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Sequential Combination of Ruthenium-, Base-, and Gold-Catalysis – A New Approach to the Synthesis of Medicinally Important Heterocycles

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A general approach to the high-yielding synthesis of medicinally important heterocycles was achieved through the sequential combination of ring-closing metathesis, base-induced ring opening (BIRO), hydroamination, and a Diels–Alder reaction of functionalized allyl-(2-allylphenyl)amines in the presence of a catalytic amount of Grubbs' second-generation catalyst, base (*t*BuOK), and [AuCl(PPh_3)]/AgOTf. Herein, we also demonstrate the important electronic factors in the BIRO of N-substituted-benzo[*b*]azepines for the regioselective synthesis of functionalized (*Z*)-N-substituted-2-(buta-1,3-dienyl)phenylamines in very good yields with high purity; these are very good, useful compounds in medicinal chemistry. We also discovered the selective cascade synthesis of privileged hexahydrophenanthridines from (*Z*)-N-substituted-2-(buta-1,3-dienyl)phenylamines by gold catalysis in moderate to good yields with >99 % diastereomeric excess. The possible reaction mechanism for the unusual hydroamination followed by [4+2] cycloaddition of functionalized (*Z*)-*N*-substituted-2-(buta-1,3-dienyl)phenylamines through gold catalysis is discussed in this work.

Introduction

Benzannulated nitrogen heterocycles are well-known biologically active compounds that display a wide range of pharmacological activities.[1] In particular, N-substituted-2,3-dihydro-1*H*-benzo[*b*]azepines, N-substituted-2-(buta-1,3-dienyl)phenylamines, N-substituted-1,2,3,4-tetrahydroquinolines, and functionalized hexahydrophenanthridines display promising biological activities.[1] Thus, the diversity-oriented synthesis of these heterocycles represents an important task because of the widespread occurrence of such structural scaffolds and their use as building blocks in pharmaceuticals. For example, OPC-31260 (**A**), OPC-41061 (**B**), an inhibitor of N-type calcium channels (**C**), Strobilurin I (**D**), a molecule with antiparasitic activity (**E**), and lycorine (**F**) are some of the compounds that are very useful in medicinal chemistry (Figure 1).[1]

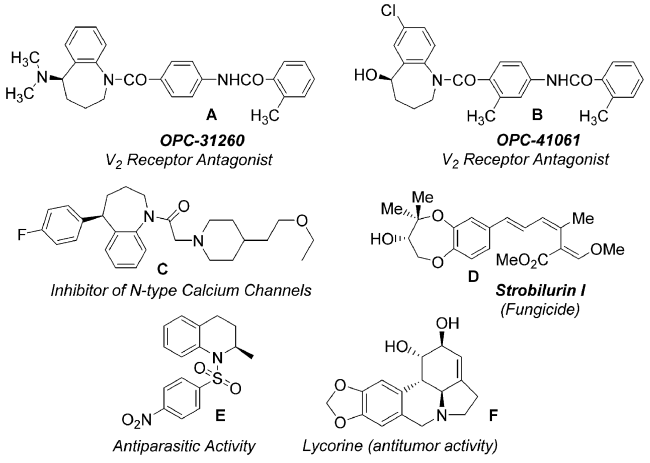
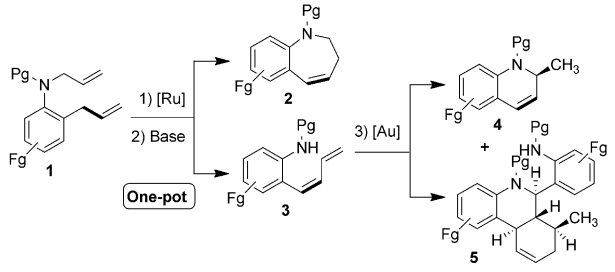


Figure 1. Examples of important heterocycles in medicinal chemistry.

We have designed a novel methodology for the synthesis of highly functionalized N-substituted-benzo[*b*]azepines, N-substituted-2-(buta-1,3-dienyl)phenylamines, N-substituted-2-methyl-2*H*-quinolines, and N-substituted-phenanthridines starting from simple dienes (Scheme 1). A ruthenium-catalyzed ring-closing metathesis (RCM), base-induced ring opening (BIRO), and gold-catalyzed hydroamination of olefins followed by [4+2] cycloaddition reactions are the crucial steps in the designed reaction sequence. Interestingly, to the best of our knowledge, there have not been any re-



Scheme 1. A sequential RCM, BIRO, and gold-catalyzed hydroamination of olefins followed by [4+2] cycloaddition in one pot. Pg = protecting group, Fg = functional group.

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ports of the synthesis of three different heterocycles from one common precursor. Herein, we report, for the first time, a sequential one-pot approach to the synthesis of highly functionalized benzo[*b*]azepines (**2**), (*Z*)-2-(buta-1,3-dienyl)-phenylamines (**3**), 2-methyl-2*H*-quinolines (**4**), and phenanthridines (**5**) starting from simple dienes (**1**) by sequential RCM/BIRO and gold-catalyzed hydroamination followed by [4+2] cycloaddition reactions.[2]

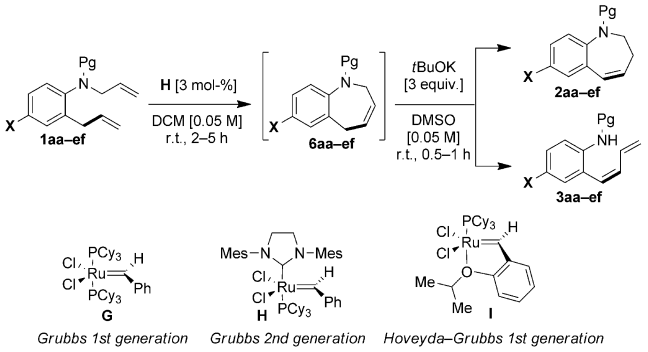
Results and Discussion

The investigation into the newly designed sequential one-pot reactions was initiated by synthesizing a library of substituted heterodienes/heteroenynes **1** as precursors in very good yields through a combination of N-allylation, N-propargylation, C-allylation, and N-protection on anilines as key steps (see Schemes S1–S4 in the Supporting Information). First, the scope of the sequential RCM/BIRO one-pot reactions was investigated with a variety of N-substituted heterodienes **1aa**–**1ef** by comparing the electronic factors, as shown in Table 1. Reaction of ethyl allyl-(2-allyl-4-chlorophenyl)carbamate (**1aa**) with Grubbs' first-generation catalyst **G** (3 mol-%) in CH_2Cl_2 at 25 °C for 15 h gave the benzo[*b*]azepine **6aa** in >95% conversion, which on further treatment with *t*BuOK (3 equiv.) in DMSO at 0–25 °C for 0.5 h gave the interesting ethyl (2-buta-1,3-dienyl-4-chlorophenyl)carbamate (*cis*-**3aa**) with moderate yield (75%) and >99% *Z* selectivity under one-pot conditions (Table 1, entry 1). In a similar manner, the sequential RCM/BIRO one-pot reaction of **1aa** using Hoveyda–Grubbs' first-generation catalyst **I** (3 mol-%) in CH_2Cl_2 at 25 °C for 3 h followed by treatment with *t*BuOK (3 equiv.) in DMSO at 0–25 °C for 0.5 h gave the carbamate *cis*-**3aa** in 85% yield with >99% *Z* selectivity (Table 1, entry 2). Interestingly, the sequential RCM/BIRO one-pot reaction of **1aa** using Grubbs' second-generation catalyst **H** (3 mol-%) in CH_2Cl_2 at 25 °C for only 5 h followed by treatment with *t*BuOK (3 equiv.) in DMSO at 0–25 °C for 0.5 h gave the carbamate *cis*-**3aa** in very good yield (92%) with >99% *Z* selectivity (Table 1, entry 3).[3]

After obtaining this preliminary information, we further investigated the sequential RCM/BIRO one-pot reactions on heterodienes containing different N-protecting groups to study the electronic factors. Interestingly, sequential RCM/BIRO one-pot reactions on heterodienes containing *N*-Ts **1ab**, *N*-COPh **1ac**, *N*-$COCH_3$ **1ad**, and *N*-$COCF_3$ **1ae** gave the expected products (*Z*)-**3ab**–**3ae** in very good yields with high *Z* selectivity, as shown in Table 1, entries 4–7. But the RCM reaction of the heterodiene **1af** (containing *N*-H/Ar-*Cl*) with catalyst **H**/*p*TSA gave the 7-chloro-2,5-dihydro-1*H*-benzo[*b*]azepine (**6af**) in 75% yield, which on further treatment with *t*BuOK (3 equiv.) in DMSO at 0–25 °C for 3 h gave only isomerized 7-chloro-2,3-dihydro-1*H*-benzo-[*b*]azepine **2af** in 55% yield instead of (*Z*)-**3af**, as shown in Table 1, entry 8. In a similar manner, the RCM reaction of the heterodiene **1ef** (containing *N*-H/Ar-*Me*) with catalyst **I**/TFA gave the 7-methyl-2,5-dihydro-1*H*-benzo[*b*]azepine (**6ef**) in 50% yield, which on further treatment with *t*BuOK (3 equiv.) in DMSO at 0–25 °C for 1 h gave only isomerized 7-methyl-2,3-dihydro-1*H*-benzo[*b*]azepine (**2ef**) in 75% yield instead of (*Z*)-**3ef**, as shown in Table 1, entry 9. From these results, sequential RCM/BIRO one-pot reactions proved to be extremely facile with heterodienes **1aa**–**1ef**, containing electron-withdrawing groups on nitrogen, as shown in Table 1. We envisioned the optimized conditions to be the reaction of **1aa** with catalyst **H** (3 mol-%) in CH_2Cl_2 at 25 °C for 5 h to give the benzo[*b*]azepine **6aa** in >99% conversion, which on in situ treatment with *t*BuOK (3 equiv.) in DMSO at 0–25 °C for 0.5 h gave the one-pot product *cis*-**3aa** in 92% yield and >99% *Z* selectivity (Table 1, entry 3). The structure and regiochemistry of (*Z*)-2-(buta-1,3-dienyl)phenylamines **3** were confirmed by NMR spectroscopic analysis and also finally confirmed by X-ray structure analysis of *cis*-**3ac**, as shown in Figure S1 in the Supporting Information.[4]

With the optimized reaction conditions in hand, the scope of the ruthenium and base-induced RCM/BIRO and RCM/isomerization one-pot reactions was investigated with a variety of heterodienes and heteroenynes **1**, as shown in Table 2. The sequential RCM reaction of the substituted heterodienes **1ba**–**1ib** (containing *N*-CO_2Et, *N*-$COCF_3$, or

Table 1. Reaction optimization for the sequential RCM/BIRO or RCM/I reaction of **1aa**–**1ef** in one pot.

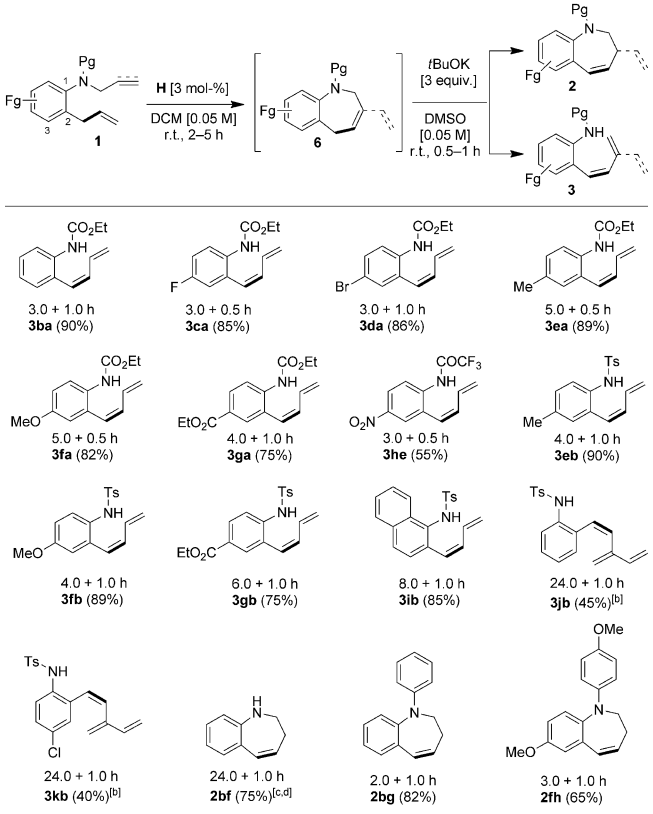


Entry	X	Pg	Time [h]	Product	Yield [%][a]
1[b]	Cl	CO_2Et (**a**)	15 + 0.5	**3aa**	75
2[c]	Cl	CO_2Et (**a**)	3 + 0.5	**3aa**	85
3	**Cl**	**CO_2Et (a)**	**5 + 0.5**	**3aa**	**92**
4	Cl	Ts[d] (**b**)	3 + 0.5	**3ab**	88
5	Cl	COPh (**c**)	4 + 0.5	**3ac**	80
6	Cl	$COCH_3$ (**d**)	4 + 0.5	**3ad**	71
7	Cl	$COCF_3$ (**e**)	3 + 1.0	**3ae**	40
8[e,f]	Cl	H (**f**)	24 + 3.0	**2af**	55
9[f,g]	Me	H (**f**)	27 + 1.0	**2ef**	75

[a] Yield refers to the product purified by column chromatography. [b] RCM reaction performed with Grubbs first-generation catalyst **G** (3 mol-%). [c] The RCM reactions were performed with Hoveyda–Grubbs first-generation catalyst **I** (3 mol-%). [d] Ts = tosyl. [e] *p*-Toluenesulfonic acid (*p*TSA) (1 equiv.) was used as a co-catalyst for the RCM reaction. [f] The BIRO reaction was performed on the isolated RCM product. [g] The RCM reactions were performed with Hoveyda–Grubbs first-generation catalyst **I** (5 mol-%) and trifluoroacetic acid (TFA; 2 equiv.) were used as co-catalysts.

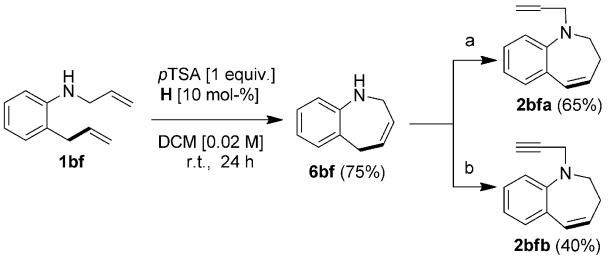
N-Ts) with Grubbs' second-generation catalyst **H** (3 mol-%) in CH_2Cl_2 at 25 °C for 3–8 h gave the functionalized benzo[*b*]azepines **6ba**–**6ib** in >99% conversion, which on in situ treatment with *t*BuOK (3 equiv.) in DMSO at 0–25 °C for 0.5–1.0 h gave the functionalized (*Z*)-2-(buta-1,3-dienyl)-phenylamines **3ba**–**3ib** in very good yields with high *Z* selectivity, as shown in Table 2, entries 1–11 (read the entry numbers from left to right sequentially). Interestingly, enyne metathesis of the substituted heteroenynes **1jb** and **1kb** [*N*-Ts] with Grubbs' first-generation catalyst **G** (8 mol-%) in CH_2Cl_2 at 25 °C for 24 h gave the benzo[*b*]azepines **6jb**–**6kb** in >99% conversion, which on in situ treatment with base gave the products *cis*-**3jb**–**3kb** in moderate yields (Table 2, entries 12 and 13). To support the role of electronic factors in BIRO reactions, we performed these sequential reactions on benzo[*b*]azepines **6bf**, **6bg**, and **6fh** (containing *N*-H, *N*-Ph, and *N*-PMP; PMP = *para*-methoxyphenyl), as shown in Table 2, entries 14–16. Interestingly, in situ treatment of benzo[*b*]azepines **6bf**, **6bg**, and **6fh** with *t*BuOK (3 equiv.) in DMSO at 0–25 °C for 1.0 h gave only the double-bond-isomerized RCM/isomerization products **2bf**, **2bg**, and **2fh** in 75, 82, and 65% yields, respectively (Table 2, entries 14–16).

Table 2. Chemically diverse libraries of functionalized amines **2/3**.[a]



[a] Yield refers to the product purified by column chromatography. [b] RCM reactions were performed with Grubbs first-generation catalyst G (8 mol-%). [c] *p*TSA (1 equiv.) was used as a co-catalyst in the RCM reaction. [d] The BIRO reaction was performed on the isolated RCM product.

We have also utilized base-induced double-bond isomerization with N-alkylation reactions in one pot to deliver the functionalized 2,3-dihydro-1*H*-benzo[*b*]azepines **2** in good yields (Scheme 2). Reaction of 2,5-dihydro-1*H*-benzo[*b*]-azepine (**6bf**) with *t*BuOK (3 equiv.) at 0–25 °C for 1 h, followed by in situ treatment with allyl bromide (**a**) or propargyl bromide (**b**) at 25 °C for 3–18 h gave the one-pot products *N*-allyl-2,3-dihydro-1*H*-benzo[*b*]azepine (**2bfa**) and 1-prop-2-ynyl-2,3-dihydro-1*H*-benzo[*b*]azepine (**2bfb**) in 65 and 40% yield, respectively; these were good starting materials for the synthesis of drug analogues of **A**–**C** (Figure 1).



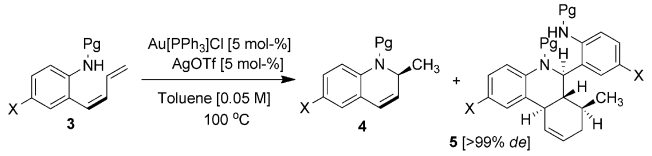
Scheme 2. Reaction conditions: (a) *t*BuOK (3 equiv.), DMSO (0.05 M), 25 °C, 1 h; $H_2C{=}CHCH_2Br$ (**a**, 2 equiv.), 25 °C, 3 h, 65%; (b) *t*BuOK (3 equiv.), DMSO (0.05 M), 25 °C, 1 h; $HC{\equiv}CCH_2Br$ (**b**, 2 equiv.), 25 °C, 18 h, 40%.

After understanding the sequential one-pot combination of RCM, BIRO, isomerization, and alkylation reactions, we were also interested in investigating the intra- and intermolecular hydroamination of (*Z*)-aminodienes **3**, as shown in Tables 3 and 4. The hydroamination of olefins is a prominent and atom-economic reaction for the synthesis of N-heterocycles.[5] In particular, intra- and intermolecular hydroamination displays an efficient route for accessing multifunctional N-heterocycles for natural-product synthesis and pharmaceuticals.[5] Since the seminal discovery of metallocene-catalyzed hydroamination by Marks and co-workers,[6] hydroamination emerged as an important reaction to study many aspects of N-heterocycles. Starting from simple aminoalkenes, the scope of metal-promoted hydroamination reactions was quickly extended to various unsaturated molecules, including aminoalkynes, aminoallenes, conjugated (*E*)-aminodienes and aminodialkenes, aminodialkynes, and aminoalkenalkynes.[5] However, the metal-catalyzed intra- or intermolecular hydroamination of conjugated (*Z*)-aminodienes **3** was not known and the resulting products **4** and **5** could have a wide range of uses in pharmaceutical chemistry (see Scheme 1).[5]

After thorough investigation of intra- and intermolecular hydroamination of conjugated (*Z*)-aminodienes **3aa**–**3ad** with gold chlorides and/or silver salts, we found that $[AuCl(PPh_3)]$/AgOTf (5 mol-%) in toluene at reflux were suitable conditions for the designed hydroaminations, as shown in Table 3 and Table S1 in the Supporting Information.[7] Interestingly, the reaction of *N*-Ts-(*Z*)-aminodiene **3ab** with $[AuCl(PPh_3)]$/AgOTf (5 mol-%) in the toluene at 100 °C for 24 h selectively gave **4ab** in 50% yield without

5ab (Table 3, entry 1). In a similar manner, treatment of *N*-Ts-(*Z*)-aminodienes **3eb**–**3gb** with [AuCl(PPh$_3$)]/AgOTf (5 mol-%) in toluene at 100 °C for 6–7 h only gave intramolecular hydroamination products **4eb**–**4gb** in moderate yields (Table 3, entries 2–4). However, the reaction of *N*-CO$_2$Et-(*Z*)-aminodiene **3aa** with [AuCl(PPh$_3$)]/AgOTf (5 mol-%) in toluene at 100 °C for 24 h gave the unexpected cascade intermolecular hydroamination/[4+2] cycloaddition product **5aa** in 55% yield with >99% diastereomeric excess (*de*) and also **4aa** in 20% yield (Table 3, entry 5).[8] In a similar manner, the reaction of *N*-COCH$_3$-(*Z*)-aminodiene **3ad** with [AuCl(PPh$_3$)]/AgOTf (5 mol-%) in toluene at 100 °C for 24 h only gave cascade product **5ad** in 40% yield with >99% *de* (Table 3, entry 6). Herein, products **4** were generated through gold-catalyzed intramolecular hydroamination of **3**, and cascade product **5aa** was formed through gold-catalyzed intermolecular hydroamination of **3aa** followed by unusual gold-catalyzed intramolecular [4+2] cycloaddition reactions. The product selectivity of these reactions was mainly controlled by electronic factors, as shown by the nature of the N-protecting groups.[8]

Table 3. Synthesis of functionalized 2-methyl-1,2-dihydroquinolines **4**.

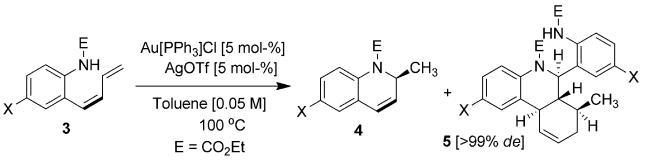


Entry	X	Pg	Time [h]	Product	Yield [%][a]
1	Cl	Ts	24	**4ab**	50
2	CH_3	Ts	6	**4eb**	30
3	OCH_3	Ts	6	**4fb**	25
4	CO_2Et	Ts	7	**4gb**	25
5	Cl	CO_2Et	24	**4aa**, **5aa**	20, 55
6	Cl	$COCH_3$	24	**5ad**	40

[a] Yield refers to the column-purified product.

To explore the unusual gold-catalyzed intra- and intermolecular hydroamination followed by selective [4+2] cycloaddition reactions, we chose a variety of (*Z*)-ethyl-2-buta-1,3-dienyl-carbamates, **3aa**–**3ga**, and *N*-(2-buta-1,3-dienyl-4-chlorophenyl)acetamide (**3ad**) as substrates (Table 4). Compounds **3aa**–**3ga** were transformed into functionalized, N-substituted 2-methyl-2*H*-quinolines **4aa**–**4ga** in moderate yields and highly functionalized N-substituted phenanthridines **5aa**–**5ga** in good yields with >99% *de* through a combination of gold/silver catalysis, as shown in Table 4, entries 1–6. Cascade products **5aa**–**5ga** were formed in good yields and with high diastereoselectivity through gold catalysis without showing much effect from substitution (X) on the benzene rings of **3aa**–**3ga**. The structure and stereochemistry of N-substituted phenanthridines **5** were confirmed by NMR spectroscopic analysis and also finally confirmed by X-ray structure analysis of **5aa** (Figure S2 in the Supporting Information).[4]

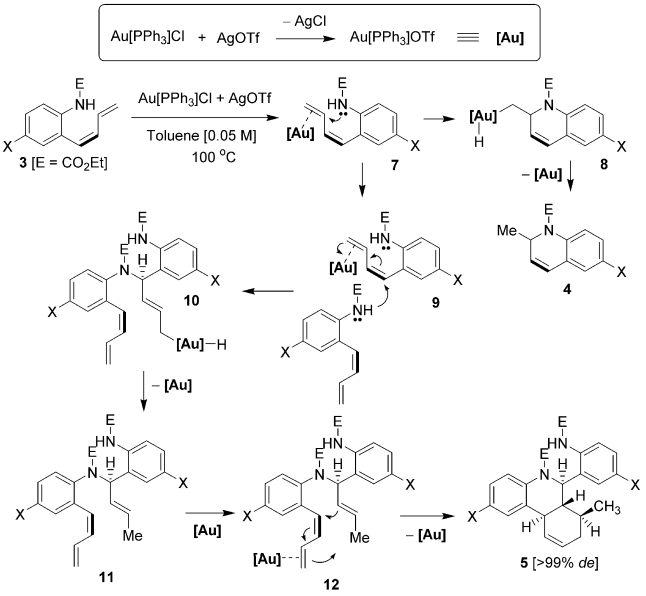
Table 4. Synthesis of N-substituted phenanthridines **5**.[a]



Entry	X	Time [h]	Product **4** (Yield [%][a])	Product **5** (Yield [%][a])
1	Cl	24	**4aa** (20)	**5aa** (55)
2	H	10	**4ba** (25)	**5ba** (40)
3	Br	24	**4da** (24)	**5da** (47)
4	CH_3	24	**4ea** (26)	**5ea** (43)
5	OCH_3	6	**4fa** (30)	**5fa** (25)
6	CO_2Et	8	**4ga** (20)	**5ga** (60)
7[b]	Cl	24	–	**5ad** (40)

[a] Yield refers to the column purified product. [b] E = $COCH_3$.

Even though further studies are required to firmly elucidate the mechanism of these sequential cascade reactions through [AuCl(PPh$_3$)]/AgOTf catalysis, a possible reaction mechanism for intra- and intermolecular hydroamination followed by selective [4+2] cycloaddition is illustrated in Scheme 3. Treatment of (*Z*)-diene **3** with in situ generated active gold catalyst [Au(PPh$_3$)]OTf forms the reactive complex **7**, which can undergo both intra- or intermolecular hydroamination based on the electronic nature of the amine group. In the first route, intramolecular hydroamination of **7** followed by reductive elimination of unstable intermediate **8** generates the expected product **4** with free catalyst [Au] for further cycles, as shown in Scheme 3. In the second route, intermolecular hydroamination of **7** with **3** followed by reductive elimination of unstable intermediate **10** generates the key intermediate **11** with free catalyst [Au], as shown in Scheme 3. Activation of the (*Z*)-diene from key intermediate **11** with [Au(PPh$_3$)]OTf gives the intramolecu-



Scheme 3. Proposed reaction mechanism.

lar [4+2] cycloaddition product **5** with high selectivity (>99% *de*) through stepwise or concerted pathways, as shown in compound **12**.

Conclusions

We have shown the strength of a sequential, multicatalytic, one-pot approach in the diversity-oriented synthesis of highly functionalized N-substituted benzo[*b*]azepines **2/6**, N-substituted 2-(buta-1,3-dienyl)phenylamines **3**, N-substituted 2-methyl-2*H*-quinolines **4**, and N-substituted phenanthridines **5** from simple substrates by RCM/BIRO, RCM/isomerization, isomerization/alkylation, intramolecular hydroamination, and cascade intermolecular hydroamination/[4+2] cycloaddition reactions.

Experimental Section

General Methods: The ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported in ppm relative to TMS (δ = 0 ppm) for ^{1}H NMR spectroscopy and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. In the ^{13}C NMR spectra, the nature of the carbon atoms (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses. The coupling constants, *J*, are given in Hz. Column chromatography was performed by using Acme silica gel (particle size 0.063–0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF mass spectrometer. GC–MS was performed on a GC–MS-QP2010 mass spectrometer. IR spectra were recorded on an FT/IR-5300 instrument. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either a VG7070H mass spectrometer using the EI technique or on an LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, $Mo_{K\alpha}$ (λ = 0.71073 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a SMART APEX CCD area detector system equipped with a graphite monochromator and a $Mo_{K\alpha}$ fine-focus sealed tube (λ = 0.71073 Å). For TLC, silica gel plates 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), concentrated H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

Experimental Procedures for the Synthesis of Highly Functionalized N-Substituted 2-(Buta-1,3-dienyl)phenylamines: The synthesis of functionalized N-substituted 2-(buta-1,3-dienyl)phenylamines (**3**) from the corresponding anilines involves the following four or five-step sequence:

Procedure A – N-Alkylations

Method A – N-Diallylations: The starting anilines (1 mmol) were diallylated by treatment with allyl bromide (3 mmol) and sodium hydride (4 mmol) in dry DMF (2 mL, 0.5 M) at 0–25 °C for 2–8 h. The crude reaction mixture was worked up with an aqueous solution of NH_4Cl and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure N-diallylated products were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Method B – N-Monoallylations: The starting anilines (1 mmol) were monoallylated by treatment with allyl bromide (1.1 mmol) and K_2CO_3 (1.2 mmol) in dry DMF (2 mL, 0.5 M) at 0–25 °C for 24 h. The crude reaction mixture was worked up with an aqueous solution of NH_4Cl and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure N-monoallylated products were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Method C – N-Propargylation: The enynes **1j** and **1k** were prepared by treating the corresponding C-allylated anilines (1.0 mmol) with propargyl bromide (130.8 mg, 1.1 mmol) and K_2CO_3 (165.8 mg, 1.2 mmol) in DMF (2 mL, 0.5 M) at room temperature for 24 h. The crude reaction mixture was worked up with an aqueous solution of NH_4Cl and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **1j** and **1k** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Procedure B – C-Allylation Through Claisen Rearrangement: The corresponding N-allylated products (1 mmol), $BF_3{\cdot}Et_2O$ (1 mmol), and freshly distilled xylene (1 mL, 1.0 M) were added to a sealed glass tube and the mixture was heated at 135–140 °C under N_2 for 2 to 8 h. Upon cooling the reaction mixture to room temperature, the mixture was diluted with dichloromethane (10 mL), and washed with an aqueous solution of NH_4Cl (2 mL) and brine (2 mL). The separated organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Pure products **1** were obtained by column chromatography (basic alumina, mixture of hexane/ethyl acetate).

Allyl-(2-allyl-4-bromophenyl)amine (1d): Prepared following the procedure B and purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): $\tilde{\nu}_{max}$ = 3412 (N–*H*), 1575, 1502, 1260, 918, 665 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.21 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.14 (d, *J* = 2.4 Hz, 1 H), 6.47 (d, *J* = 8.4 Hz, 1 H), 5.96–5.84 (m, 2 H, olefinic-*H*), 5.23 (dd, *J* = 16.8, 1.6 Hz, 1 H, olefinic-*H*), 5.17–5.07 (m, 3 H, olefinic-*H*), 3.82 (s, 1 H, N-*H*), 3.74 (d, *J* = 5.2 Hz, 2 H, NCH_2), 3.24 (d, *J* = 6.4 Hz, 2 H, ArCH_2) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 145.0 (C), 135.0 (CH), 134.8 (CH), 132.2 (CH), 130.1 (CH), 125.6 (C), 116.9 (CH_2), 116.2 (CH_2), 112.2 (CH), 108.9 (C), 46.2 (CH_2), 36.0 (CH_2) ppm. MS: *m*/*z* = 251.90 [M + H$^+$].

(2-Allyl-4-chlorophenyl)prop-2-ynylamine (1k): Prepared by following procedures A and B and purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): $\tilde{\nu}_{max}$ = 3295 (C≡C–*H*), 1606, 1503, 1436, 1260, 1000, 666 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.19 (d, *J* = 8.0 Hz, 1 H), 7.09 (s, 1 H, Ar-*H*), 6.69 (d, *J* = 7.6 Hz, 1 H), 5.99–5.90 (m, 1 H, olefinic-*H*), 5.21 (d, *J* = 10.0 Hz, 1 H, olefinic-*H*), 5.14 (d, *J* = 17.2 Hz, 1 H, olefinic-*H*), 3.96 (s, 3 H, NCH_2C≡C-H, N-*H*), 3.29 (d, *J* = 4.8 Hz, 2 H), 2.26 (s, 1 H, NCH_2C≡C-*H*) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 143.6 (C), 134.9 (CH), 129.7 (CH), 127.3 (CH), 126.2 (C), 123.1 (C), 117.1 (CH_2), 112.4 (CH), 80.6 (C, NCH_2C≡C-H), 71.5 (CH, NCH_2C≡*C*-H), 35.9 (CH_2, N*C*H_2C≡C-H), 33.6 (CH_2) ppm. MS: *m*/*z* = 206.05 [M + H$^+$].

Procedure C – N-Protection

Method A – Synthesis of 1aa–1ga, 1ab, 1eb–1kb, and 1ac: The corresponding amines **1a**–**k** (1 mmol) were protected by treatment with pyridine (6 mmol) and Pg-Cl [Pg = CO_2Et (**a**), Ts (**b**), or COPh (**c**); 2 mmol] in dry CH_2Cl_2 (10 mL, 0.1 M) at 0–25 °C for 24 h. The reaction mixture was quenched with water and extracted with

CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with dilute HCl (2 mL) and brine, dried with (Na_2SO_4), filtered, and concentrated. Pure products were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Ethyl Allyl-(2-allyl-4-chlorophenyl)carbamate (1aa): Prepared by following the procedure C, method A, and purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): $\tilde{\nu}_{max}$ = 1708 (N–C=O), 1644, 1485, 1408, 1297, 1027, 771, 648 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.24 (d, J = 2.0 Hz, 1 H), 7.17 (dd, J = 8.4, 2.0 Hz, 1 H), 7.01 (d, J = 8.4 Hz, 1 H), 5.94–5.84 (m, 2 H, olefinic-*H*), 5.14–5.05 (m, 4 H, olefinic-*H*), 4.37–4.29 (m, 1 H, NCH_2), 4.20–4.05 (m, 2 H, OCH_2CH$_3$), 3.86 (dd, J = 13.2, 5.6 Hz, 1 H, NCH_2), 3.25 (d, J = 5.6 Hz, 2 H, ArCH_2), 1.31–1.12 (m, 3 H, OCH$_2$CH_3) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 155.3 (C, N-C=O), 139.8 (C), 138.4 (C), 135.4 (CH), 133.2 (CH), 132.9 (C), 130.0 (CH), 129.9 (CH), 127.0 (CH), 118.4 (CH_2), 117.1 (CH_2), 61.6 (CH_2, OCH_2CH$_3$), 53.2 (CH_2), 35.1 (CH_2), 14.5 (CH_3, OCH$_2$CH_3) ppm. MS: m/z = 280.00 [M + H^+].

Method B – Synthesis of 1ad: Acetic anhydride (1 mL) was added to the diallyl derivative **1a** (51.75 mg, 0.25 mmol) and the reaction mixture was stirred at 25 °C for 15 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The separated organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Pure product **1ad** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

***N*-Allyl-*N*-(2-allyl-4-chlorophenyl)acetamide (1ad):** Prepared by following procedure C, method B, and purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): $\tilde{\nu}_{max}$ = 1659 (N–C=O), 1483, 1385, 1097, 654 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.32 (s, 1 H, Ar-*H*), 7.23 (dd, J = 8.4, 2.4 Hz, 1 H), 7.01 (d, J = 8.4 Hz, 1 H), 5.89–5.82 (m, 2 H, olefinic-*H*), 5.18–5.10 (m, 3 H, olefinic-*H*), 5.04 (d, J = 16.8 Hz, 1 H, olefinic-*H*), 4.68 (dd, J = 14.4, 5.6 Hz, 1 H, NCH_2), 3.69 (dd, J = 14.0, 7.2 Hz, 1 H, NCH_2), 3.29 (d, J = 6.4 Hz, 2 H, ArCH_2), 1.76 (s, 3 H, COCH_3) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 170.2 (C, N-C=O), 139.6 (C), 139.5 (C), 134.8 (CH), 134.2 (C), 132.5 (CH), 130.8 (CH), 130.7 (CH), 127.6 (CH), 118.7 (CH_2), 117.8 (CH_2), 51.6 (CH_2), 34.9 (CH_2), 22.4 (CH_3) ppm. MS: m/z = 248.10 [M – H^+].

Method C – Synthesis of 1ae: Trifluoroacetic anhydride (420 mg, 2 mmol) was added to a solution of **1a** (207 mg, 1 mmol), Et_3N (101.2 mg, 1 mmol), and 4-dimethylaminopyridine (DMAP; 122.2 mg, 1 mmol) in dry CH_2Cl_2 (5 mL), and the reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with dilute HCl (2 mL) and brine, dried with (Na_2SO_4), filtered, and concentrated. Pure product **1ae** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

***N*-Allyl-*N*-(2-allyl-4-chlorophenyl)-2,2,2-trifluoroacetamide (1ae):** Prepared by following procedure C, method C, and purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): $\tilde{\nu}_{max}$ = 1702 (N–C=O), 1487, 1415, 1211, 925, 680 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.33 (s, 1 H, Ar-*H*), 7.22 (dd, J = 8.4, 2.0 Hz, 1 H), 7.03 (d, J = 8.4 Hz, 1 H), 5.90–5.79 (m, 2 H, olefinic-*H*), 5.24–5.10 (m, 4 H, olefinic-*H*), 4.76 (dd, J = 14.4, 6.0 Hz, 1 H, NCH_2), 3.66 (dd, J = 16.8, 8.0 Hz, 1 H, NCH_2), 3.29 (t, J = 6.0 Hz, 2 H, ArCH_2) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 156.8 (q, J = 36.0 Hz, C, NCOCF$_3$), 139.9 (C), 135.5 (C), 135.4 (C), 134.6 (CH), 131.2 (CH), 130.5 (CH), 130.1 (CH), 127.1 (CH), 120.8 (CH_2), 118.2 (CH_2), 116.1 (q, J = 287.0 Hz, C, NCOCF$_3$), 54.1 (CH_2), 34.5 (CH_2) ppm. MS: m/z = 304.00 [M + H^+].

Procedure D – RCM/BIRO Reactions in One Pot

Method A: A 10 mL oven-dried round-bottomed flask equipped with a stirring bar was charged with diene **1aa**–**1ib** (0.5 mmol) and Grubbs' second-generation catalyst **H** (12.73 mg, 0.015 mmol, 3 mol-%) in dry CH_2Cl_2 (10 mL, 0.05 M) and the reaction mixture was stirred under N_2 at room temperature for 2–5 h. CH_2Cl_2 was distilled off at ambient pressure and the crude reaction mixture was dissolved in dry DMSO (10 mL, 0.05 M) before potassium *tert*-butoxide (168.3 mg, 1.5 mmol, 3 equiv.) was added at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The crude reaction mixture was worked up with water and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **3aa**–**3ib** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Ethyl (2-Buta-1,3-dienyl-4-chlorophenyl)carbamate (3aa): Prepared by following procedure D, method A, and purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): $\tilde{\nu}_{max}$ = 3277 (N–*H*), 1689 (N–C=O), 1529, 1249, 1065, 659 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.96 (d, J = 7.2 Hz, 1 H), 7.24 (dd, J = 8.8, 2.4 Hz, 1 H), 7.14 (d, J = 2.0 Hz, 1 H), 6.54 (br. s, 1 H, N-*H*), 6.48–6.38 (m, 2 H, olefinic-*H*), 6.26 (d, J = 9.2 Hz, 1 H, olefinic-*H*), 5.46–5.38 (m, 1 H, olefinic-*H*), 5.27 (d, J = 8.4 Hz, 1 H, olefinic-*H*), 4.20 (q, J = 7.2 Hz, 2 H, OCH_2CH$_3$), 1.29 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 153.4 (C, N-C=O), 135.0 (CH), 134.2 (2× C), 132.2 (CH), 129.4 (CH), 128.2 (CH), 128.0 (C), 124.1 (CH), 121.7 (CH_2), 120.9 (CH), 61.4 (CH_2, OCH_2CH$_3$), 14.5 (CH_3, OCH$_2$CH_3) ppm. MS: m/z = 252.00 [M + H^+]. $C_{13}H_{14}ClNO_2$ (251.07): calcd. C 62.03, H 5.61, N 5.56; found C 62.12, H 5.55, N 5.61.

Method B: A 10 mL oven-dried round-bottomed flask equipped with a stirring bar was charged with enyne **1jb**–**1kb** (0.5 mmol) and Grubbs' first-generation catalyst **G** (32.9 mg, 0.04 mmol, 8 mol-%) in dry CH_2Cl_2 (25 mL, 0.02 M) and the reaction mixture was stirred under N_2 at room temperature for 24 h. CH_2Cl_2 was distilled off at ambient pressure and the crude reaction mixture was dissolved in dry DMSO (10 mL, 0.05 M) before potassium *tert*-butoxide (168.3 mg, 1.5 mmol, 3 equiv.) was added at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The crude reaction mixture was worked up with water and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **3jb**–**3kb** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

4-Methyl-*N*-[2-(3-methylene-penta-1,4-dienyl)phenyl]benzenesulfonamide (3jb): Prepared by following procedure D, method B, and purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): $\tilde{\nu}_{max}$ = 3263 (N–*H*), 1490, 1332, 1161, 1091, 820, 736 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.61 (d, J = 7.6 Hz, 2 H), 7.46 (d, J = 8.4 Hz, 1 H), 7.22–7.18 (m, 3 H, Ph-*H*), 7.08 (d, J = 7.2 Hz, 1 H), 7.03 (d, J = 7.2 Hz, 1 H), 6.59 (s, 1 H, N-*H*), 6.31–6.24 (m, 2 H, olefinic-*H*), 6.13 (d, J = 12.0 Hz, 1 H, olefinic-*H*), 5.29 (d, J = 17.6 Hz, 1 H, olefinic-*H*), 5.12 (d, J = 10.8 Hz, 1 H, olefinic-*H*), 5.01 (s, 1 H, olefinic-*H*), 4.72 (s, 1 H, olefinic-*H*), 2.38 (s, 3 H, Ar-CH_3) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 143.8 (C), 141.7 (C), 137.5 (CH), 136.6 (C), 133.4 (C), 131.6 (CH), 130.1 (C), 129.6 (CH), 129.5 (2× CH), 128.2 (CH), 127.2 (2× CH), 126.9 (CH), 125.2 (CH), 122.7 (CH), 119.9 (CH_2), 115.6 (CH_2), 21.5 (CH_3, Ar-*C*H$_3$) ppm. MS: m/z = 326.20 [M + H^+]. $C_{19}H_{19}NO_2S$ (325.11): calcd. C 70.12, H 5.88, N 4.30; found C 70.21, H 5.81, N 4.23.

Procedure E – Synthesis of 6af and 6bf: A 25 mL oven-dried round-bottomed flask equipped with a stirring bar was charged with diene **1af**–**1bf** (0.25 mmol), *p*TSA (0.25 mmol, 47.5 mg) and Grubbs' second-generation catalyst **H** (21.22 mg, 0.025 mmol, 10 mol-%) in dry CH_2Cl_2 (10 mL, 0.02 M) and the reaction mixture was stirred under N_2 at room temperature for 24 h. The crude reaction mixture was worked up with an aqueous solution of $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **6af**–**6bf** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7-Chloro-2,5-dihydro-1*H*-benzo[*b*]azepine (6af): Prepared by following procedure **E** and purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): $\tilde{\nu}_{max}$ = 3440 (N–*H*), 3060, 1502, 1411, 1261, 1143, 804 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.04 (s, 2 H, Ar-*H*), 6.73 (d, *J* = 8.4 Hz, 1 H), 5.83–5.80 (m, 1 H, olefinic-*H*), 5.54 (d, *J* = 10.8 Hz, 1 H, olefinic-*H*), 3.76 (br. s, 2 H, NCH_2), 3.44 (br. s, 2 H, ArCH_2) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 147.4 (C), 136.3 (C), 129.0 (CH), 127.2 (CH), 126.9 (CH), 126.6 (C), 125.4 (CH), 121.8 (CH), 48.1 (CH_2), 32.8 (CH_2) ppm. MS: *m*/*z* = 180.10 [M + H^+].

Procedure F – Base-Induced Double-Bond-Isomerization Reactions

Method A – Synthesis of 2af–2fh: A 10 mL oven-dried round-bottomed flask equipped with a stirrer bar was charged with **6af**–**6fh** (0.2 mmol) and dry DMSO (4 mL, 0.05 M) before potassium *tert*-butoxide (67.3 mg, 0.6 mmol, 3.0 equiv.) was added at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The crude reaction mixture was worked up with water and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **2af**–**2fh** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

7-Chloro-2,3-dihydro-1*H*-benzo[*b*]azepine (2af): Prepared by following procedure F, method A, and purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): $\tilde{\nu}_{max}$ = 3391 (N–*H*), 2916, 1593, 1566, 1491, 1251, 1089, 767 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.08 (d, *J* = 2.4 Hz, 1 H), 6.94 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.54 (d, *J* = 8.4 Hz, 1 H), 6.25 (d, *J* = 12.0 Hz, 1 H, olefinic-*H*), 5.96–5.49 (m, 1 H, olefinic-*H*), 4.32 (s, 1 H, N-*H*), 3.30 (t, *J* = 4.8 Hz, 2 H), 2.57–2.53 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 147.3 (C), 132.3 (CH), 131.2 (CH), 128.8 (CH), 126.9 (CH), 125.4 (C), 123.6 (C), 118.4 (CH), 44.6 (CH_2), 34.7 (CH_2) ppm. MS: *m*/*z* = 179.95 [M + H^+].

Method B – Synthesis of 2bfa: A 10 mL oven-dried round-bottomed flask equipped with a stirrer bar was charged with **6bf** (0.2 mmol) and dry DMSO (4 mL, 0.05 M) before potassium *tert*-butoxide (67.3 mg, 0.6 mmol, 3.0 equiv.) was added at 0 °C. After 1 h, allyl bromide (**a**; 48.4 mg, 0.4 mmol, 2 equiv.) was added to the reaction mixture. The reaction mixture was stirred at 25 °C for another 3 h. The crude reaction mixture was worked up with water and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product **2bfa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Method C – Synthesis of 2bfb: A 10 mL oven-dried round-bottomed flask equipped with a stirrer bar was charged with **6bf** (0.2 mmol) and dry DMSO (4 mL, 0.05 M) before potassium *tert*-butoxide (67.3 mg, 0.6 mmol, 3.0 equiv.) was added at 0 °C. After 1 h, propargyl bromide (**b**; 47.5 mg, 0.4 mmol, 2 equiv.) was added to the reaction mixture. The reaction mixture was stirred at 25 °C for another 18 h. The crude reaction mixture was worked up with water and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product **2bfa** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

1-Prop-2-ynyl-2,3-dihydro-1*H*-benzo[*b*]azepine (2bfb): Prepared by following procedure F, method C, and purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): $\tilde{\nu}_{max}$ = 3293 (C≡C–*H*), 2921, 1594, 1495, 1448, 1215, 752, 670 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.17 (d, *J* = 7.2 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 6.86 (t, *J* = 7.2 Hz, 1 H), 6.40 (d, *J* = 12.0 Hz, 1 H, olefinic-*H*), 5.96 (td, *J* = 12.0, 4.4 Hz, 1 H, olefinic-*H*), 4.01 (d, *J* = 2.0 Hz, 2 H, NCH_2C≡C-H), 3.29 (t, *J* = 5.2 Hz, 2 H), 2.57–2.56 (m, 2 H), 2.27 (t, *J* = 2.0 Hz, 1 H, NCH_2C≡C-*H*) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 149.4 (C), 133.4 (CH), 130.2 (CH), 130.0 (CH), 127.4 (CH), 126.9 (C), 120.0 (CH), 115.3 (CH), 80.2 (C, NCH_2C≡C-H), 71.9 (CH, NCH_2C≡*C*-H), 50.6 (CH_2, N*C*H_2C≡C-H), 42.4 (CH_2), 33.6 (CH_2) ppm. MS: *m*/*z* = 184.00 [M + H^+].

Procedure G – Gold-Catalyzed Cascade Hydroamination and Diels–Alder Reactions

Method A – Synthesis of 4ab and 4eb–4gb: Compounds **3ab** and **3eb**–**3gb** (0.1 mmol) were added to mixture of [AuCl(PPh_3)] (2.42 mg, 0.005 mmol, 5 mol-%) and AgOTf (1.28 mg, 0.005 mmol, 5 mol-%) in dry toluene (2 mL, 0.05 M), taken in a sealed glass tube and the mixture is heated at 100 °C under N_2 for 6 to 24 h. The crude reaction mixture was purified by column chromatography (silica gel, mixture of hexane/ethyl acetate). Pure products **4ab** and **4eb**–**4gb** were obtained in moderate yields.

6-Chloro-2-methyl-1-(toluene-4-sulfonyl)-1,2-dihydroquinoline (4ab): Prepared by following procedure G, method A, and purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): $\tilde{\nu}_{max}$ = 1473, 1345, 1091, 1037, 737, 661 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.68 (d, *J* = 8.8 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.24 (dd, *J* = 8.4, 2.4 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 6.94 (d, *J* = 2.4 Hz, 1 H), 5.92 (d, *J* = 9.6 Hz, 1 H, olefinic-*H*), 5.70 (dd, *J* = 9.6, 5.6 Hz, 1 H, olefinic-*H*), 4.94 (quintet, *J* = 6.4 Hz, 1 H, NC*H*), 2.35 (s, 3 H, Ar-CH_3), 1.16 (d, *J* = 6.8 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 143.5 (C), 136.0 (C), 131.8 (C), 131.1 (C & CH), 129.7 (C), 129.2 (2× CH), 129.1 (CH), 127.8 (CH), 127.1 (2× CH), 125.9 (CH), 122.7 (CH), 51.0 (CH), 21.5 (CH_3, Ar-*C*H_3), 19.8 (CH_3) ppm. MS: *m*/*z* = 334.01 [M + H^+]. $C_{17}H_{16}ClNO_2S$ (333.05): calcd. C 61.16, H 4.83, N 4.20; found C 61.22, H 4.78, N 4.32. HRMS: *m*/*z* = 356.0485 [M + Na], calcd. for $C_{17}H_{16}NO_2SNa$ 356.0488.

Method B – Synthesis of 4aa–4ga, 5aa–5ga, and 5ad: Compounds **3aa**–**3ga** and **3ad** (0.1 mmol) were added to mixture of [AuCl(PPh_3)] (2.42 mg, 0.005 mmol, 5 mol-%) and AgOTf (1.28 mg, 0.005 mmol, 5 mol-%) in dry toluene (2 mL, 0.05 M), placed in a sealed glass tube, and the mixture was heated at 100 °C under N_2 for 6–24 h. Purification of crude reaction mixtures by column chromatography (silica gel, mixture of hexane/ethyl acetate) gave products **4aa**–**4ga**, **5aa**–**5ga**, and **5ad** in moderate to good yields.

Ethyl 6-Chloro-2-methyl-2*H*-quinoline-1-carboxylate (4aa): Prepared by following procedure G, method B, and purified by column chromatography using EtOAc/hexane and isolated as a liquid. IR (neat): $\tilde{\nu}_{max}$ = 1719 (N–C=O), 1671, 1498, 1216, 1043, 732 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.57–7.55 (m, 1 H), 7.18 (dd, *J* = 8.8, 2.8 Hz, 1 H), 7.07 (d, *J* = 2.4 Hz, 1 H), 6.38 (d, *J* = 9.6 Hz, 1 H, olefinic-*H*), 6.08 (dd, *J* = 9.6, 6.0 Hz, 1 H, olefinic-*H*), 5.13 (quintet, *J* = 6.4 Hz, 1 H, NC*H*), 4.33–4.24 (m, 2 H, OCH_2CH_3), 1.34 (t, *J* = 7.2 Hz, 3

H, OCH_2CH_3), 1.12 (d, J = 6.8 Hz, 3 H, $CHCH_3$) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 154.0 (C, N-C=O), 132.8 (C), 132.0 (CH), 129.0 (C), 128.4 (C), 127.2 (CH), 125.8 (CH), 125.7 (CH), 123.3 (CH), 62.2 (CH_2, OCH_2CH_3), 48.9 (CH), 18.5 (CH_3), 14.5 (CH_3, OCH_2CH_3) ppm. MS: m/z = 252.25 [M + H^+]. $C_{13}H_{14}ClNO_2$ (251.07): calcd. C 62.03, H 5.61, N 5.56; found C 62.13, H 5.58, N 5.65. HRMS: m/z = 274.0611 [M + Na], calcd. for $C_{13}H_{14}ClNO_2Na$ 274.0611.

Ethyl 2-Chloro-6-(5-chloro-2-ethoxycarbonylaminophenyl)-7-methyl-6a,7,8,10a-tetrahydro-6*H*-phenanthridine-5-carboxylate (5aa): Prepared by following procedure G, method B, and purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): $\tilde{\nu}_{max}$ = 1726 (N–C=O), 1682 (N–C=O), 1481, 1401, 1221, 1053, 739 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 9.26 (s, 1 H, N-*H*), 7.69 (br. d, J = 5.2 Hz, 1 H), 7.33 (d, J = 2.0 Hz, 1 H), 7.26 (dd, J = 8.8, 2.4 Hz, 1 H), 7.21 (dd, J = 8.8, 2.4 Hz, 1 H), 7.10 (d, J = 8.4 Hz, 1 H), 6.46 (d, J = 2.4 Hz, 1 H), 6.14 (br. d, J = 10.4 Hz, 1 H, olefinic-*H*), 6.03–5.99 (m, 1 H, olefinic-*H*), 5.32 (d, J = 10.4 Hz, 1 H, NC*H*), 4.30 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.26–4.13 (m, 2 H, OCH_2CH_3), 3.15 (d, J = 10.0 Hz, 1 H), 2.15–2.09 (m, 1 H), 2.05–1.95 (m, 1 H), 1.77–1.65 (m, 2 H), 1.38 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.23 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 0.61 (d, J = 6.4 Hz, 3 H, $CHCH_3$) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 155.8 (C, N-C=O), 154.6 (C, N-C=O), 139.4 (2× C), 136.3 (CH), 134.7 (C), 134.6 (C), 131.6 (C), 130.0 (CH), 129.4 (C), 128.2 (CH), 127.4 (CH), 127.1 (CH), 126.5 (CH), 123.4 (2× CH), 62.8 (CH_2, OCH_2CH_3), 61.2 (CH_2, OCH_2CH_3), 56.7 (CH), 54.4 (CH), 39.1 (CH), 34.9 (CH_2), 34.5 (CH), 18.8 (CH_3), 14.7 (CH_3, OCH_2CH_3), 14.3 (CH_3, OCH_2CH_3) ppm. MS: m/z = 503.30 [M + H^+]. $C_{26}H_{28}Cl_2N_2O_4$ (502.14): calcd. C 62.03, H 5.61, N 5.56; found C 62.18, H 5.67, N 5.46. HRMS: m/z = 525.1323 [M + Na], calcd. for $C_{26}H_{28}Cl_2N_2O_4Na$ 525.1324.

***N*-[2-(5-Acetyl-2-chloro-7-methyl-5,6,6a,7,8,10a-hexahydrophenanthridin-6-yl)-4-chlorophenyl]acetamide (5ad):** Prepared by following procedure G, method B, and purified by column chromatography using EtOAc/hexane and isolated as a solid. IR (neat): $\tilde{\nu}_{max}$ = 2917, 1692 (N–C=O), 1637, 1603, 1482, 1298, 1038, 737 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 10.38 (s, 1 H, N-*H*), 7.82 (d, J = 8.8 Hz, 1 H), 7.39 (d, J = 1.6 Hz, 1 H), 7.31 (dd, J = 8.8, 2.4 Hz, 1 H), 7.20 (dd, J = 8.8, 2.4 Hz, 1 H), 6.92 (d, J = 8.0 Hz, 1 H), 6.34 (d, J = 2.0 Hz, 1 H), 6.13 (d, J = 8.8 Hz, 1 H, olefinic-*H*), 6.03–5.99 (m, 1 H, olefinic-*H*), 5.57 (d, J = 8.4 Hz, 1 H, NC*H*), 3.09 (d, J = 10.8 Hz, 1 H), 2.32 (s, 3 H, $COCH_3$), 2.16–2.08 (m, 1 H), 2.08 (s, 3 H, $COCH_3$), 1.97–1.94 (m, 1 H), 1.76–1.65 (m, 2 H), 0.59 (d, J = 6.4 Hz, 3 H, $CHCH_3$) ppm. ^{13}C NMR ($CDCl_3$, DEPT-135): δ = 171.0 (C, N-C=O), 168.9 (C, N-C=O), 140.8 (C), 135.5 (C), 135.0 (C), 134.6 (C), 133.4 (C), 130.5 (CH), 129.6 (C), 128.3 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 126.4 (CH), 124.2 (CH), 122.9 (CH), 55.7 (CH), 53.8 (CH), 39.2 (CH), 34.8 (CH_2), 34.6 (CH), 24.3 (CH_3, $COCH_3$), 22.4 (CH_3, $COCH_3$), 19.0 (CH_3) ppm. MS: m/z = 443.35 [M + H^+]. $C_{24}H_{24}Cl_2N_2O_2$ (442.12): calcd. C 65.02, H 5.46, N 6.32; found C 65.12, H 5.51, N 6.23. HRMS: m/z = 465.1112 [M + Na], calcd. for $C_{24}H_{24}Cl_2N_2O_2Na$ 465.1113.

Supporting Information (see footnote on the first page of this article): Experimental procedures, synthesis of starting materials, X-ray crystal structures, and analytical data for all new compounds.

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