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Heck-Suzuki Tandem Reaction for the Synthesis of 3-Benzazepines

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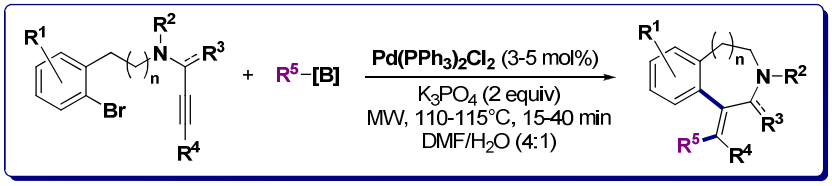
ABSTRACT



A novel procedure for the Heck-Suzuki tandem reaction suitable for the construction of nitrogen-containing medium rings was developed to provide access towards the 3-benzazepine framework.

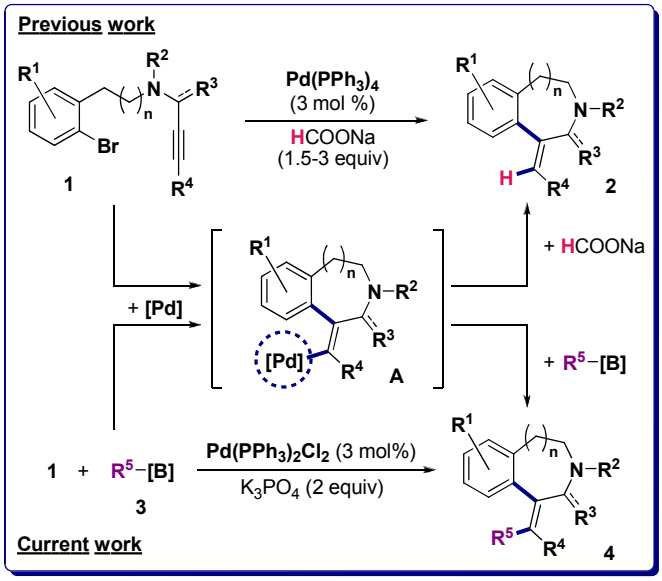
INTRODUCTION

The 3-benzazepine core is present in a large variety of natural products and important pharmaceuticals and might be rightfully regarded as a *privileged structure*.[1] Therefore it has been served as a target motif for a large number of synthetic studies. Successful examples include various types of ring-expansion reactions,[2] insertion of allenes into the Pd–C bond of *ortho*-palladated phenethylamines[3] and heterocyclizations involving either intramolecular reductive amination[4] or transition metal-catalyzed triple-bond hydroamination.[5] Radical,[6]

Friedel-Crafts[7] and Heck-type[8] carbocyclizations are also among the most applied methodologies for the 3-benzazepine assembly.

In 1994 Tietze and Schimpf described an efficient route towards 3-benzazepines starting from propargylamides containing an aryliodide moiety by applying an intramolecular version of the reductive Heck reaction that is also referred to as formal triple bond hydroaryation.[9,10] Later on our group has established a more general protocol that utilizes readily accessible propargylamides derived from 3-substituted propiolic acids and *ortho*-bromo-phenethylamines.[11] Subsequently we have expanded this approach to the use of Ugi reaction-derived propargylamides[12] and A^3-coupling-derived propargylamines[13] aiming to introduce an additional diversity in the resulting 3-benzazepines.

Scheme 1. Synthesis of the 3-benzazepine framework through palladium-catalyzed carbocyclizations of propargylic precursors



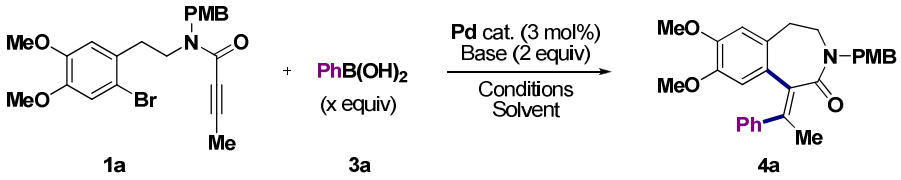
These reductive Heck approaches operate through the cyclic intermediate **A**, resulting from the oxidative addition of arylbromide to the Pd(0)-species and subsequent triple bond insertion, which then undergoes the reduction with HCOONa (sodium formate) into the 3-benzazepine of type **2**. Trapping this intermediate with an organoboron reagent **3** should hypothetically result in the formation of the 3-benzazepine of type **4** (Scheme 1). Such Heck-Suzuki tandem reactions are well known in the literature and have been previously demonstrated to be highly efficient for the assembly of five- and six-membered hetero-[14] and alicycles.[15] Moreover, this strategy proved to be useful for the synthesis of seven-membered dibenzoxapine derivatives.[16] However, to the best of our knowledge, no general protocol allowing the application of this process for the synthesis of nitrogen-containing medium-rings is known in the literature. In order to fill this gap we aimed to examine the Heck-

Suzuki tandem reaction for the synthesis and further diversification of the 3-benzazepine scaffold. Herein we present the detailed studies on the scope and limitations of the resulting procedure.

RESULTS AND DISCUSSION

The reaction conditions for the Heck-Suzuki tandem process were adjusted using propargylamide **1a** and phenylboronic acid **3a** as model substrates (Table 1). $Pd(PPh_3)_4$-catalyzed reaction of **1a** with 1.5 equiv of **3a** and K_3PO_4 as a base being conducted under microwave irradiation at 110°C for 15 min in DMF resulted in 70% conversion of **1a** but gave only 13% yield of a desired 3-benzazepine **4a** as was determined by ^1H NMR of the crude material after work-up (Table 1, entry 1). Switching to a DMF/water (3:1) mixture as solvent system lead to full conversion of **1a** and an improved 31% yield for **4a** (Table 1, entry 2). An attempt to decrease the excess of phenyl boronic acid **3a** resulted in incomplete conversion of **1a** (Table 1, entry 3). Next we have screened various bases in a combination with different Pd catalysts (Table 1, entries 4-10). The $Pd(PPh_3)_2Cl_2/K_3PO_4$ combination was found to be the best, delivering target **4a** in a good NMR yield of 55% (Table 1, entry 9). Interestingly, increasing the excess of phenyl boronic acid **3a** up to 1.8 equiv did not provide a better yield of **4a** (Table 1, entry 11). Changing the DMF-water ratio to (1:1) led to a significant drop in the **4a** yield (Table 1, entry 12). The reaction in a DMA/water (3:1) mixture gave a slightly decreased yield of **4a** compared to the analogous reaction in DMF/water(3:1) (Table 1, entry 13 *vs* entry 9). Finally, reaction in DMF/water (4:1) delivered 3-benzazepine **4a** in a best observed NMR yield of 58%, which corresponds to 51% isolated yield after column chromatography and recrystallization from diethyl ether (Table 1, entry 14). Further attempts to increase the yield of **4a** by tuning the catalytic system were unproductive (Table 1, entries 15 and 16). Also no further improvement was achieved by changing the reaction temperature as well as by applying conventional oil bath heating (Table 1, entries 17-20).

Table 1. Screening of parameters for the model reaction of **1a** and **3a**[a]



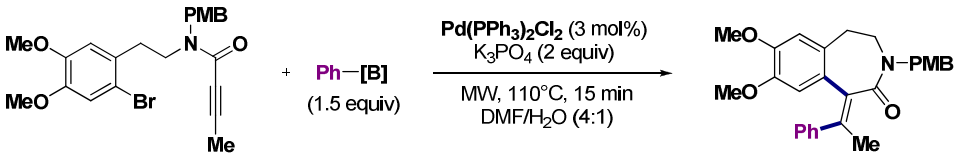
Entry	x	Pd cat.	Base	Conditions	Solvent	Yield[b]	Conversion[b]
1	1.5	$Pd(PPh_3)_4$	K_3PO_4	MW, 110°C, 15 min	DMF	13	70
2	1.5	$Pd(PPh_3)_4$	K_3PO_4	MW, 110°C, 15 min	DMF/H_2O(3:1)	31	100
3	1.2	$Pd(PPh_3)_4$	K_3PO_4	MW, 110°C, 15 min	DMF/H_2O(3:1)	16	95
4	1.5	$Pd(PPh_3)_4$	KOAc	MW, 110°C, 15 min	DMF/H_2O(3:1)	48	86
5	1.5	$Pd(PPh_3)_4$	Na_2CO_3	MW, 110°C, 15 min	DMF/H_2O(3:1)	30	100
6	1.5	$Pd(PPh_3)_4$	Cs_2CO_3	MW, 110°C, 15 min	DMF/H_2O(3:1)	21	100
7	1.5	$Pd(PPh_3)_4$	*t*BuOK	MW, 110°C, 15 min	DMF/H_2O(3:1)	16	100

8	1.5	$Pd(PPh_3)_2Cl_2$	KOAc	MW, 110°C, 15 min	DMF/H_2O(3:1)	36	90
9	1.5	$Pd(PPh_3)_2Cl_2$	K_3PO_4	MW, 110°C, 15 min	DMF/H_2O(3:1)	55	100
10	1.5	$Pd(OAc)_2/PPh_3$	KOAc	MW, 110°C, 15 min	DMF/H_2O(3:1)	41	88
11	1.8	$Pd(PPh_3)_2Cl_2$	K_3PO_4	MW, 110°C, 15 min	DMF/H_2O(3:1)	48	100
12	1.5	$Pd(PPh_3)_2Cl_2$	K_3PO_4	MW, 110°C, 15 min	DMF/H_2O(1:1)	17	100
13	1.5	$Pd(PPh_3)_2Cl_2$	K_3PO_4	MW, 110°C, 15 min	DMA/H_2O(3:1)	50	100
14	**1.5**	**$Pd(PPh_3)_2Cl_2$**	**K_3PO_4**	**MW, 110°C, 15 min**	**DMF/H_2O(4:1)**	**58 (51)[c]**	**100**
15	1.5	$Pd(OAc)_2/PPh_3$	K_3PO_4	MW, 110°C, 15 min	DMF/H_2O(4:1)	43	100
16	1.5	Pd_2dba_3/PPh_3	K_3PO_4	MW, 110°C, 15 min	DMF/H_2O(4:1)	37	100
17	1.5	$Pd(PPh_3)_2Cl_2$	K_3PO_4	MW, 90°C, 25 min	DMF/H_2O(4:1)	44	94
18	1.5	$Pd(PPh_3)_2Cl_2$	K_3PO_4	MW, 120°C, 10 min	DMF/H_2O(4:1)	31	88
19	1.5	$Pd(PPh_3)_2Cl_2$	K_3PO_4	oil bath, 90°C, 2 h	DMF/H_2O(4:1)	39	100
20	1.5	$Pd(PPh_3)_2Cl_2$	K_3PO_4	oil bath, 110°C, 1 h	DMF/water(4:1)	35	100

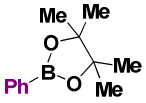
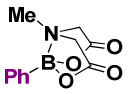
[a] The reactions were run on a 0.2 mmol scale in 2.25 mL of solvent. [b] Yields and conversions were determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [c] Isolated yield is given in parenthesis.

Then we decided to compare the reactivity of several common phenylorganoboron reagents **3a-d** in the model reaction with **1a** (Table 2). Phenylboronic acid **3a** was found to be the most efficient coupling partner (Table 2, entry 1). Nonetheless, the use of potassium phenyltrifluoroborate **3b** and phenylboronic acid pinacol ester **3c** also resulted in a full conversion of **1a**, although the yields for the desired 3-benzazepine **4a** were lower in these cases (Table 2, entries 2 and 3 *versus* entry 1). The application of phenylboronic acid MIDA ester **3d** gave a very low conversion of **1a** and as a result a poor yield for target compound **4a** (Table 2, entry 4).

Table 2. Comparison of the reactivity of different organoboron reagents **3**[a]



1a **3** **4a**

Entry	Ph—[B] (3)	Yield[b]	Conversion[b]
1	$PhB(OH)_2$ **3a**	58 (51)[c]	100
2	$PhBF_3K$ **3b**	29	100
3	 **3c**	52 (45)[c]	100
4	 **3d**	14	34

[a] The reactions were run on a 0.2 mmol scale in 2.25 mL of solvent. [b] Yields and conversions were determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard. [c] Isolated yields are given in parenthesis.

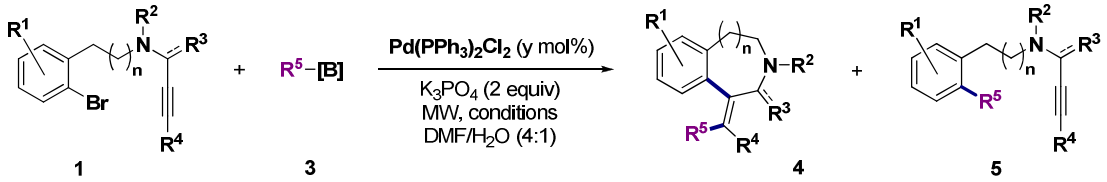
Having these results at hand we decided to evaluate the scope and limitations of our procedure (Table 3). First we have screened a number of aromatic **3a,e-k** and heteroaromatic **3l,m** boronic acids in combination with propargylamide **1a**. All reactions were successful, delivering desired 3-benzazepines **4a-j** in up to 60% yield

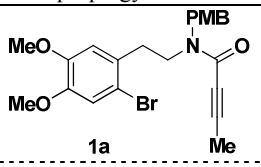
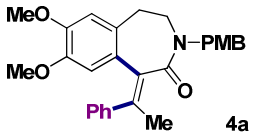
(Table 3, entries 1-10). The reaction of **1a** with penten-1-ylboronic acid **3n** also resulted in a good 52% yield of 3-benzazepine **4k** (Table 3, entry 11). At the same time the application of vinyl potassium trifluoroborate **3p** required some adjustments of the reaction conditions in order to reach a full conversion of **1a**, but finally allowed to obtain 3-benzazepine **4l** in a very good yield of 72% (Table 3, entries 12-14). Next we have screened the reactivity of various propargylamides **1b-e** in combination with phenylboronic acid **3a** and with vinyl potassium trifluoroborate **3p** (Table 3, entries 15-22). Gratifyingly, the isolated yields of the desired 3-benzazepines in several cases have reached the 80% yield. However, in the reactions with propargylamide **1c** derived from phenylpropiolic acid, only very poor yields were obtained (Table 3, entries 17 and 18). In case of reactions with propargyl amide **1f** an expanded eight-membered ring could be constructed although the yields for the resulting 3-benzazocines **4u** and **4v** are significantly lower than for analogues 3-benzazepines **4a** and **4l** (Table 3, entries 23 and 24 *versus* entries 1 and 14). Importantly, A^3-coupling-derived propargylamine **1g** was also found to be applicable in this process (Table 3, entries 25 and 26).

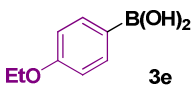
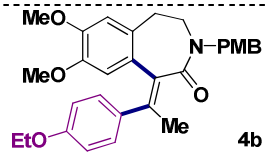
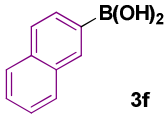
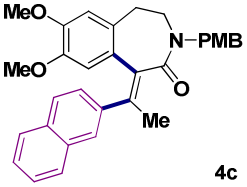
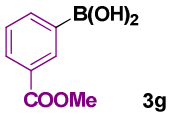
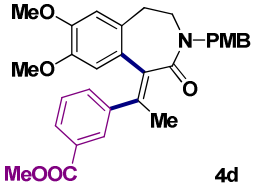
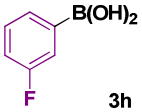
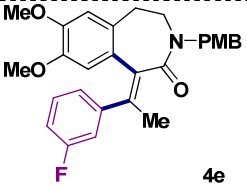
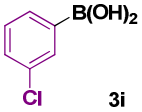
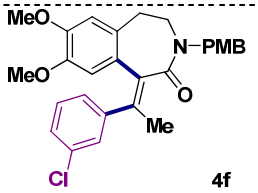
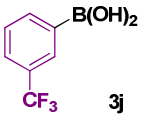
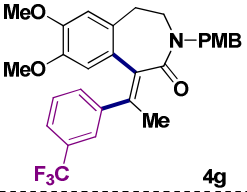
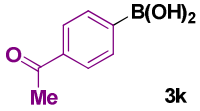
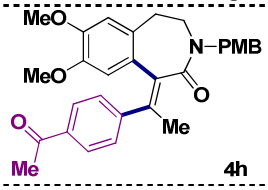
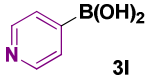
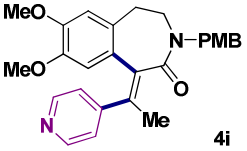
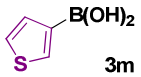
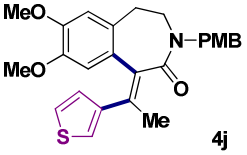
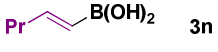
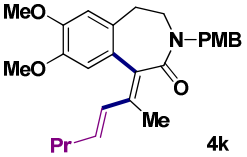
The reactions with vinyl potassium trifluoroborate **3p** in all cases led to the higher yields of desired benzazepine and benzazocine products compared to the analogues reactions with phenylboronic acid **3a** (Table 3, entries 14, 16, 18, 20, 22, 24 and 26 versus entries 1, 15, 17, 19, 21, 23 and 25). This result could be attributed to the smaller size of the introduced vinyl fragment compared to the phenyl one.

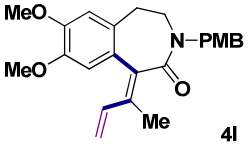
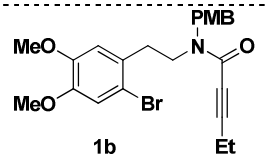
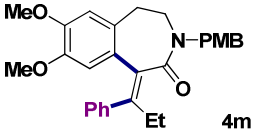
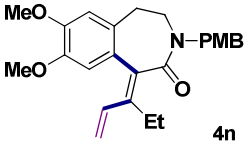
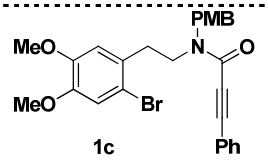
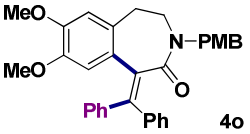
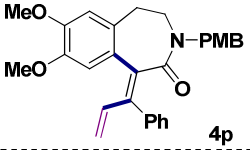
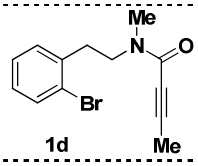
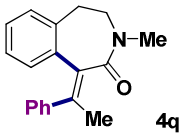
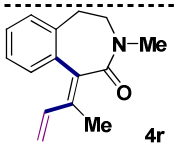
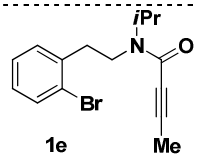
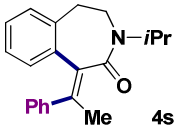
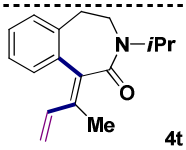
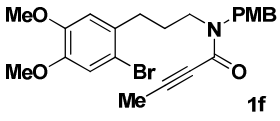
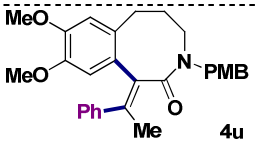
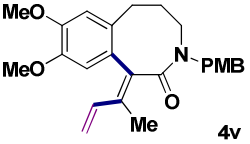
In some cases in addition to the desired Heck-Suzuki product **4** the formation of byproduct **5** that results from the direct Suzuki coupling of the arylbromide moiety of **1** with organoboron reagent **3** could be observed. In several instances such products **5** could be isolated and characterized (Table 3, entries 7, 10, 17, 23 and 25).

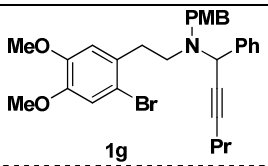
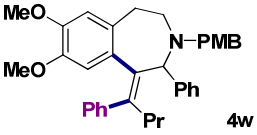
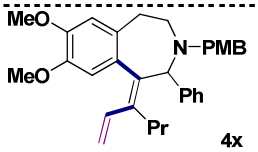
Table 3. Scope and limitation of the Heck-Suzuki tandem reaction procedure for the synthesis of 3-benzazepine and 3-benzazocine frameworks[a]



Entry	y	Conditions	Propargylamide or propargylamine **1**	Organoboron reagent **3**	Product **4**	Yield[b] **4**	Yield[b] **5**
1	3	110°C, 15 min	 **1a**	$PhB(OH)_2$ **3a**	 **4a**	51	nd[c]

2	3	110°C, 15 min	**1a**	 **3e**	 **4b**	35	nd[c]
3	3	110°C, 15 min	**1a**	 **3f**	 **4c**	47	nd[c]
4	3	110°C, 15 min	**1a**	 **3g**	 **4d**	34	nd[c]
5	3	110°C, 15 min	**1a**	 **3h**	 **4e**	52	nd[c]
6	3	110°C, 15 min	**1a**	 **3i**	 **4f**	48	nd[c]
7	3	110°C, 25 min	**1a**	 **3j**	 **4g**	42	16
8	3	110°C, 15 min	**1a**	 **3k**	 **4h**	53	nd[c]
9	3	110°C, 15 min	**1a**	 **3l**	 **4i**	60	nd[c]
10	3	110°C, 15 min	**1a**	 **3m**	 **4j**	37	27
11	3	110°C, 15 min	**1a**	 **3n**	 **4k**	52	nd[c]

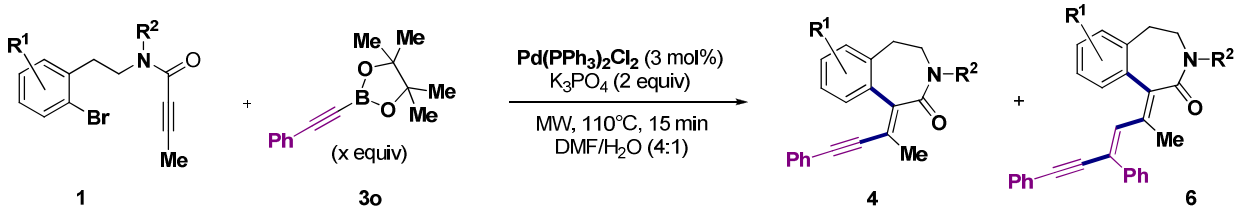
12	3	110°C, 15 min	**1a**	BF_3K	**3p**	 **4l**	40 (50)[d]	nd[e]
13	4	115°C, 30 min	**1a**				67 (90)[d]	nd[e]
14	3+2	115°C, 20+15 min	**1a**				72 (100)[d]	nd[e]
15	4	110°C, 25 min	 **1b**		**3a**	 **4m**	49	nd[e]
16	3+2	115°C, 20+15 min	**1b**		**3p**	 **4n**	80	nd[e]
17	3	110°C, 15 min	 **1c**		**3a**	 **4o**	15	6
18	3+2	115°C, 20+15 min	**1c**		**3p**	 **4p**	18	nd[e]
19	3	110°C, 15 min	 **1d**		**3a**	 **4q**	69	nd[e]
20	3+2	115°C, 20+15 min	**1d**		**3p**	 **4r**	83	nd[e]
21	3	110°C, 15 min	 **1e**		**3a**	 **4s**	45	nd[e]
22	3+2	115°C, 20+15 min	**1e**		**3p**	 **4t**	79	nd[e]
23	3	110°C, 15 min	 **1f**		**3a**	 **4u**	13	34
24	3+2	115°C, 20+15 min	**1f**		**3p**	 **4v**	59	nd[e]

25	3+2	110°C, 25+15 min	 1g	3a	 4w	27	35[e]
26	3+3	115°C, 25+15 min	1g	3p	 4x	55	nd[c]

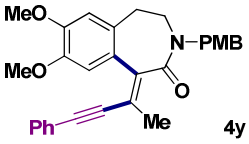
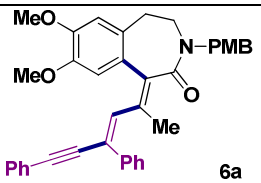
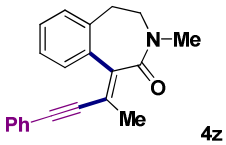
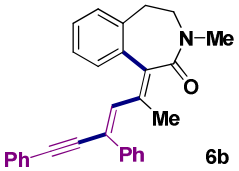
[a] The reactions were run on a 0.2 mmol scale in 2.25 mL of solvent. [b] Isolated yields. [c] nd = not detected or difficult to determine clearly. [d] Conversions are given in parenthesis. [e] Yield was determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard.

Finally we investigated the reactions of propargylamides **1a** and **1d** with 2-phenyl-1-ethynylboronic acid pinacol ester **3o** (Table 4). Interestingly, in this case in addition to the standard product **4** another unexpected 3-benzazepine product **6** was formed resulting from the double incorporation of organoboron reagent **3o**. We have attempted to tune the **4** to **6** ratio by changing the amounts of **3o** added to the reaction, however, no significant effect was achieved.

Table 4. Heck-Suzuki tandem reaction with 2-phenyl-1-ethynylboronic acid pinacol ester **3o**[a]



1 3o 4 6

Entry	Propargylamide **1**	x	Product **4**	Yield of **4**[b]	Product **6**	Yield of **6**[b]
1	**1a**	1.5	 4y	24	 6a	10
2	**1d**	1.5	 4z	19	 6b	13
3		1.2		23		9
4		2.5		20[c]		14[c]

[a] The reactions were run on a 0.2 mmol scale in 2.25 mL of solvent. [b] Isolated yields. [c] Yields were determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard.

The structures of all prepared 3-benzazepines **4a-t,w-z, 6** and 3-benzazocines **4u,v** were confirmed by ^{1}H and ^{13}C NMR spectroscopy and HRMS. In addition, the structures of four representative products **4m**, **4t**, **4z** and **6b** were assured by X-ray crystallographic analysis.[17]

CONCLUSION

In summary, we have developed a novel protocol for the tandem Heck-Suzuki reaction showing that it can be successfully applied for the construction of nitrogen-containing medium-rings. Importantly our methodology employs propargylamides/amines comprising an arylbromide functionality, while most of known procedures leading to nitrogen-containing five- and six-membered heterocycles[14a-c] generally rely on more reactive aryliodides. The adaptability of the developed procedure towards the various organoboron sources has also been evaluated.

EXPERIMENTAL SECTION

General information

^{1}H and ^{13}C NMR spectra were recorded with 300 and 75 MHz respectively. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference. High-resolution EI mass spectra were recorded with a resolution of 10000. The ion source temperature was 150-250 °C, as required. High-resolution ESI mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer. Samples were infused at 3 μL/min and spectra were obtained in positive ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass. Reversed phase HPLC separation was performed using C18 (5 μm×150 nm×22 mm) preparative column.

The microwave reactions were carried out in 10-mL glass tubes, sealed with Teflon septum using a dedicated CEM-Discover monomode microwave apparatus, operating with a frequency of 2.45 GHz. The temperature of microwave reactions was measured by an inbuilt infrared temperature probe.

Synthesis of the starting materials

The preparation procedures and analytical data for compounds **1a,c-f**[11a] and **1g**[13] are described by us previously.

Synthesis of N-(2-bromo-4,5-dimethoxyphenethyl)-N-(4-methoxybenzyl)pent-2-ynamide (**1b**): 2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(4-methoxybenzyl)ethanamine (496 mg, 1.3 mmol) was added in one portion to a mixture of pent-2-ynoic acid (134 mg, 1.37 mmol) and DCC (283 mg, 1.37 mmol) in dry DCM (6 mL). The reaction mixture was stirred overnight at rt. The subsequently formed precipitate of N,N'-dicyclohexylurea was filtered off and washed with DCM. The combined organic layers were concentrated and subjected to column chromatography on silica gel with EtOAc/hepthane (3:7) as eluent delivering pure **1b** as a 2:3 mixture of rotamers. Yield: 382 mg, 64%. Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.14 (m, 2H), 6.99 (s, 0.4H), 6.97 (s, 0.6H), 6.90-6.81 (m, 2H), 6.74 (s, 0.6H), 6.56 (s, 0.4H), 4.53 (s, 2H), 3.87-3.76 (m, 9H), 3.70-

3.62 (m, 0.8H), 3.50-3.41 (m, 1.2H), 2.97-2.85 (m, 2H), 2.43-2.30 (m, 2H), 1.24-1.15 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 159.1, 154.9, 154.7, 148.52, 148.49, 148.4, 148.2, 130.1, 129.8, 129.6, 129.1, 128.9, 128.5, 115.5, 115.3, 114.3, 114.04, 113.96, 113.6, 113.5, 94.2, 93.9, 73.8, 73.4, 56.2, 56.11, 56.09, 55.3, 55.2, 52.8, 47.8, 47.2, 44.0, 35.0, 33.1, 12.93, 12.86, 12.8, 12.7; HRMS (EI): m/z $[M]^+$ calcd. for $C_{23}H_{26}BrNO_4$: 459.1045; found: 459.1059.

General procedure for the Heck-Suzuki tandem reaction for the synthesis of 3-benzazepines 4a-k,m,o,q,s,y,z and 6a,b and benzazocine 4u

$Pd(PPh_3)_2Cl_2$ (4.2 mg, 3 mol%), organoboron reagent **3** (0.3 mmol) and propargylamide **1** (0.2 mmol) were loaded into a microwave instrument vial and dissolved in DMF (1.8 mL). Then K_3PO_4 (85 mg, 0.4 mmol) was added followed by distilled water (0.45 mL). The reaction vial was evacuated, flushed with argon, sealed and irradiated under stirring at the set temperature of 110 °C for 15 min utilizing a maximum power of 100 W. Upon completion of the reaction the vial was cooled with a stream of air. The reaction mixture was diluted with EtOAc (50 mL), washed with water (2×50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude material was subjected to the appropriate purification procedure.

(*E*)-7,8-dimethoxy-3-(4-methoxybenzyl)-1-(1-phenylethylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4a**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by recrystallization/washing with diethyl ether delivering pure **4a**. Yield: 45 mg, 51%. White amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.22 (m, 2H), 7.20-7.05 (m, 5H), 6.88 (d, J = 8.2 Hz, 2H), 6.45 (s, 1H), 6.18 (s, 1H), 5.02 (d, J = 14.8 Hz, 1H), 4.39-4.17 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.39-3.25 (m, 4H), 2.98-2.88 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 159.1, 147.9, 146.5, 141.9, 137.5, 134.6, 129.7, 129.4, 128.6, 128.1, 127.7, 126.7, 125.5, 115.4, 114.1, 111.9, 55.7, 55.32, 55.30, 47.5, 44.5, 31.8, 22.1; HRMS (EI): m/z $[M]^+$ calcd. for $C_{28}H_{29}NO_4$: 443.2097; found: 443.2096.

(*E*)-1-(1-(4-ethoxyphenyl)ethylidene)-7,8-dimethoxy-3-(4-methoxybenzyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4b**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by recrystallization/washing with diethyl ether delivering pure **4b**. Yield: 34 mg, 35%. White solid; m.p. 174-176 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 8.3 Hz, 2H), 6.45 (s, 1H), 6.23 (s, 1H), 5.01 (d, J = 14.6 Hz, 1H), 4.37-4.16 (m, 2H), 4.01-3.89 (m, 2H), 3.81 (s, 3H), 3.79 (m, 3H), 3.38-3.26 (m, 4H), 2.97-2.87 (m, 2H), 2.30 (s, 3H), 1.36 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 159.0, 157.7, 147.9, 146.6, 137.0, 133.9, 133.7, 129.8, 129.7, 129.4, 127.6, 125.8, 115.4, 114.1, 114.0, 111.9, 63.3, 55.7, 55.4, 55.3, 47.5, 44.5, 31.8, 22.0, 14.8; HRMS (EI): m/z $[M]^+$ calcd. for $C_{30}H_{33}NO_5$: 487.2359; found: 487.2354.

(*E*)-7,8-dimethoxy-3-(4-methoxybenzyl)-1-(1-(naphthalen-2-yl)ethylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4c**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by recrystallization/washing with diethyl ether delivering pure **4c**. Yield: 46 mg, 47%. Beige solid; m.p. 243-246 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.62 (m, 3H), 7.57 (d, J = 8.5 Hz, 1H), 7.44-7.36 (m, 2H), 7.28 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 8.0 Hz, 2H), 6.46 (s, 1H), 6.22 (s, 1H), 5.04 (d, J = 14.7 Hz, 1H), 4.43-4.25 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.43-3.32 (m, 1H), 3.07 (s, 3H), 3.01-2.92 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 159.1, 148.0, 146.5, 139.5, 137.3, 135.0, 133.2, 132.1, 129.7, 129.4, 127.8, 127.7, 127.5, 127.34, 127.30, 127.0, 126.1, 125.9, 125.4, 115.5, 114.1, 112.0, 55.6, 55.3, 55.2, 47.5, 44.6, 31.9, 22.3; HRMS (EI): m/z $[M]^+$ calcd. for $C_{32}H_{31}NO_4$: 493.2253; found: 493.2269.

(*E*)-methyl 3-(1-(7,8-dimethoxy-3-(4-methoxybenzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-1-ylidene)ethyl)benzoate (**4d**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by recrystallization/washing with diethyl ether delivering pure **4d**. Yield: 34 mg, 34%. Beige solid; m.p. 132-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.76 (m, 2H), 7.31-7.16 (m, 4H), 6.88 (d, J = 8.5 Hz, 2H), 6.46 (s, 1H), 6.15 (s. 1H), 4.99 (d, J = 14.7 Hz, 1H), 4.41-4.18 (m, 2H), 3.87 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.42-3.22 (m, 4H), 3.01-2.84 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 166.7, 159.1, 148.1, 146.6, 142.3, 136.3, 135.6, 133.3, 130.1, 129.7, 129.6, 129.4, 128.1, 128.0, 127.9, 124.9, 115.2, 114.1, 112.1, 55.7, 55.4, 55.3, 52.1, 47.5, 44.6, 31.8, 22.0; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{30}H_{32}NO_6$: 502.2224; found: 502.2218.

(*E*)-1-(1-(3-fluorophenyl)ethylidene)-7,8-dimethoxy-3-(4-methoxybenzyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4e**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by recrystallization/washing with diethyl ether delivering pure **4e**. Yield: 48 mg, 52%. White solid; m.p. 163-165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 8.0 Hz, 2H), 7.13 (q, J = 7.2 Hz, 1H), 6.92-6.76 (m, 5H), 6.46 (s, 1H), 6.20 (s, 1H), 4.99 (d, J = 14.7 Hz, 1H), 4.34 (d, J = 14.7 Hz, 1H), 4.26-4.13 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.39-3.29 (m, 4H), 2.97-2.89 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 162.5 (d, J = 245.9 Hz), 159.1, 148.2, 146.6, 144.3 (d, J = 7.5 Hz), 136.1 (d, J = 1.9 Hz), 135.5, 129.59, 129.55 (d, J = 7.3 Hz), 129.4, 127.8, 125.0, 124.4 (d, J = 2.8 Hz), 115.6 (d, J = 21.6 Hz), 115.1, 114.1, 113.7 (d, J = 21.1 Hz), 112.1, 55.7, 55.4, 55.3, 47.5, 44.5, 31.8, 21.9; HRMS (EI): m/z $[M]^+$ calcd. for $C_{28}H_{28}FNO_4$: 461.2002; found: 461.2025.

(*E*)-1-(1-(3-chlorophenyl)ethylidene)-7,8-dimethoxy-3-(4-methoxybenzyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4f**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by recrystallization/washing with diethyl ether delivering pure **4f**. Yield: 46 mg, 48%. White solid; m.p. 161-163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 8.6 Hz, 2H), 7.15-7.03 (m, 3H), 6.98-6.92 (m, 1H), 6.88 (d, J = 8.6 Hz, 2H), 6.46 (s, 1H), 6.19 (s, 1H), 4.99 (d, J = 14.7 Hz,

1H), 4.34 (d, J = 14.7 Hz, 1H), 4.26-4.12 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.39-3.29 (m, 4H), 2.97-2.87 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 159.1, 148.2, 146.6, 143.9, 136.0, 135.7, 133.9, 129.6, 129.4, 129.3, 128.6, 127.8, 126.89, 126.86, 124.9, 115.2, 114.1, 112.1, 55.7, 55.4, 55.3, 47.5, 44.5, 31.8, 22.0; HRMS (EI): m/z $[M]^+$ calcd. for $C_{28}H_{28}ClNO_4$: 477.1707; found: 477.1720.

(*E*)-7,8-dimethoxy-3-(4-methoxybenzyl)-1-(1-(3-(trifluoromethyl)phenyl)ethylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4g**): The reaction time was 25 min. The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by recrystallization from diethyl ether delivering pure **4g**. The mother liquor was evaporated and subjected to reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-70-70-80-90-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering a second portion of pure **4g** (t_r = 42 min). Combined yield: 43 mg, 42%. White solid; m.p. 142-144 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.36 (m, 2H), 7.31-7.19 (m, 4H), 6.88 (d, J = 8.3 Hz, 2H), 6.46 (s, 1H), 6.11 (s, 1H), 5.00 (d, J = 14.7 Hz, 1H), 4.35 (d, J = 14.7 Hz, 1H), 2.30-2.15 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.42-3.26 (m, 4H), 2.98-2.88 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 159.1, 148.3, 146.7, 142.9, 136.2, 135.9, 132.0, 130.6 (q, J = 32.1 Hz), 129.6, 129.4, 128.6, 128.0, 125.4 (q, J = 3.6 Hz), 123.9 (d, J = 272.2 Hz), 124.7, 123.4 (q, J = 4.1 Hz), 115.1, 114.1, 112.2, 55.8, 55.3, 47.6, 44.6, 31.8, 21.8; HRMS (EI): m/z $[M]^+$ calcd. for $C_{29}H_{28}F_3NO_4$: 511.1970; found: 511.1975. Further elution provided ***N*-(2-(4,5-dimethoxy-3'-(trifluoromethyl)biphenyl-2-yl)ethyl)-*N*-(4-methoxybenzyl)but-2-ynamide** (**5g**) as a ~ 3:2 mixture of rotamers (t_r = 45 min). Yield: 16 mg, 16%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.40 (m, 4H), 6.95-6.85 (m, 2H), 6.84-6.72 (m, 2.6H), 6.72-6.68 (m, 0.8H), 6.67 (s, 0.6H), 4.31 (s, 1.2H), 4.17 (s, 0.8H), 3.92 (s, 1.8H), 3.91 (s, 1.2H), 3.87 (s, 1.2H), 3.86 (s, 1.8H), 3.79 (s, 1.8H), 3.77 (s, 1.2H), 3.48-3.36 (m, 0.8H), 3.30-3.17 (m, 1.2H), 2.85-2.65 (m, 2H), 1.97 (s, 1.8H), 1.92 (s, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 159.0, 154.64, 154.56, 148.84, 148.77, 147.65, 147.4, 142.14, 142.08, 133.1, 132.9, 132.6, 130.7 (m), 129.5, 128.9, 128.7, 128.6, 128.52, 128.45, 128.2, 128.0, 126.1 (m), 123.7 (m), 114.0, 113.9, 113.2, 113.0, 112.9, 112.8, 89.0, 88.6, 73.5, 73.4, 56.09, 56.05, 56.02, 55.3, 55.2, 52.3, 48.9, 46.6, 45.1, 31.6, 30.0, 4.0, 3.9; HRMS (EI): m/z $[M]^+$ calcd. for $C_{29}H_{28}F_3NO_4$: 511.1970; found: 511.1987.

(*E*)-1-(1-(4-acetylphenyl)ethylidene)-7,8-dimethoxy-3-(4-methoxybenzyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4h**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-70-70-80-90-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering pure **4h** (t_r = 31 min). Yield: 51.5 mg, 53%. Yellow amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.47 (s, 1H), 6.15 (s, 1H), 5.00 (d, J = 14.7 Hz, 1H), 4.35 (d, J = 14.7 Hz, 1H), 4.30-4.16 (m, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.41-3.32 (m, 1H), 3.28 (s, 3H), 2.98-2.90 (m, 2H), 2.53 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$): δ 197.4, 171.1, 159.1, 148.3, 147.2, 146.6, 136.3, 136.1, 135.3, 129.6, 129.4, 128.9, 128.1, 127.9, 125.0, 115.2, 114.1, 112.1, 55.7, 55.4, 55.3, 47.5, 44.5, 31.8, 26.5, 21.8; HRMS (EI): m/z $[M]^+$ calcd. for $C_{30}H_{31}NO_5$: 485.2202; found: 485.2207.

(*E*)-7,8-dimethoxy-3-(4-methoxybenzyl)-1-(1-(pyridin-4-yl)ethylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4i**): The material after workup was subjected to column chromatography on silicagel with EtOAc as eluent followed by reversed phase preparative HPLC using gradient pump mode and MeCN/H_2O (20-30-30-40-100%, 10 min intervals) as eluent with a flow rate of 10 mL/min delivering pure **4i** (t_r = 37 min). Yield: 53 mg, 60%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (bs, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.08-7.00 (m, 2H), 6.88 (d, J = 8.3 Hz, 2H), 6.49 (s, 1H), 6.14 (s, 1H), 4.97 (d, J = 14.7 Hz, 1H), 4.36 (d, J = 14.7 Hz, 1H), 4.26-4.12 (m, 1H), 3.84-3.76 (m, 6H), 3.42-3.30 (m, 4H), 2.98-2.89 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 159.2, 150.5, 149.1, 148.6, 146.8, 137.2, 134.4, 129.5, 129.4, 128.0, 124.3, 123.7, 114.9, 114.1, 112.3, 55.7, 55.5, 55.3, 47.6, 44.5, 31.8, 21.3; HRMS (EI): m/z $[M]^+$ calcd. for $C_{27}H_{28}N_2O_4$: 444.2049; found: 444.2065.

(*E*)-7,8-dimethoxy-3-(4-methoxybenzyl)-1-(1-(thiophen-3-yl)ethylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4j**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-60-70-70-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering pure **4j** (t_r = 35 min). Yield: 33 mg, 37%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, J = 8.3 Hz, 2H), 7.08-7.01 (m, 2H), 6.87 (d, J = 8.3 Hz, 2H), 6.66-6.60 (m, 1H), 6.49 (s, 1H), 6.36 (s, 1H), 4.98 (d, J = 14.7 Hz, 1H), 4.34 (d, J = 14.7 Hz, 1H), 4.25-4.10 (m, 1H), 3.86-3.75 (m, 6H), 3.43 (s, 3H), 3.36-3.25 (m, 1H), 2.96-2.86 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 159.0, 148.4, 146.8, 141.9, 134.1, 131.7, 129.7, 129.4, 128.3, 127.5, 125.7, 124.3, 123.7, 114.8, 114.0, 112.1, 55.7, 55.5, 55.3, 47.5, 44.5, 31.7, 21.6; HRMS (EI): m/z $[M]^+$ calcd. for $C_{26}H_{27}NO_4S$: 449.1661; found: 449.1648. Further elution provided ***N*-(4,5-dimethoxy-2-(thiophen-3-yl)phenethyl)-*N*-(4-methoxybenzyl)but-2-ynamide** (**5j**) as a ~ 3:2 mixture of rotamers (t_r = 39 min). Yield: 24 mg, 27%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.34 (m, 1H), 7.17-7.10 (m, 1H), 7.10-7.04 (m, 1H), 7.03-6.94 (m, 2H), 6.87-6.73 (m, 3.6H), 6.67 (s, 0.4H), 4.39 (s, 1.2H), 4.25 (s, 0.8H), 3.90 (s, 1.8H), 3.89 (s, 1.2H), 3.86 (s, 1.2H), 3.85 (s, 1.8H), 3.80 (s, 1.8H), 3.78 (s, 1.2H), 3.52-3.41 (m, 0.8H), 3.35-3.23 (m, 1.2H), 2.91-2.73 (m, 2H), 1.98 (s, 1.8H), 1.96 (s, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 159.0, 154.7, 154.6, 148.5, 148.4, 147.5, 147.2, 141.55, 141.54, 129.6, 129.3, 129.14, 129.10, 128.9, 128.80, 128.77, 128.73, 128.5, 128.4, 125.5, 125.3, 122.6, 122.5, 114.0, 113.9, 113.5, 113.3, 112.9, 112.8, 88.9, 88.6, 73.6, 73.5, 56.1, 56.00, 55.98, 55.95, 55.30, 55.26, 52.2, 49.1, 46.5, 45.2, 31.9, 30.3, 4.06, 4.05; HRMS (EI): m/z $[M]^+$ calcd. for $C_{26}H_{27}NO_4S$: 449.1661; found: 449.1670.

(*E*)-1-((*E*)-hept-3-en-2-ylidene)-7,8-dimethoxy-3-(4-methoxybenzyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4k**): The material obtained after workup was subjected to column chromatography on silicagel with

heptane/EtOAc (4:1→7:3) as eluent delivering pure **4k**. Last fractions containing **4k** overlapping with other impurities were concentrated separately and resubjected to column chromatography delivering a second portion of pure **4k**. Combined yield: 45 mg, 52%. Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.74 (s, 1H), 6.53 (s, 1H), 6.36 (dt, J = 15.6, 1.2 Hz, 1H), 5.92 (dt, J = 15.6, 7.0 Hz, 1H), 4.93 (d, J = 14.7 Hz, 1H), 4.29 (d, J = 14.7 Hz, 1H), 4.05-3.92 (m, 1H), 3.88-3.75 (m, 9H), 3.26-3.13 (m, 1H), 2.89-2.75 (m, 2H), 2.14-1.96 (m, 5H), 1.46-1.31 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 159.0, 148.4, 146.5, 134.0, 133.9, 133.2, 129.8, 129.34, 129.28, 128.0, 125.1, 115.4, 114.0, 112.5, 55.9, 55.8, 55.3, 47.4, 44.4, 35.3, 31.7, 22.5, 16.3, 13.7; HRMS (EI): m/z $[M]^+$ calcd. for $C_{27}H_{33}NO_4$: 435.2410; found: 435.2415.

(*E*)-7,8-dimethoxy-3-(4-methoxybenzyl)-1-(1-phenylpropylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4m**): An increased $Pd(PPh_3)_2Cl_2$ (5.6 mg, 4 mol%) loading and extended reaction time of 25 min were used. The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-60-70-70-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering pure **4m** (t_r = 39 min). Yield: 45 mg, 49%. White solid; m.p. 191-193 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.04 (m, 8H), 6.88 (d, J = 8.3 Hz, 2H), 6.43 (s, 1H), 6.18 (s, 1H), 5.05 (d, J = 14.7 Hz, 1H), 4.37-4.18 (m, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.39-3.25 (m, 4H), 3.14-3.01 (m, 1H), 2.97-2.87 (m, 2H), 2.68-2.53 (m, 1H), 1.60 (s, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 159.0, 147.8, 146.4, 143.7, 140.3, 134.3, 129.7, 129.4, 129.2, 128.0, 127.6, 126.7, 125.6, 115.3, 114.0, 111.9, 55.6, 55.32, 55.30, 47.5, 44.6, 31.8, 28.2, 12.4; HRMS (EI): m/z $[M]^+$ calcd. for $C_{29}H_{31}NO_4$: 457.2253; found: 457.2251.

1-(diphenylmethylene)-7,8-dimethoxy-3-(4-methoxybenzyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4o**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (50-60-70-80-80-90-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min (8 mL/min for two first intervals) delivering pure **4o** (t_r = 24 min). Yield: 15 mg, 15%. White amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.46 (m, 2H), 7.42-7.32 (m, 3H), 7.16-7.00 (m, 5H), 6.69-6.59 (m, 4H), 6.53 (s, 1H), 6.37 (s, 1H), 5.05 (d, J = 14.9 Hz, 1H), 4.32-4.17 (m, 1H), 3.87 (d, J = 14.9 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.41 (s, 3H), 3.25-3.96 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 158.7, 148.3, 146.9, 140.71, 140.66, 140.63, 136.4, 130.1, 129.7, 129.3, 128.8, 127.93, 127.85, 127.8, 127.3, 126.8, 125.5, 114.3, 113.8, 112.2, 55.7, 55.5, 55.2, 46.9, 44.4, 31.8; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{33}H_{32}NO_4$: 506.2326; found: 506.2318. Further elution provided ***N*-(2-(4,5-dimethoxybiphenyl-2-yl)ethyl)-*N*-(4-methoxybenzyl)-3-phenylpropiolamide** (**5o**) as a ~ 1:1 mixture of rotamers (t_r = 31 min). Yield: 6 mg, 6%. Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.24 (m, 10H), 7.01-6.89 (m, 2H), 6.85-6.74 (m, 2.5H), 6.72 (s, 0.5H), 6.71 (s, 0.5H), 6.67 (s, 0.5H), 4.39 (s, 1H), 4.24 (s, 1H), 3.92 (s, 1.5H), 3.85 (s, 1.5H), 3.83 (s,

1.5H), 2×3.79 (s, 1.5H), 3.63 (s, 1.5H), 3.56-3.44 (m, 1H), 3.37-3.25 (m, 1H), 2.95-2.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 159.0, 154.5, 154.4, 148.33, 148.30, 147.4, 147.2, 141.4, 141.3, 134.6, 134.3, 132.4, 132.2, 130.04, 130.01, 129.8, 129.5, 129.4, 128.9, 128.7, 128.6, 128.5, 128.4, 128.31, 128.27, 128.24, 127.6, 127.1, 126.9, 120.6, 120.5, 114.0, 113.9, 113.4, 113.3, 112.8, 112.6, 90.0, 89.7, 81.9, 81.8, 56.1, 55.9, 55.7, 55.29, 55.27, 52.3, 49.3, 46.8, 45.4, 32.0, 30.1; HRMS (EI): m/z $[M]^+$ calcd. for $C_{33}H_{31}NO_4$: 505.2253; found: 505.2283.

(*E*)-3-methyl-1-(1-phenylethylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4q**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (50-60-70-80-80-90-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min (8 mL/min for two first intervals) delivering pure **4q** (t_r = 14 min). Yield: 38 mg, 69%. White amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-6.97 (m, 7H), 6.82-6.68 (m, 2H), 4.55-4.39 (m, 1H), 3.40-3.06 (m, 6H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 141.5, 137.8, 135.3, 134.9, 133.7, 132.6, 129.9, 128.8, 127.9, 127.0, 126.8, 125.8, 47.7, 32.8, 31.5, 22.1; HRMS (ESI^+): m/z $[M+H]^+$ calcd. for $C_{19}H_{20}NO^+$: 278.1539; found: 278.1534.

(*E*)-3-isopropyl-1-(1-phenylethylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4s**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (7:3) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-60-70-70-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering pure **4s** (t_r = 33 min). Yield: 27.5 mg, 45%. White amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19-6.96 9m, 7H), 6.82-6.67 (m, 2H), 4.92 (sept, J = 6.8 Hz, 1H), 4.24-4.08 (m, 1H), 3.58-3.45 (m, 1H), 3.29-2.98 (m, 2H), 2.23 (s, 3H), 1.23 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 141.6, 137.3, 135.7, 135.2, 133.9, 132.3, 129.8, 128.8, 127.9, 127.0, 126.7, 125.7, 43.6, 39.1, 34.5, 21.9, 20.8, 20.6; HRMS (EI): m/z $[M]^+$ calcd. for $C_{21}H_{23}NO$: 305.1780; found: 305.1773.

(*E*)-8,9-dimethoxy-3-(4-methoxybenzyl)-1-(1-phenylethylidene)-3,4,5,6-tetrahydrobenzo[*d*]azocin-2(1*H*)-one (**4u**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (7:3→1:1) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-60-70-70-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering pure **4u** (t_r = 36 min). Yield: 12 mg, 13%. White amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23-7.10 (m, 6H), 6.88-6.80 (m, 3H), 6.47 (s, 3H), 4.49 (bs, 2H), 3.84-3.74 (m, 8H), 3.58-3.49 (m, 2H), 2.67-2.57 (m, 2H), 2.24-2.14 (m, 3H), 1.76-1.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 159.0, 147.9, 147.0, 140.6, 134.9, 133.4, 131.9, 129.72, 129.69, 129.6, 127.9, 127.6, 126.9, 114.2, 113.9, 112.8, 55.9, 55.7, 55.3, 49.5, 49.1, 36.0, 28.9, 21.2; HRMS (EI): m/z $[M]^+$ calcd. for $C_{29}H_{31}NO_4$: 457.2253; found: 457.2251. Further elution provided ***N*-(3-(4,5-dimethoxybiphenyl-2-yl)propyl)-*N*-(4-methoxybenzyl)but-2-ynamide** (**5u**) as a ~ 1:1 mixture of rotamers (t_r = 43 min). Yield: 31 mg, 34%. Colorless oil; ^{1}H NMR (300 MHz,

$CDCl_3$): δ 7.46-7.30 (m, 3H), 7.30-7.21 (m, 2H), 7.10-7.00 (m, 2H), 6.88-6.77 (m, 2H), 6.74 (s, 0.5H), 6.73 (s, 0.5H), 6.71 (s, 0.5H), 6.67 (s, 0.5H), 4.46 (s, 1H), 4.32 (s, 1H), 2×3.90 (s, 1.5H), 2×3.85 (s, 1.5H), 3.80 (s, 1.5H), 3.78 (s, 1.5H), 3.34-3.24 (m, 1H), 3.18-3.07 (m, 1H), 2.56-2.39 (m, 2H), 2.00 (s, 1.5H), 1.89 (s, 1.5H), 1.70-1.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 159.0, 154.8, 154.6, 148.1, 146.9, 146.8, 141.7, 141.6, 134.2, 133.9, 131.1, 130.8, 129.5, 129.41, 129.38, 128.9, 128.4, 128.23, 128.17, 126.9, 126.7, 114.0, 113.9, 113.4, 113.3, 112.20, 112.17, 89.0, 88.9, 73.7, 73.4, 56.05, 56.02, 55.96, 55.95, 55.3, 55.2, 51.6, 47.3, 46.2, 43.1, 30.03, 29.97, 29.8, 28.4, 4.1, 3.9; HRMS (EI): m/z $[M]^+$ calcd. for $C_{29}H_{31}NO_4$: 457.2253; found: 457.2276.

(*E*)-7,8-dimethoxy-3-(4-methoxybenzyl)-1-(4-phenylbut-3-yn-2-ylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4y**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (7:3→3:2) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-70-70-80-90-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering pure **4y** (t_r = 42 min). Yield: 22.4 mg, 24%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.19 (m, 8H), 6.88 (d, J = 8.5 Hz, 2H), 6.53 (s, 1H), 4.95 9d, J = 14.7 Hz, 1H), 4.32 (d, J = 14.7 Hz, 1H), 4.07-3.94 (m, 1H), 3.86 (s, 3H), 3.81 (s, 6H), 3.32-3.20 (m, 1H), 2.97-2.80 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 159.1, 148.8, 146.4, 142.6, 131.4, 129.5, 128.4, 128.0, 125.2, 123.1, 119.2, 114.3, 114.1, 112.1, 94.2, 90.3, 55.84, 55.80, 55.3, 47.6, 44.5, 31.9, 21.0; HRMS (EI): m/z $[M]^+$ calcd. for $C_{30}H_{29}NO_4$: 467.2097; found: 467.2075. Further elution provided **(*E*)-1-((*Z*)-4,6-diphenylhex-3-en-5-yn-2-ylidene)-7,8-dimethoxy-3-(4-methoxybenzyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one** (**6a**) (t_r = 63 min). Yield: 11.4 mg, 10%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62-7.48 (m, 4H), 7.43-7.18 (m, 8H), 7.07 (s, 1H), 6.88 (d, J = 8.5 Hz, 2H), 6.82 (s, 1H). 6.55 (s, 1H), 4.99 (d, J = 14.7 Hz, 1H), 4.31 (d, J = 14.7 Hz, 1H), 4.12-3.97 (m, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H), 3.30-3.20 (m, 1H), 2.98-2.78 (m, 2H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 159.1, 148.8, 146.6, 139.6, 139.5, 134.7, 134.1, 131.2, 129.6, 129.4, 128.6, 128.48, 128.45, 128.3, 127.9, 126.2, 125.0, 123.4, 123.2, 115.7, 114.1, 112.6, 98.7, 88.8, 55.9, 55.8, 55.3, 47.4, 44.3, 31.8, 19.3; HRMS (EI): m/z $[M]^+$ calcd. for $C_{38}H_{35}NO_4$: 569.2566; found: 569.2596.

(*E*)-3-methyl-1-(4-phenylbut-3-yn-2-ylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (4z): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (7:3) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-70-70-80-90-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering pure **4z** (t_r = 35 min). Yield: 11.5 mg, 19%. Yellow solid; m.p. 144-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79-7.68 (m, 1H), 7.31-7.18 (m, 7H), 7.17-7.09 (m, 1H), 4.30-4.14 (m, 1H), 3.33-2.96 (m, 6H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 142.8, 135.3, 133.2, 132.0, 131.5, 129.9, 128.3, 128.2, 128.1, 125.6, 123.1, 119.9, 93.6, 90.0, 47.6, 32.8, 31.6, 20.9; HRMS (EI): m/z $[M]^+$ calcd. for $C_{21}H_{19}NO$: 301.1467; found: 301.1489. Further elution provided **(*E*)-1-((*Z*)-4,6-diphenylhex-3-en-5-yn-2-ylidene)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one** (**6b**) (t_r = 55 min). Yield: 10.5 mg, 13%. Yellow solid; m.p. 180-183 °C; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.60-7.46 (m, 4H), 7.41-7.12 (m, 10H), 7.00 (s, 1H), 4.35-4.20 (m, 1H), 3.32-2.95 (m,6H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 139.9, 139.6, 135.7, 134.6, 134.5, 133.2, 132.9, 131.2, 130.4, 128.5, 128.44, 128.38, 128.1, 127.8, 126.4, 125.8, 123.5, 123.4, 98.6, 88.9, 47.5, 32.6, 31.5, 19.2; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{29}H_{26}NO$: 404.2009; found: 404.2004.

General procedure for the Heck-Suzuki tandem reaction for the synthesis of 3-benzazepines 4l,n,p,r,t and benzazocine 4v

$Pd(PPh_3)_2Cl_2$ (4.2 mg, 3 mol%), vinyl potassium trifluoroborate **3p** (40 mg, 0.3 mmol) and propargylamide **1** (0.2 mmol) were loaded into a microwave instrument vial and dissolved in DMF (1.8 mL). Then K_3PO_4 (85 mg, 0.4 mmol) was added followed by distilled water (0.45 mL). The reaction vial was evacuated, flushed with argon, sealed and irradiated under stirring at the set temperature of 115 °C for 20 min utilizing a maximum power of 100 W. Upon completion of the irradiation time the vial was cooled with a stream of air. When a fresh portion of $Pd(PPh_3)_2Cl_2$ (2.8 mg, 2 mol%) was added. The reaction vial was evacuated, flushed with argon, sealed and irradiated under stirring at the set temperature of 115 °C for another 15 min. Upon completion of the reaction the vial was cooled with a stream of air. The reaction mixture was diluted with EtOAc (50 mL), washed with water (2×50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude material was subjected to the appropriate purification procedure.

(*E*)-1-(but-3-en-2-ylidene)-7,8-dimethoxy-3-(4-methoxybenzyl)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4l**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent delivering pure **4l**. Yield: 57 mg, 72%. Beige amorphous solid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.72 (s, 1H), 6.69 (dd, J = 17.4, 10.9 Hz, 1H), 6.53 (s, 1H), 5.44 (d, J = 17.4 Hz, 1H), 5.20 (d, J = 10.9 Hz, 1H), 4.92 (d, J = 14.7 Hz, 1H), 4.31 (d, J = 14.7 Hz, 1H), 4.04-3.91 (m, 1H), 3.87-3.77 (m, 9H), 3.27-3.15 (m, 1H), 2.89-2.77 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 159.0, 148.6, 146.6, 136.6, 135.6, 133.1, 129.6, 129.3, 128.1, 124.6, 116.4, 115.3, 114.0, 112.6, 56.0, 55.9, 55.3, 47.4, 44.4, 31.7, 15.4; HRMS (EI): m/z $[M]^+$ calcd. for $C_{24}H_{27}NO_4$: 393.1940; found: 393.1943.

(*E*)-7,8-dimethoxy-3-(4-methoxybenzyl)-1-(pent-1-en-3-ylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4n**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by recrystallization/washing with diethyl ether delivering pure **4n**. Yield: 65 mg, 80%. Yellow solid; m.p. 164-166 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.70 (s, 1H), 6.61-6.47 (m, 2H), 5.46 (d, J = 17.5 Hz, 1H), 5.21 (d, J = 11.0 Hz, 1H), 4.94 (d, J = 14.7 Hz, 1H), 4.29 (d, J = 14.7 Hz, 1H), 4.05-3.74 (m, 11H), 3.27-3.15 (m, 1H), 2.90-2.66 (m, 3H), 2.55-2.40 (m, 1H), 1.14 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 159.0, 148.6, 146.6, 138.8,

136.2, 133.9, 129.7, 129.4, 128.1, 124.8, 116.3, 115.3, 114.0, 112.6, 56.0, 55.8, 55.3, 47.3, 44.3, 31.7, 22.1, 13.5; HRMS (EI): m/z $[M]^+$ calcd. for $C_{25}H_{29}NO_4$: 407.2097; found: 407.2097.

(*Z*)-7,8-dimethoxy-3-(4-methoxybenzyl)-1-(1-phenylallylidene)-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4p**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (1:1) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O with 0.1% HCOOH (30-40-50-60-70-70-80-90-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering pure **4p** (t_r = 40 min). Yield: 16.4 mg, 18%. White amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.28 (m, 5H), 6.97-6.82 (m, 2H), 6.70 (s, 4H), 6.60 (s, 1H), 5.26 (d, J = 10.9 Hz, 1H), 4.95 (d, J = 15.8 Hz, 2H), 4.15-4.00 (m, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.84-3.73 (m, 4H), 3.21-3.10 (m, 1H), 3.04-2.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 158.8, 148.9, 146.8, 138.8, 137.5, 137.3, 135.4, 129.7, 129.3, 129.2, 128.3, 127.9, 127.4, 124.2, 120.6, 114.8, 113.7, 112.8, 56.1, 55.9, 55.3, 46.7, 44.1, 31.6; HRMS (EI): m/z $[M]^+$ calcd. for $C_{29}H_{29}NO_4$: 455.2097; found: 455.2086.

(*E*)-1-(but-3-en-2-ylidene)-3-methyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4r**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (3:2) as eluent delivering pure **4r**. Yield: 37.7 mg, 83%. Yellow amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.08 (m, 4H), 6.64 (dd, J = 17.4, 10.9 Hz, 1H), 5.44 (d, J = 17.4 Hz, 1H), 5.19 (d, J = 10.9 Hz, 1H), 4.26-4.09 (m, 1H), 3.28-2.94 (m, 6H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 136.8, 135.7, 135.4, 133.6, 132.7, 132.6, 130.3, 127.8, 125.7, 116.7, 47.6, 32.6, 31.4, 15.4; HRMS (EI): m/z $[M]^+$ calcd. for $C_{15}H_{17}NO$: 227.1310; found: 227.1328.

(*E*)-1-(but-3-en-2-ylidene)-3-isopropyl-4,5-dihydro-1*H*-benzo[*d*]azepin-2(3*H*)-one (**4t**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (7:3→1:1) as eluent delivering pure **4t**. Yield: 40.3 mg, 79%. Pale yellow solid; m.p. 136-138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.08 (m, 4H), 6.63 (dd, J = 17.4, 10.9 Hz, 1H), 5.42 (dd, J = 17.4, 1.1 Hz, 1H), 5.17 (dd, J = 10.9, 1.1 Hz, 1H), 4.87 (sept, J = 6.8 Hz, 1H), 3.95-3.80 (m, 1H), 3.45-3.34 (m, 1H), 3.16-2.92 (m, 2H), 2.00 (s, 3H), 1.19 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 137.6, 135.5, 133.1, 132.8, 132.5, 130.3, 127.7, 125.6, 116.4, 43.5, 38.9, 34.4, 20.7, 20.5, 15.1; HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{17}H_{22}NO$: 256.1696; found: 256.1697.

(*E*)-1-(but-3-en-2-ylidene)-8,9-dimethoxy-3-(4-methoxybenzyl)-3,4,5,6-tetrahydrobenzo[*d*]azocin-2(1*H*)-one (**4v**): The material obtained after workup was subjected to column chromatography on silicagel with heptane/EtOAc (4:1→3:1) as eluent delivering pure **4v**. Last fractions containing **4v** overlapping with other impurities were concentrated separately and resubjected to column chromatography delivering a second portion of pure **4v**. Combined yield: 48 mg, 59%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, J = 8.5 Hz, 2H), 6.86-6.78 (m, 3H), 6.62 (s, 1H), 6.26 (dd, J = 17.4, 10.8 Hz, 1H), 5.34 (d, J = 17.4, 0.8 Hz, 1H), 5.10 (d, J = 10.8, 0.8 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.45-3.30 (m, 2H), 2.71-2.59 (m, 2H), 1.95 (s, 3H),

1.74-1.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 158.9, 148.2, 147.4, 136.9, 134.8, 132.3, 130.6, 129.7, 129.6, 129.2, 115.8, 113.9, 112.9, 112.8, 56.0, 55.9, 55.3, 49.8, 49.3, 36.2, 29.1, 14.6; HRMS (EI): m/z $[M]^+$ calcd. for $C_{25}H_{29}NO_4$: 407.2097; found: 407.2078.

Synthesis of (*E*)-7,8-dimethoxy-3-(4-methoxybenzyl)-2-phenyl-1-(1-phenylbutylidene)-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (**4w**): $Pd(PPh_3)_2Cl_2$ (4.2 mg, 3 mol%), phenylboronic acid **3a** (36.6 mg, 0.3 mmol) and propargylamine **1g** (107 mg, 0.2 mmol) were loaded into a microwave instrument vial and dissolved in DMF (1.8 mL). Then K_3PO_4 (85 mg, 0.4 mmol) was added followed by distilled water (0.45 mL). The reaction vial was evacuated, flushed with argon, sealed and irradiated under stirring at the set temperature of 110 °C for 25 min utilizing a maximum power of 100 W. Upon completion of the irradiation time the vial was cooled with a stream of air. When a fresh portion of $Pd(PPh_3)_2Cl_2$ (2.8 mg, 2 mol%) was added. The reaction vial was evacuated, flushed with argon, sealed and irradiated under stirring at the set temperature of 110 °C for another 15 min. Upon completion of the reaction the vial was cooled with a stream of air. The reaction mixture was diluted with EtOAc (50 mL), washed with water (2×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was subjected to column chromatography on silicagel with heptane/EtOAc (23:2→17:3) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O (60-70-80-90-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min delivering pure **4w** (t_r = 37 min). Yield: 29 mg, 27%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.10 (m, 7H), 7.06-6.92 (m, 3H), 6.91-6.78 (m, 4H), 6.47 (s, 1H), 5.66 (s, 1H), 4.94 (s, 1H), 3.82-3.71 (m, 7H), 3.40 (d, J = 13.7 Hz, 1H), 3.25 (s, 3H), 3.19-3.06 (m, 2H), 3.05-2.92 (m, 2H), 2.76-2.62 (m, 1H), 2.49-2.36 (m, 1H), 1.51-1.35 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 146.9, 145.5, 143.4, 142.8, 141.3, 139.2, 132.4, 131.7, 131.0, 129.4, 129.0, 128.0, 127.8, 127.4, 126.5, 125.8, 117.2, 113.5, 111.1, 69.2, 57.9, 55.7, 55.5, 55.2, 47.2, 36.0, 35.2, 21.6, 14.4; HRMS (EI): m/z $[M]^+$ calcd. for $C_{36}H_{39}NO_3$: 533.2930; found: 533.2959. Further elution provided ***N*-(2-(4,5-dimethoxybiphenyl-2-yl)ethyl)-*N*-(4-methoxybenzyl)-1-phenylhex-2-yn-1-amine** (**5w**) contaminated with unknown impurities (t_r = 40 min). Amount of obtained material: 43 mg. NMR yield: 35%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.44 (m, 2H), 7.35-7.00 (m, 10H), 6.80 (d, J = 8.5 Hz, 2H), 6.66 (s, 1H), 6.58 (s, 1H), 4.61 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.57 (d, J = 13.4 Hz, 1H), 3.32 (d, J = 13.4 Hz, 1H), 2.81-2.65 (m, 1H), 2.64-2.44 (m, 3H), 2.40-2.23 (m, 2H), 1.62 (q, J = 7.2 Hz, 2H), 1.06 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 147.8, 146.7, 141.5, 140.0, 134.2, 131.9, 130.1, 129.9, 129.3, 128.2, 128.0, 127.8, 127.0, 126.6, 113.5, 113.1, 112.9, 88.0, 75.4, 56.2, 55.92, 55.87, 55.3, 54.5, 51.9, 31.5, 22.6, 20.9, 13.7; HRMS (EI): m/z $[M]^+$ calcd. for $C_{36}H_{39}NO_3$: 533.2930; found: 533.2930.

Synthesis of (*E*)-1-(hex-1-en-3-ylidene)-7,8-dimethoxy-3-(4-methoxybenzyl)-2-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (**4x**): $Pd(PPh_3)_2Cl_2$ (4.2 mg, 3 mol%), vinyl potassium trifluoroborate **3p** (40 mg, 0.3 mmol) and propargylamine **1g** (107 mg, 0.2 mmol) were loaded into a microwave instrument vial and dissolved in DMF (1.8 mL). Then K_3PO_4 (85 mg, 0.4 mmol) was added followed by distilled water (0.45 mL). The

reaction vial was evacuated, flushed with argon, sealed and irradiated under stirring at the set temperature of 115 °C for 25 min utilizing a maximum power of 100 W. Upon completion of the irradiation time the vial was cooled with a stream of air. When a fresh portion of $Pd(PPh_3)_2Cl_2$ (4.2 mg, 3 mol%) was added. The reaction vial was evacuated, flushed with argon, sealed and irradiated under stirring at the set temperature of 115 °C for another 15 min. Upon completion of the reaction the vial was cooled with a stream of air. The reaction mixture was diluted with EtOAc (50 mL), washed with water (2×50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was subjected to column chromatography on silicagel with heptane/EtOAc (17:3) as eluent followed by reversed phase preparative HPLC with gradient pump mode, MeCN/H_2O (50-60-70-80-80-90-100%, 10 min intervals) as eluent and a flow rate of 10 mL/min (8 mL/min for two first intervals) delivering pure **4x** (t_r = 51 min). Yield: 53 mg, 55%. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.04 (m, 7H), 6.80 (d, J = 8.6 Hz, 2H), 6.63 (s, 1H), 6.21 (dd, J = 17.5, 11.0 Hz, 1H), 6.08 (s, 1H), 5.17 (dd, J = 17.5, 1.1 Hz, 1H), 4.89 (dd, J = 11.0, 1.1 Hz, 1H), 4.79 (s, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.70-3.58 (m, 4H), 3.27 (d, J = 13.8 Hz, 1H), 3.01-2.78 (m, 3H), 2.73-2.37 (m, 3H), 1.70-1.40 (m, 2H), 1.04 9t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 147.7, 145.7, 142.4, 141.8, 137.0, 136.1, 132.2, 131.5, 129.9, 129.4, 128.2, 127.8, 126.7, 116.4, 113.5, 112.7, 111.7, 69.6, 57.8, 56.1, 55.8, 55.2, 47.2, 34.4, 29.8, 22.4, 14.8; HRMS (EI): m/z $[M]^+$ calcd. for $C_{32}H_{37}NO_3$: 483.2773; found: 483.2787.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for **1b**, **4a-z**, **5g,j,o,u,w** and **6a,b**. X-ray crystallographic structures and CIF files for **4m,t,z** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org

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[17] CCDC 1044489 (**4m**), CCDC 1044492 (**4t**), CCDC 1044490 (**4z**) and CCDC 1044491 (**6b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via: www.ccdc.cam.ac.uk/data_request/cif.