.60.

3.3.8. Compound 2h. Yield: 86%. R_f (cyclohexane/AcOEt 1:1)=0.18; mp (yellow solid)=89–90 °C; IR (neat) ν_{max}/cm^{-1}: 2927, 2828, 1592, 1511, 1109; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.13 (d, J=8.8 Hz, 2H), 7.53 (d, J=8.8 Hz, 2H), 3.73 (t, J=4.7 Hz, 4H), 3.51 (s, 2H), 2.60 (t, J=4.7 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 147.0, 132.3 (2C), 129.8, 123.4 (2C), 89.9, 66.7 (2C), 52.4 (2C), 47.9; MS (IE) m/z 247 ([M+H]$^+$ 100%). Anal. Calcd for **2h** ($C_{13}H_{14}N_2O_3$): C, 63.40; H, 5.73; N, 11.38. Found: C, 63.09; H, 5.82; N, 11.71.

3.3.9. Compound 2i. Yield: 98%. R_f (MeOH/AcOEt 2:8)=0.55; mp (yellow solid)=110–114 °C; IR (neat) ν_{max}/cm^{-1}: 2925, 2824, 1504, 1460; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34 (s, 4H), 3.75 (t, J=4.8 Hz, 8H), 3.49 (s, 4H), 2.62 (t, J=4.8 Hz, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 131.5 (4C), 122.7 (2C), 85.8 (2C), 85.1 (2C), 66.8 (4C), 52.4 (4C), 48.0 (2C); MS (IE) m/z 325 ([M+H]$^+$ 100%). Anal. Calcd for **2i** ($C_{20}H_{24}N_2O_2$): C, 74.04; H, 7.46; N, 8.64. Found: C, 73.82; H, 7.72; N, 8.75.

3.3.10. Compound 2j. Yield: 62%. R_f (MeOH/AcOEt 2:8)=0.22; IR (neat) ν_{max}/cm^{-1}: 2854, 2812, 1581, 1112; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36 (s, 3H), 3.70 (t, J=4.7 Hz, 12H), 3.43 (s, 6H), 2.56 (t, J=4.7 Hz, 12H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.1 (3C), 123.4 (3C), 85.3 (3C), 83.8 (3C), 66.7 (6C), 52.2 (6C), 47.8 (3C); MS (IE) m/z 448 ([M+H]$^+$ 100%). Anal. Calcd for **2j** ($C_{27}H_{33}N_3O_3$): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.22; H, 7.61; N, 9.55.

3.3.11. Compound 2k. Yield: 74%. R_f (MeOH/AcOEt 2:8)=0.40; IR (neat) ν_{max}/cm^{-1}: 2970, 1582, 1462, 1427, 778; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.53 (br s, 1H), 7.58 (t, J=7.7 Hz, 1H), 7.36 (d, J=7.4 Hz, 1H), 7.17 (br s, 1H), 3.64 (s, 2H), 2.61 (q, J=7.1 Hz, 4H), 1.07 (t, J=7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.7, 143.3, 135.9, 127.1, 122.5, 84.9, 84.6, 47.3 (2C), 41.2, 12.6 (2C); MS (IE) m/z 189 ([M+H]$^+$ 100%), 211 ([M+Na]$^+$ 19%). Anal. Calcd for **2k** ($C_{12}H_{16}N_2$): C, 76.55; H, 8.57; N, 14.88. Found: C, 76.19; H, 8.61; N, 14.95.

3.3.12. Compound 2l. Yield: 78%. R_f (Et_2O)=0.27; IR (neat): 2932, 2806, 1344, 1106, 993 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81 (d, J=2.0 Hz, 1H), 8.40 (d, J=1.8 Hz, 1H), 7.98 (d, J=8.4 Hz, 1H), 7.66 (d, J=8.1 Hz, 1H), 7.60 (dt, J=8.4, 1.4 Hz, 1H), 7.44 (td, J=8.0, 1.0 Hz, 1H), 3.45 (s, 2H); 2.54–2.50 (m, 4H), 1.59–1.46 (m, 4H), 1.38–1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.3, 146.7, 138.3, 133.1, 129.8, 129.3, 127.4, 127.1, 117.4, 88.7, 82.2, 53.5 (2C), 48.5, 25.9 (2C), 23.8; MS m/z (ES$^+$) 251.0 [M+H]$^+$.

3.3.13. Compound 2m. Yield: 79%. R_f (Et_2O)=0.41; IR (neat): 2934, 1726, 1484, 1249, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, J=2.1 Hz, 1H), 7.56 (dd, J=8.3, 2.3 Hz, 1H), 7.17 (d, J=8.7 Hz, 1H), 3.55 (s, 2H), 2.50 (q, J=7.2 Hz, 4H), 1.02 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.2, 150.2, 141.0, 123.7, 119.3, 89.5, 80.3, 47.3 (2C), 41.5, 12.5 (2C); MS m/z (ES$^+$) 223.0 [M+H]$^+$. Anal. Calcd for **2m** ($C_{12}H_{15}ClN_2$): C, 64.71; H, 6.79; N, 12.58. Found: C, 64.41; H, 6.93; N, 12.75.

3.3.14. Compound 2n. Yield: 87%. R_f (CH_2Cl_2)=0.5; IR (neat): 2934, 2796, 1489, 1106, 781 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.15 (m, 5H), 6.10 (d, J=16.0 Hz, 1H), 5.99 (d, J=16.0 Hz, 1H), 3.32 (s, 2H), 3.44–3.39 (m, 4H), 1.56–1.50 (m, 4H), 1.37–1.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.5 (2C), 128.5, 128.3 (2C), 122.9, 120.7, 120.5, 94.1, 91.1, 87.8, 83.5, 53.5 (2C), 48.6, 25.9 (2C), 23.9; MS m/z (ES$^+$) 250.0 [M+H]$^+$. Anal. Calcd for **2n** ($C_{18}H_{19}N$): C, 86.70; H, 7.68; N, 5.62. Found: C, 86.18; H, 7.91; N, 5.85.

3.3.15. Compound 2o. Under an inert atmosphere, propargyl bromide (1.0 equiv) purchased from Aldrich was slowly added, at 0 °C, to a solution containing CuI (10 mol %), dichloroethylene (*E*/*Z*=1:1, 10 equiv), piperidine (4 equiv) and $PdCl_2(PPh_3)_2$ (5 mol %) in Et_2O. The reaction mixture was stirred at room temperature for 4 h and then concentrated in vacuo. Purification by chromatography on silica gel afforded pure propargylic amine **2o**. Yield: 63% (mixture *E*/*Z*=9:1). R_f neutral alumina (cyclohexane/CH_2Cl_2 2:8)=0.30. *E*-Isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.50 (d, J=13.6 Hz, 1H), 5.94 (td, J=13.6, 2.2 Hz, 1H), 3.34 (d, J=2.2 Hz, 2H), 2.47 (t, J=5.4 Hz, 4H), 1.67–1.41 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 129.7, 113.5, 88.0, 79.7, 53.3 (2C), 48.2, 25.7, 23.7 (2C). *Z*-Isomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.34 (d, J=7.4 Hz, 1H), 5.88 (td, J=7.4, 1.8 Hz, 1H), 3.46 (d, J=1.8 Hz, 2H), 2.54 (t, J=5.2 Hz, 4H), 1.67–1.41 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 127.6, 111.8, 93.7, 78.8, 53.0 (2C), 48.2, 25.7, 23.7 (2C); MS (IE) m/z 184 ([M]$^+$ 100%).

3.3.16. Compound 2p. Yield: 74%. R_f (cyclohexane/AcOEt 9:1)=0.27; IR (neat) ν_{max}/cm^{-1}: 2931, 1726, 1605; ^1H NMR (200 MHz, $CDCl_3$): δ 7.94 (d, J=8.0 Hz, 2H), 7.44 (d, J=8.0 Hz, 2H), 3.88 (s, 3H), 3.67 (t, J=7.3 Hz, 1H), 2.80–2.35 (m, 4H), 1.70–1.30 (m, 8H), 1.08 (t, J=7.2 Hz, 6H), 0.89 (t, J=6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.4, 131.5 (2C), 129.3, 129.0 (2C), 128.4, 92.7, 84.0, 53.7, 52.0, 44.9 (2C), 34.0, 31.5, 26.4, 22.5, 13.9, 13.7 (2C); MS (IE) m/z 316 ([M+H]$^+$ 100%). Anal. Calcd for **2p** ($C_{20}H_{29}NO_2$): C, 76.15; H, 9.27; N, 4.44. Found: C, 76.02; H, 9.62; N, 4.65.

3.3.17. Compound 2q. Yield: 89%. R_f (cyclohexane/AcOEt 9:1)=0.31; ^1H NMR (200 MHz, $CDCl_3$): δ 7.60–7.45 (m, 4H), 3.49 (t, J=7.4 Hz, 1H), 2.58 (m, 2H), 2.40 (m, 2H), 1.80–1.10 (m, 14H), 0.89 (t, J=6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 132.2 (2C), 131.9 (2C), 128.5, 118.5, 111.1, 93.5, 84.3, 58.6 (2C), 50.6, 33.1, 31.5, 26.4, 26.1, 24.5 (2C), 22.5, 14.0; MS (IE) m/z 295 ([M+H]$^+$ 100%). Anal. Calcd for **2q** ($C_{20}H_{26}N_2$): C, 81.59; H, 9.51; N, 8.90. Found: C, 81.05; H, 9.72; N, 9.35.

3.3.18. Compound 2r. Yield: 71%. ^1H NMR (200 MHz, $CDCl_3$): δ 7.32 (m, 2H), 6.92 (m, 2H), 4.68 (s, 1H), 4.48 (s, 2H), 1.58 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.9, 151.4 (2C), 131.2, 130.5, 120.0, 114.7, 114.2, 92.8, 83.5, 83.3 (2C), 36.5, 28.1 (6C). Anal. Calcd for **2r** ($C_{19}H_{25}NO_5$): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.28; H, 7.41; N, 4.18.

3.3.19. Compound 2s. Yield: 92%. R_f (Et_2O/MeOH 9:1)=0.32; IR (neat): 3306, 2974, 2828, 1660, 1531, 1448, 1244, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, J=8.2 Hz, 1H), 7.98 (s, 1H), 7.80 (dd, J=7.7, 1.4 Hz, 1H), 7.16 (td, J=8.6, 1.4 Hz, 1H), 6.89 (td, J=7.6, 0.7 Hz, 1H), 3.61 (s, 2H), 2.54 (q, J=7.2 Hz, 4H), 2.02 (s, 3H), 1.02 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 138.9, 131.7, 128.9, 123.1, 119.3, 112.2, 91.5, 80.2, 47.3 (2C), 41.4, 24.52, 12.55 (2C); MS m/z (ES$^+$) 268.0 [M+Na$^+$+H]$^+$. Anal. Calcd for **2s** ($C_{15}H_{20}N_2O$): C, 73.74; H, 8.25; N, 11.47. Found: C, 73.52; H, 8.51; N, 11.55.

3.4. Typical procedure for the three-component formation of di-Boc- and phthalimide-protected propargylic amines 3

To a suspension of potassium phthalimide or potassium di-*tert*-butyliminodicarbonate (2 mmol, 2 equiv) in anhydrous DMF (5 mL) was added propargyl bromide purchased from Aldrich (80 wt % solution in toluene, 2 mmol, 2 equiv). The mixture was stirred at room temperature for 2 h and then added via a cannula to a solution containing $PdCl_2(PPh_3)_2$ (0.05 mmol, 0.05 equiv), CuI (0.10 mmol, 0.1 equiv), and aryl halide (1 mmol, 1 equiv) in NEt_3 (10 mL). The resulting solution was stirred at room temperature (for aryl iodides) or heated at 80 °C (for aryl bromides) until the disappearance of starting material as judged by TLC. Solvents were removed in vacuum and the crude product was purified by silica gel column chromatography to yield the expected adducts **3**.

3.4.1. Compound 3a. The reaction was performed from 2-bromopyridine at 80 °C; yield: 93%. R_f (cyclohexane/EtOAc 7:3)=0.30; mp (white solid)=71–73 °C; IR (neat) ν_{max}/cm^{-1}: 2979, 1725, 1688, 1459, 1142; ^1H NMR (200 MHz, $CDCl_3$): δ 8.53 (d, J=4.9 Hz, 1H), 7.60 (td, J=7.7, 1.8 Hz, 1H), 7.35 (d, J=7.7 Hz, 1H), 7.19 (td, J=4.9, 1.8 Hz, 1H), 4.60 (s, 2H), 1.52 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.6 (2C), 150.0, 143.2, 136.1, 127.2, 122.8, 85.6, 83.1, 81.9 (2C), 36.5, 28.2 (6C); MS (ESI) m/z 333 [M+H]$^+$, 355 [M+Na]$^+$. Anal. Calcd for **3a** ($C_{18}H_{24}N_2O_4$): C, 65.04; H, 7.28; N, 8.43. Found: C, 64.86; H, 7.39; N, 8.25.

3.4.2. Compound 3b. The reaction was performed from 3-bromopyridine at 80 °C; yield: 74%. R_f (cyclohexane/EtOAc 7:3)=0.30; IR (neat) ν_{max}/cm^{-1}: 2980, 1790, 1749, 1391, 1367, 1258, 1144; ^1H NMR (300 MHz, $CDCl_3$): δ 8.60 (br s, 1H), 8.47 (dd, J=4.9, 1.8 Hz, 1H), 7.65 (dt, J=7.9, 1.8 Hz, 1H), 7.19 (ddd, J=7.9, 4.9, 0.9 Hz, 1H), 4.67 (s, 2H), 1.65 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.5, 151.7 (2C), 148.7, 138.7, 123.0, 120.1, 88.9, 83.2 (2C), 79.1, 36.6, 28.1 (6C); MS (ESI) m/z 333 [M+H]$^+$. Anal. Calcd for **3b** ($C_{18}H_{24}N_2O_4$): C, 65.04; H, 7.28; N, 8.43. Found: C, 64.86; H, 7.40; N, 8.20.

3.4.3. Compound 3c. The reaction was performed from 4-bromopyridine at 80 °C; yield: 82%. R_f (cyclohexane/EtOAc 7:3)=0.24; ^1H NMR (200 MHz, $CDCl_3$): δ 8.55 (br s, 2H), 7.25 (br s, 2H), 4.60 (s, 2H), 1.55 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.6 (2C), 149.8 (2C), 131.2, 128.6 (2C), 80.4, 83.3, 80.0 (2C), 36.5, 28.2 (6C); MS (ESI) m/z 333 [M+H]$^+$. Anal. Calcd for **3c** ($C_{18}H_{24}N_2O_4\cdot 0.3H_2O$): C, 64.00; H, 7.36; N, 8.29. Found: C, 64.26; H, 7.73; N, 7.87.

3.4.4. Compound 3d. The reaction was performed from 2,6-dibromopyridine at 80 °C; yield: 53%. R_f (cyclohexane/EtOAc 7:3)=0.30; IR (neat) ν_{max}/cm^{-1}: 2975, 2935, 1740, 1720, 1700, 1365, 1145, 1110; ^1H NMR (200 MHz, $CDCl_3$): δ 7.52 (dd, J=7.3, 8.3 Hz, 1H), 7.23 (d, J=7.8 Hz, 2H), 4.55 (s, 4H), 1.46 (s, 36H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.5 (4C), 143.3 (2C), 136.3, 126.1 (2C), 86.1 (2C), 83.1 (4C), 81.4 (2C), 36.4 (2C), 28.1 (12C); MS (ESI) m/z 586 [M+H]$^+$. Anal. Calcd for **3d** ($C_{31}H_{43}N_3O_8.0.75\ H_2O$): C, 62.13; H, 7.50; N, 7.01. Found: C, 62.34; H, 7.83; N, 6.66.

3.4.5. Compound 3e. The reaction was performed from 2-bromopyridine at 80 °C; yield: 82%. R_f (cyclohexane/EtOAc 7:3)=0.12; mp (beige solid)=127–129 °C; IR (neat) ν_{max}/cm^{-1}: 3044, 1774, 1708, 1582, 1560, 1465, 1411, 1387, 1269, 781; ^1H NMR (200 MHz, $CDCl_3$): δ 8.50 (d, J=4.9 Hz, 1H), 7.87–7.69 (m, 4H), 7.59 (td, J=7.7, 1.8 Hz, 1H), 7.37 (d, J=7.7 Hz, 1H), 7.18 (td, J=4.9, 1.8 Hz, 1H), 4.68 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.0 (2C), 150.0, 136.2, 134.3 (2C), 132.0 (2C), 127.3, 123.6 (2C), 123.2, 85.2, 82.9, 26.9; MS (ESI) m/z 263 [M+H]$^+$. Anal. Calcd for **3e** ($C_{16}H_{10}N_2O_2\cdot 0.4H_2O$): C, 71.31; H, 4.05; N, 10.40. Found: C, 71.50; H, 3.98; N, 9.66.

3.4.6. Compound 3f. The reaction was performed from 3-bromopyridine at 80 °C; yield 50%. R_f (cyclohexane/EtOAc 1:1)=0.12; mp (beige solid)=175–177 °C; ^1H NMR (200 MHz, $CDCl_3$): δ 8.64 (br s, 1H), 8.50 (br s, 1H), 7.94 (m, 2H), 7.74 (m, 3H), 7.20 (dd, J=4.9, 7.6 Hz, 1H), 4.69 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.5 (2C),

152.0, 148.3, 138.3, 133.7 (2C), 131.5, 123.0 (2C), 122.3, 85.6, 79.3, 27.2; MS (ESI) *m/z* 263 $[M+H]^+$. Anal. Calcd for **3f** ($C_{16}H_{10}N_2O_2 \cdot 0.4H_2O$): C, 71.31; H, 4.05; N, 10.40. Found: C, 71.25; H, 3.94; N, 9.81.

3.5. Typical procedure for the three-component formation of propargylic amides, sulfonamides, and Boc-protected amines 6

To a solution of amide, sulfonamide or Boc-protected amine (1.20 mmol, 1.20 equiv) in anhydrous DMF (1 mL per mmol of amide and Boc-protected amine, 2 mL per mmol of sulfonamide) was added NaH (60% in mineral oil, 1.45 mmol, 1.45 equiv) and the mixture was stirred for 0.5 h at room temperature. Propargyl bromide (80 wt % solution in toluene, 1.55 mmol, 1.55 equiv) was then introduced dropwise. The resulting mixture was stirred at room temperature for 2 h and then added via a cannula to a solution containing $PdCl_2(PPh_3)_2$ (0.05 mmol, 0.05 equiv), CuI (0.10 mmol, 0.10 equiv), and aryl halide (1 mmol, 1 equiv) in NEt_3 (10 mL). The resulting solution was stirred at room temperature (for aryl iodides) or heated at 80 °C (for aryl bromides) until the disappearance of starting material as judged by TLC. Solvents were removed in vacuum and the crude product was purified by silica gel column chromatography to yield the expected adducts.

3.5.1. Compound 6a. The reaction was performed from 4-iodobenzoic acid ethyl ester at room temperature; yield: 81%. Mp (white solid)=87–89 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.94 (d, J=8.5 Hz, 2H), 7.43 (d, J=8.5 Hz, 2H), 4.33 (m, 4H), 3.52 (t, J=7.1 Hz, 2H), 2.39 (t, J=8.0 Hz, 2H), 2.03 (m, 2H), 1.35 (t, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.6, 165.6, 131.7 (2C), 130.2, 129.4 (2C), 127.1, 86.3, 83.3, 61.8, 46.6, 32.8, 30.7, 17.7, 14.3; MS (ESI) *m/z* 294 $[M+Na]^+$. Anal. Calcd for **6a** ($C_{16}H_{17}NO_3$): C, 70.83; H, 6.32; N, 5.16. Found: C, 69.95; H, 6.69; N, 4.86.

3.5.2. Compound 6b. The reaction was performed from 4-iodoanisole at room temperature; yield: 82%. R_f (cyclohexane/AcOEt 2:8)=0.24; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33 (d, J=8.8 Hz, 2H), 6.80 (d, J=8.8, Hz, 2H), 4.28 (s, 2H), 3.77 (s, 3H), 3.52 (t, J=7.0 Hz, 2H), 2.39 (t, J=8.0 Hz, 2H), 2.03 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.4, 159.8, 133.3 (2C), 114.7 (2C), 114.0, 83.9, 81.8, 55.3, 46.5, 32.8, 30.8, 29.7, 17.8; MS (ESI) *m/z* 252 $[M+Na]^+$. Anal. Calcd for **6b** ($C_{14}H_{15}NO_2$): C, 73.34; H, 6.59; N, 6.11. Found: C, 71.84; H, 6.86; N, 5.70.

3.5.3. Compound 6c. The reaction was performed from 4-iodoanisole at room temperature; yield: 48%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33 (d, J=8.8 Hz, 2H), 6.80 (d, J=8.8 Hz, 2H), 4.22 (s, 2H), 3.77 (s, 3H), 3.35 (t, J=7.3 Hz, 2H), 1.58 (m, 2H), 1.47 (s, 9H), 1.32 (m, 2H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.6, 155.2, 133.1 (2C), 115.3, 114.0 (2C), 84.0, 83.0, 79.8, 55.3, 46.2, 36.9, 30.3, 28.5 (3C), 20.1, 14.0; MS (ESI) *m/z* 340 $[M+Na]^+$. Anal. Calcd for **6c** ($C_{19}H_{27}NO_3$): C, 71.89; H, 8.57; N, 4.41. Found: C, 69.56; H, 8.26; N, 4.15.

3.5.4. Compound 6d. The reaction was performed from 2-bromopyridine at 80 °C; yield: 70%. R_f (cyclohexane/AcOEt 7:3)=0.27; mp (beige solid)=103–105 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.54 (d, J=4.3 Hz, 1H), 7.81 (d, J=8.3 Hz, 2H), 7.60 (dt, J=7.7, 1.7 Hz, 1H), 7.24 (m, 3H), 6.99 (d, J=7.8 Hz, 1H), 4.38 (s, 2H), 3.08 (d, J=7.5 Hz, 2H), 2.34 (s, 3H), 1.99 (m, 1H), 1.00 (d, J=6.6 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.2, 143.3, 142.4, 136.1, 135.9, 129.5 (2C), 127.8 (2C), 127.0, 123.0, 84.9, 82.1, 54.1, 37.4, 26.4, 21.4, 20.0 (2C); MS (ESI) *m/z* 365 $[M+Na]^+$, 343 $[M+H]^+$. Anal. Calcd for **6d** ($C_{19}H_{22}N_2O_2S$): C, 66.64; H, 6.48; N, 8.18. Found: C, 66.41; H, 6.35; N, 7.99.

3.5.5. Compound 6e. Yield: 68%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.08 (m, 1H), 7.62 (m, 3H), 7.15 (d, J=8.8 Hz, 2H), 6.78 (d, J=8.8 Hz, 2H), 4.39 (s, 2H), 3.79 (s, 3H), 3.46 (t, J=7.4 Hz, 2H), 1.61 (m, 2H), 1.37 (m, 2H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.9, 148.5, 131.2 (2C), 133.5, 133.1, 131.5, 130.9, 124.1, 114.0 (2C), 85.7, 80.7, 55.4, 46.8, 37.3, 29.7, 19.8, 13.6; MS (ESI) *m/z* 403 $[M+H]^+$. Anal. Calcd for **6e** ($C_{20}H_{22}N_2O_5S$): C, 56.69; H, 5.51; N, 6.96. Found: C, 56.41; H, 5.75; N, 7.19.

3.6. Typical procedure for the three-component formation of 2-(aminomethyl)benzo[*b*]furans and indoles 7

3.6.1. From secondary amine. Under an inert atmosphere, propargyl bromide (1.2 equiv) purchased from Aldrich was slowly added, at 0 °C, to a solution containing *o*-substituted aryl iodide (1 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %) and secondary amine (used as a solvent). The reaction mixture was stirred at 50 °C and monitored by TLC until complete consumption of starting materials then concentrated in vacuo. Purification by chromatography on silica gel yielded the expected cyclized products **7a**, **7b**, and **7e**.

3.6.1.1. Compound 7a. Yield: 75%. R_f (cyclohexane/AcOEt 1:1)=0.20; IR (neat) ν_{max}/cm^{-1}: 2970, 2810, 1600; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60–7.50 (m, 2H), 7.30–7.20 (m, 2H), 6.61 (s, 1H), 3.83 (s, 2H), 2.66 (q, J=7.1 Hz, 4H), 1.16 (t, J=7.1 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.8, 155.0, 128.4, 123.6, 122.4, 120.5, 111.1, 104.9, 49.7, 47.0 (2C), 11.8 (2C); MS (ESI) *m/z* 204 $[M+H]^+$. Anal. Calcd for **7a** ($C_{13}H_{17}NO$): C, 76.81; H, 8.43; N, 6.89. Found: C, 76.11; H, 8.71; N, 7.09.

3.6.1.2. Compound 7b. Yield: 62%. R_f (cyclohexane/AcOEt 1:1)=0.30; IR (neat) ν_{max}/cm^{-1}: 2940, 2850, 2800, 1450; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55–7.45 (m, 2H), 7.25–7.15 (m, 2H), 6.55 (s, 1H), 3.64 (s, 2H), 2.47 (t, J=5.3 Hz, 4H), 1.65–1.40 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.0, 154.95, 128.3, 123.6, 122.5, 120.5, 111.2, 105.3, 56.1, 54.3 (2C), 25.7 (2C), 24.0; MS (ESI) *m/z* 216 $[M+H]^+$. Anal. Calcd for **7b** ($C_{14}H_{17}NO$): C, 78.10; H, 7.96; N, 6.51. Found: C, 77.62; H, 8.23; N, 6.89.

3.6.1.3. Compound 7e. Yield: 97%. R_f (cyclohexane/AcOEt 1:1)=0.20; mp (white solid)=119–120 °C; IR (neat) ν_{max}/cm^{-1}: 2937, 2800, 2760, 1450, 1370; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00–7.90 (m, 3H), 7.40–7.30 (m, 1H), 7.20–7.00 (m, 4H), 6.41 (s, 1H), 3.71 (s, 2H), 2.40–2.30 (m, 4H), 2.20 (s, 3H), 1.50–1.30 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.3, 138.5, 137.1, 136.5, 129.3 (2C), 129.0, 127.2 (2C), 134.0, 123.1, 120.4, 114.5, 111.1,

56.2, 54.6 (2C), 25.9 (2C), 24.3, 21.4; MS (ESI) *m/z* 369 $[M+H]^+$. Anal. Calcd for **7e** ($C_{21}H_{24}N_2O_2S$): C, 68.45; H, 6.56; N, 7.60. Found: C, 68.12; H, 6.92; N, 7.29.

3.6.2. From potassium amide. To a suspension of potassium phthalimide or potassium di-*tert*-butyliminodicarbonate (2 mmol, 2 equiv) in anhydrous DMF (5 mL) was added propargyl bromide (80 wt % solution in toluene, 2 mmol, 2 equiv). The mixture was stirred at room temperature for 2 h and then added via a cannula to a solution containing $PdCl_2(PPh_3)_2$ (0.05 mmol, 0.05 equiv), CuI (0.10 mmol, 0.1 equiv), and *o*-substituted aryl halide (1 mmol, 1 equiv) in NEt_3 (10 mL). The resulting solution was stirred at 80 °C until the disappearance of starting material as judged by TLC. Solvents were removed in vacuum and the crude product was purified by silica gel column chromatography to yield the expected adducts **7c**, **7d**, **7f**, and **7g**.

3.6.2.1. Compound 7c. Yield: 20%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58 (m, 1H), 7.49 (m, 1H), 7.29 (m, 2H), 6.64 (s, 1H), 4.99 (s, 2H), 1.58 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.8 (2C), 152.1 (2C), 128.4, 124.0, 122.7, 120.9, 111.2, 103.9, 83.0 (2C), 43.3, 28.1 (6C); MS (ESI) *m/z* 348 $[M+H]^+$. Anal. Calcd for **7c** ($C_{19}H_{25}NO_5$): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.36; H, 7.06; N, 4.15.

3.6.2.2. Compound 7d. Yield: 66%. R_f (cyclohexane/AcOEt 7:3)=0.52; mp (white solid)=155–157 °C; IR (neat) ν_{max}/cm^{-1}: 2990, 1775, 1705, 1390, 950; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J*=5.4, 3.1 Hz, 2H), 7.72 (dd, *J*=5.4, 3.1 Hz, 2H), 7.50 (dd, *J*=7.7, 1.1 Hz, 1H), 7.42 (dd, *J*=8.0, 0.6 Hz, 1H), 7.26–7.20 (m, 1H), 7.18 (dt, *J*=7.5, 1.1, 1H), 6.73 (s, 1H), 5.01 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5 (2C), 155.0, 152.0, 134.2 (2C), 132.1 (2C), 128.2, 124.4, 123.5 (2C), 122.9, 121.1, 111.4, 105.4, 35.0; MS (ESI) *m/z* 332 $[M+Na+MeOH]^+$. Anal. Calcd for **7d** ($C_{17}H_{11}NO_3$): C, 73.64; H, 4.00; N, 5.05. Found: C, 73.49; H, 4.03; N, 5.01.

3.6.2.3. Compound 7f. Yield: 93%. R_f (Et_2O/cyclohexane 3:7)=0.50; IR (neat) ν_{max}/cm^{-1}: 2980, 1790, 1745, 1700, 1475, 1455, 1143, 730; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, *J*=7.9 Hz, 1H), 7.75 (d, *J*=8.3 Hz, 2H), 7.42 (m, 1H), 7.23 (m, 4H), 6.43 (s, 1H), 5.28 (s, 2H,), 2.30 (s, 3H), 1.47 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.1 (2C), 144.9, 138.5, 137.0, 135.6, 129.9 (2C), 129.5, 126.6 (2C), 124.1, 123.5, .120.5, 114.3, 107.3, 82.8 (2C), 45.2, 27.9 (6C), 21.4; MS (ESI) *m/z* 523 $[M+Na]^+$. Anal. Calcd for **7f** ($C_{26}H_{32}N_2O_6S$): C, 62.38; H, 6.44; N, 5.60. Found: C, 62.10; H, 6.60; N, 5.32.

3.6.2.4. Compound 7g. Yield: 80%. R_f (cyclohexane/AcOEt 4:6)=0.35; mp (amber solid)=99–101 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.44 (br s, 1H), 8.28 (d, *J*=8.4 Hz, 1H), 7.71 (d, *J*=8.4 Hz, 2H), 7.20 (m, 3H), 6.59 (s, 1H), 5.26 (s, 2H), 2.31 (s, 3H), 1.44 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.2 (2C), 147.9, 146.3, 146.2, 145.5, 142.7, 135.3, 130.2 (2C), 126.7 (2C), 121.4, 118.9, 108.4, 83.2 (2C), 45.0, 28.0, 21.6 (6C); MS (ESI) *m/z* 502 $[M+H]^+$, 1025 $[2M+Na]^+$. Anal. Calcd for **7g** ($C_{25}H_{31}N_3O_6S$): C, 59.86; H, 6.23; N, 8.38. Found: C, 59.14; H, 6.39; N, 8.22.

3.7. Typical procedure for the deprotection of di-Boc- and phthalyl-protected amines

Conditions A. To a stirred solution of di-Boc-protected compound (1.0 equiv) in anhydrous acetonitrile (2 mL) was added LiBr (3.0 equiv) and the mixture was heated at 65 °C overnight. After cooling at room temperature, the solvent was concentrated in vacuum and the crude product was purified by silica gel column chromatography to yield the mono-Boc-protected adduct.

Conditions B. To a solution of di-Boc-protected compound (1 equiv) in MeOH (15 mL) was added 2 mL of 4.9 N HCl/MeOH solution at 0 °C. The reaction was stirred at room temperature for 3 h. After evaporation of the solvent under vacuum and drying, anhydrous Et_2O (20 mL) was added and the hydrochloride salt precipitated was collected by filtration.

Conditions C. To a stirred solution of phthalylamine (1.0 equiv) in EtOH (35 mL) was added at room temperature hydrazine hydrate (4.0 equiv), and the mixture was heated at reflux for 2 h. After cooling at 0 °C, a gray-white solid precipitated and was collected by filtration then rinsed with ice-cold EtOH (2×25 mL). The filtrate was concentrated in vacuum and the crude product was purified by silica gel column chromatography to yield the expected adducts.

3.7.1. Compound 4a. Prepared from **3a** according to conditions A. Yield: 73%. R_f (CH_2Cl_2/MeOH 98:2)=0.17; mp (beige solid)=83–85 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.51 (d, *J*=4.6 Hz, 1H), 7.59 (dt, *J*=7.7, 1.8 Hz, 1H), 7.36 (d, *J*=7.8 Hz, 1H), 7.18 (ddd, *J*=7.6, 4.9, 1.1 Hz, 1H), 5.00 (br s, 1H), 4.14 (d, *J*=5.6 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.4, 150.0, 143.0, 136.2, 127.1, 123.0, 85.9, 82.5, 80.1, 31.1, 28.4 (3C). Anal. Calcd for **4a** ($C_{13}H_{16}N_2O_2\cdot 0.25H_2O$): C, 65.94; H, 7.04; N, 11.83. Found: C, 66.00; H, 7.00; N, 11.27.

3.7.2. Compound 4b. Prepared from **3b** according to conditions A. Yield: 75%. R_f (cyclohexane/AcOEt 1:1)=0.27; mp (beige solid)=79–81 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.58 (br s, 2H), 7.66 (d, *J*=7.8 Hz, 1H), 7.21 (br s, 1H), 5.08 (br s, 1H), 4.14 (d, *J*=5.6 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.4, 152.4, 148.7, 138.7, 126.6, 118.2, 89.3, 80.2, 79.8, 31.3, 28.5 (3C). Anal. Calcd for **4b** ($C_{13}H_{16}N_2O_2\cdot H_2O$): C, 66.44; H, 7.01; N, 11.92. Found: C, 66.78; H, 6.99; N, 11.34.

3.7.3. Compound 4c. Prepared from **3c** according to conditions A. Yield: 71%; mp (beige solid)=85–87 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.38 (d, *J*=5.7 Hz, 2H), 7.08 (d, *J*=5.9 Hz, 2H), 4.84 (br s, 1H), 3.99 (d, *J*=5.6 Hz, 2H), 1.30 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.4, 149.8 (2C), 131.1, 125.8 (2C), 90.8, 80.6, 80.3, 31.2, 28.5 (3C). Anal. Calcd for **4c** ($C_{13}H_{16}N_2O_2$): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.07; H, 7.27; N, 12.13.

3.7.4. Compound 4d. Prepared from **3d** according to conditions A. Yield: 65%. R_f (cyclohexane/AcOEt 6:4)=0.23; mp (beige solid)=140–142 °C; IR (neat) ν_{max}/cm^{-1}: 3355, 2970, 2930, 1690, 1615, 1440, 1265, 1165, 1135; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.63 (dd, J=7.5, 8.2 Hz, 1H) 7.35 (d, J=7.8 Hz, 2H) 4.80 (br s, 2H) 4.20 (d, J=5.5 Hz, 4H), 1.48 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.1 (2C), 143.1 (2C), 136.5, 126.2 (2C), 86.2 (2C), 82.0 (2C), 80.2 (2C), 31.0 (2C), 28.4 (6C); MS (ESI) m/z 386 $[M+H]^+$. Anal. Calcd for **4d** ($C_{21}H_{27}N_3O_4$): C, 65.44; H, 7.06; N, 10.90. Found: C, 65.48; H, 6.95; N, 10.83.

3.7.5. Compound 5a. Prepared from **3a** according to conditions B. Yield: 94%. R_f (AcOEt/MeOH/$NH_4OH_{aq,20\%}$ 87:10:3)=0.18; IR (neat) ν_{max}/cm^{-1}: 3387, 3082, 1728; ^{1}H NMR (200 MHz, CD_3OD): δ 8.62 (br s, 1H), 7.92 (t, J=7.7 Hz, 1H), 7.64 (m, 1H), 7.51 (m, 1H), 4.09 (s, 2H); ^{13}C NMR (50 MHz, CD_3OD): δ 149.0, 141.3, 140.4, 130.2, 126.5, 85.6, 84.0, 30.5. The compound **5a** is not sufficiently stable to be fully characterized.

3.7.6. Compound 5b. Prepared from **3b** according to conditions B. Yield: 94%. R_f (AcOEt/MeOH/$NH_4OH_{aq,20\%}$ 87:10:3)=0.21; IR (neat) ν_{max}/cm^{-1}: 3380, 3013, 2922, 1609, 1555; ^{1}H NMR (200 MHz, CD_3OD): δ 7.25 (br s, 1H), 7.05 (d, J=5.6 Hz, 1H), 6.90 (d, J=8.0 Hz, 1H), 6.30 (m, 1H), 2.31 (s, 2H); ^{13}C NMR (50 MHz, CD_3OD): δ 151.2, 147.2, 142.3, 139.5, 125.7, 86.8, 77.4, 27.4. The compound **5b** is not sufficiently stable to be fully characterized.

3.7.7. Compound 5c. Prepared from **3e** according to conditions C. Yield: 63%. R_f (AcOEt/MeOH/$NH_4OH_{aq,20\%}$ 88:10:2)=0.18; IR (neat) ν_{max}/cm^{-1}: 3360, 1585, 1560, 1465, 1430, 1380, 1270; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.48 (m, 1H), 7.58 (td, J=7.8, 1.8 Hz, 1H), 7.32 (d, J=7.8 Hz, 1H), 7.14 (m, 1H), 3.60 (s, 2H), 1.60 (br s, 2H); ^{13}C NMR (50 MHz, CD_3OD): δ 149.8, 143.1, 136.0, 126.7, 122.6, 90.4, 81.9, 32.00; MS (ESI) m/z 133 $[M+H]^+$. Anal. Calcd for **5c** ($C_8H_8N_2$): C, 72.70; H, 6.10; N, 21.20. Found: C, 72.52; H, 6.20; N, 21.25.

3.7.8. Compound 8d. Prepared from **7d** according to conditions C. Yield: 77%. R_f (AcOEt/MeOH/$NH_4OH_{aq,20\%}$ 88:10:2)=0.54; IR (neat) ν_{max}/cm^{-1}: 3055, 2917, 1600, 1585, 1475, 1455, 1254, 740; ^{1}H NMR (300 MHz, CD_3OD): δ 7.52 (m, 1H), 7. 45 (m, 1H), 7.21 (m, 2H), 6.64 (m, 1H), 4.85 (s, 2H), 3.93 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ 159.4, 156.4, 132.4, 125.0, 123.8, 122.0, 111.8, 103.7, 39.7; MS (ESI) m/z 148 $[M+H]^+$. Anal. Calcd for **8d** (C_9H_9NO): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.52; H, 6.01; N, 9.62.

3.7.9. Compound 8f. Prepared from **7f** according to conditions A. Yield: 89%. R_f (cyclohexane/AcOEt 7:3)=0.64; IR (neat) ν_{max}/cm^{-1}: 3345, 2978, 2930, 1700, 1600, 1500, 1450, 1365, 1270, 1245, 1225, 1170, 1090, 935; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J=8.4 Hz, 1H), 7.54 (d, J=8.4 Hz, 2H), 7.34 (m, 1H), 7.15 (m, 2H), 6.86 (d, J=8.4 Hz, 2H), 6.51 (s, 1H), 5.42 (br s, 1H), 4.53 (d, J=6.4 Hz, 2H), 2.21 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 145.1, 138.4, 137.1, 135.8, 130.0 (2C), 129.4, 126.4 (2C), 124.7, 123.8, 121.1, 114.6, 111.3, 79.6, 38.7, 28.4 (3C), 21.5; MS (ESI) m/z 401 $[M+H]^+$. Anal. Calcd for **8f** ($C_{21}H_{24}N_2O_4S$): C, 62.98; H, 6.04; N, 6.99. Found: C, 70.01; H, 5.95; N, 7.02.

Acknowledgements

The CNRS is gratefully acknowledged for support of this research and for a doctoral fellowship to N.O. Thanks also to the MNSER for a doctoral fellowship to O.R.

References and notes

1. (a) Shirota, F. N.; DeMaster, E. G.; Nagasawa, H. T. *J. Med. Chem.* **1979**, *22*, 463–464; (b) Yu, P. H.; Davies, B. A.; Boulton, A. A. *J. Med. Chem.* **1992**, *35*, 3705–3713.
2. Connolly, P. J.; Wetter, S. K.; Beers, K. N.; Hamel, S. C.; Chen, R. H. K.; Wachter, M. P.; Ansell, J.; Singer, M. M.; Steber, M.; Ritchie, D. M.; Argentieri, D. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 979–984.
3. (a) Corriu, R. J. P.; Bolin, G.; Moreau, J. J. E. *Tetrahedron Lett.* **1991**, *32*, 4121–4124; (b) Campi, E. M.; Jackson, W. R.; Nilsson, Y. *Tetrahedron Lett.* **1991**, *32*, 1093–1094; (c) Mandai, T.; Ryoden, K.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1991**, *32*, 7683–7686; (d) Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396–1406.
4. Ripin, D. H. B.; Bourassa, D. E.; Brandt, T.; Castaldi, M. J.; Frost, H. N.; Hawkins, J.; Johnson, P. J.; Massett, S. S.; Neumann, K.; Phillips, J.; Raggon, J. W.; Rose, P. R.; Rutherford, J. L.; Sitter, B.; Stewart, A. M., III; Vetelino, M. G.; Wei, L. *Org. Process Res. Dev.* **2005**, *9*, 440–450.
5. Hertner, F. W.; Hsiao, Y.; Eng, K. K.; Rivera, N. R.; Palucki, M.; Tan, L.; Yasuda, N.; Hughes, D. L.; Weissman, S.; Zewge, D.; King, T.; Tschaen, D.; Volante, R. P. *J. Org. Chem.* **2004**, *69*, 8723–8730.
6. (a) Kopka, I. E.; Fataftah, Z.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4616–4622; (b) Imada, Y.; Yuassa, M.; Nakamura, I.; Murahashi, S. I. *J. Org. Chem.* **1994**, *59*, 2282–2284; (c) Czernecki, S.; Valery, J. M. *J. Carbohydr. Chem.* **1990**, *9*, 767–770; (d) Basak, A.; Rudra, K. R. *Tetrahedron Lett.* **2000**, *41*, 7231–7234; (e) Basak, A.; Shain, J. C. *Tetrahedron Lett.* **1998**, *39*, 3029–3030; (f) Glase, S. A.; Akunne, H. C.; Heffner, T. G.; Jaen, J. C.; Mackenzie, R. G.; Meltzer, L. T.; Pudsley, T. A.; Smith, S. J.; Wise, L. D. *J. Med. Chem.* **1996**, *39*, 3179–3187.
7. Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **2001**, *42*, 1655–1656.
8. (a) Fisher, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319–4321; (b) Wie, C.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639; (c) Jiang, B.; Si, Y. G. *Tetrahedron Lett.* **2003**, *44*, 6767–6768; (d) Díez, R.; Badorrey, R.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Eur. J. Org. Chem.* **2007**, 2114–2120.
9. (a) Mladenova, M.; Alami, M.; Linstrumelle, G. *Synth. Commun.* **1995**, *25*, 1401–1410; (b) Bleicher, L. S.; Cosford, N. D. P.; Herbaut, A.; Mc Callum, J. S.; Mc Donald, I. A. *J. Org. Chem.* **1998**, *63*, 1109–1118; (c) Lemhadri, M.; Doucet, H.; Santelli, M. *Synthesis* **2005**, 1359–1367.
10. (a) Tramontini, M. *Synthesis* **1973**, 703–775; (b) Li, C. J.; Wei, C. *Chem. Commun.* **2002**, 268–269; (c) Wie, C.; Li, Z.; Li, C. *J. Org. Lett.* **2003**, *5*, 4473–4475; (d) Wie, C.; Li, C. *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585; (e) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729–731; (f) Lo, V. K.-Y.; Liu, Y.; Wong, M. K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529–1532; (g) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437–2440.
11. Kwatra, M. M.; Simon, D. Z.; Salvador, R. L.; Cooper, P. D. *J. Med. Chem.* **1978**, *21*, 253–257.

12. (a) Olivi, N.; Spruyt, P.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2004**, *45*, 2607–2610; (b) Russo, O.; Alami, M.; Brion, J.-D.; Sicsic, S.; Berque-Bestel, I. *Tetrahedron Lett.* **2004**, *45*, 7069–7072.
13. Youngman, M. A.; Dax, S. L. *J. Comb. Chem.* **2001**, *3*, 469–472.
14. For the multicomponent synthesis of heterocycles, see for instance: (a) Braun, R. U.; Müller, T. J. J. *Synthesis* **2004**, 2391–2406; (b) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297–3300.
15. (a) Wyatt, P. G.; Allen, M. J.; Chilcott, J.; Gardner, C. J.; Livermore, D. G.; Mordaunt, J. E.; Nerozzi, F.; Patel, M.; Perren, M. J.; Weingarten, G. G.; Shabbir, S.; Woollard, P. M.; Zhou, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1405–1411; (b) Kessler, A.; Faure, H.; Petrel, C.; Ruat, M.; Dauban, P.; Dodd, R. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3345–3349; (c) Mustafa, S. M.; Bavadekar, S. A.; Ma, G.; Moore, B. M.; Feller, D. R.; Miller, D. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2758–2760.
16. Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403–6406.
17. Unroe, M. R.; Reinhardt, B. A. *Synthesis* **1987**, 981–985.
18. Alami, M.; Peyrat, J.-F.; Brion, J.-D. *Synthesis* **2000**, 1499–1518.
19. (a) Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1991**, *32*, 6109–6112; (b) Alami, M.; Ferri, F.; Gaslain, Y. *Tetrahedron Lett.* **1996**, *37*, 57–58; (c) Alami, M.; Crousse, B.; Ferri, F. *J. Organomet. Chem.* **2001**, *624*, 114–123.
20. Alami, M.; Peyrat, J.-F.; Brion, J.-D. *Tetrahedron Lett.* **2002**, *43*, 3007–3009 and references cited therein.
21. Hashmi, A. S. K.; Haufe, P.; Rivas, N. A.; Bats, J. W. *Adv. Synth. Catal.* **2004**, *346*, 421–424.
22. Denton, T. T.; Zhang, X.; Cashman, J. R. *J. Med. Chem.* **2005**, *48*, 224–239.
23. Kitbunnadaj, R.; Zuiderveld, O. P.; De Esch, I. J.; Vollinga, R. C.; Bakker, R.; Lutz, M.; Spek, A. L.; Cavoy, E.; Deltent, M. F.; Menge, W. M.; Timmerman, H.; Leurs, R. *J. Med. Chem.* **2003**, *46*, 5445–5457.
24. Hernandez, J. N.; Ramirez, M. A.; Martin, V. S. *J. Org. Chem.* **2003**, *68*, 743–746.
25. Berque-Bestel, I.; Soulier, J. L.; Giner, M.; Rivail, L.; Langlois, M.; Sicsic, S. *J. Med. Chem.* **2003**, *46*, 2606–2620.
26. (a) Hilt, G.; Galbiati, F. *Synlett* **2005**, 829–833; (b) Nilsson, B. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1990**, *33*, 580–584; (c) Youseung, K.; Soon bang, K.; Gyochang, K.; Min Seok, J.; Jae Yang, K.; Dae Yong, J. U.S. Pat. Appl. Publ. 2003, 119,880, 26 June 2003.
27. (a) Seefeld, M. A.; Miller, W. H.; Newlander, K. A.; Burgess, W. J.; Payne, D. J.; Rittenhouse, S. F.; Moore, T. D.; DeWolf, W. E.; Keller, P. M.; Qiu, X.; Janson, C. A.; Vaidya, K.; Fosberry, A. P.; Smyth, M. G.; Joworski, D. D.; Slatter-Radosti, C.; Huffman, W. F. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2241–2244; (b) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron Lett.* **2001**, *42*, 6049–6051; (c) Zhang, H.-C.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4449–4452.
28. For reviews, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2857–2911; (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920; (c) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2001**, *56*, 613–632.