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A Metal-Catalyzed Tandem 1,4-Benzodiazepine Synthesis Based on Two Hydrogen-Transfer Reactions

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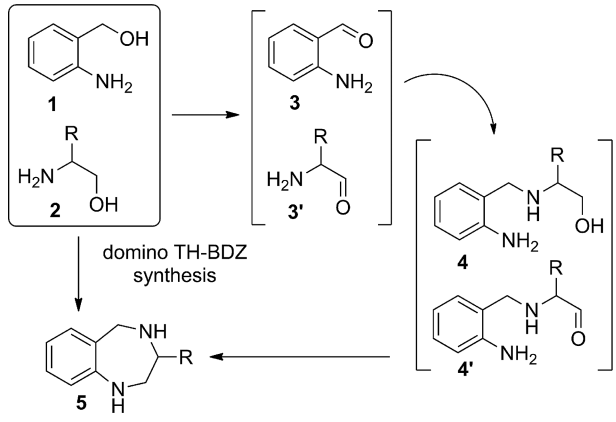
Starting from 2-aminobenzyl alcohols and 1,2-amino alcohols, 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines (TH-BDZ) can be prepared through a one-pot ruthenium-catalyzed reaction encompassing two consecutive borrowing hydrogen cycles. First, benzyl alcohol oxidation, condensation with the amino alcohol, and imine reduction occurs. This is followed by oxidation of the other alcohol functionality and reductive cyclocondensation to give the TH-BDZ derivatives. A single catalyst does the entire job, with two molecules of water being the only waste product. Many new substituted 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines have been prepared to demonstrate the versatility of this method, which can be used for the preparation of privileged scaffolds for drug discovery.

Introduction

The development of more efficient processes is one of the major goals of contemporary synthetic organic chemistry.[1] Multicomponent and cascade reactions play a key role in reducing the number of steps, with savings in time and in the materials required for purification of intermediates. Catalysis, meanwhile, helps to increase atom economy and to use milder and more sustainable reaction conditions.[2]

Among the metal-catalyzed reactions regularly used in organic synthesis, the redox process called "borrowing hydrogen" (or hydrogen autotransfer)[3] has found several interesting applications, especially in the field of heterocyclic chemistry. Under the influence of a catalyst, often containing iridium or ruthenium, an alcohol is oxidized to an aldehyde, which may undergo a nucleophilic addition. The condensation product can be further manipulated to prepare diverse heterocyclic scaffolds such as pyrroles, pyridines, quinolines, quinoxalines, benzimidazoles, benzoxazoles, and indoles.[4] Among the various heterocyclic compounds, benzodiazepines (BDZ) are important molecules with several applications[5] in medicinal chemistry (treatment of central nervous system (CNS) disorders and muscle spasms) or in oncology.[6] Benzodiazepinones are prepared from isatoic anhydride and amino acids,[7] and the multistep synthesis of benzodiazepinones and BDZs has also been reported.[8] However, the direct synthesis of saturated simple 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines (TH-BDZ) is less well explored. The reduction of the corresponding benzodiazepin(edi)ones with $LiAlH_4$ or other strong metal hydrides is often the method of choice for TH-BDZ synthesis.[9] In view of the numerous applications of the BDZ scaffold in medicinal chemistry, a simple and direct access to TH-BDZs is highly desirable.

Following our interest in hydrogen-autotransfer strategies,[4d,4k–4m] we decided to explore a tandem process[10] encompassing two consecutive series of oxidation, condensation, cyclocondensation, and reduction to provide TH-BDZs starting from 2-aminobenzyl alcohols and β-amino alcohols (Scheme 1).



Scheme 1. Proposal for a new simple 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (TH-BDZ) synthesis.

Results and Discussion

For a test reaction, benzyl alcohol **1** and phenylalaninol (**2a**) were chosen as model substrates, and treated with dif-

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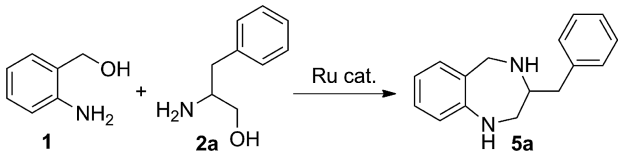
ferent ruthenium-based catalysts to investigate the feasibility of the reaction. Various catalytic species obtained by mixing different ruthenium precursors and phosphorus ligands were explored, working in toluene at 160 °C in a closed vial (Table 1). Among the metal catalysts tested, $[Ru(p\text{-cymene})Cl_2]_2$ and $[Ru(CO)(PPh_3)_3HCl]$ turned out to be compatible with all the bidentate P-ligands used, providing the product (i.e., **5a**) in moderate yields (Table 1, Entries 9–13 and 14–17). Interestingly, $[Ru(CO)(PPh_3)_3HCl]$ also worked without any added ligand (Table 1, Entry 13), while $[Ru(benzene)Cl_2]_2$ and $[Ru(COD)Cl_2]_n$ required the presence of Xantphos to achieve acceptable yields of TH-BDZ **5a** (Table 1, Entries 5 and 18).

Table 1. Optimization of reaction conditions.[a]



Entry	Ru catalyst	Ligand[b]	Yield of **5a** [%][c]
1	$Ru_3(CO)_{12}$	Xantphos	9
2[d]		Xantphos	–
3		DPEphos	≤ 5
4		dppf	≤ 5
5	$[Ru(benzene)Cl_2]_2$	Xantphos	58
6		dppf	–
7		DPEphos	–
8		BIPHEP	–
9	$[Ru(CO)(PPh_3)_3HCl]$	Xantphos	20
10		DPEphos	30
11		BIPHEP	51
12		dppf	45
13		–	15
14	$[Ru(p\text{-cymene})Cl_2]_2$	Xantphos	65
15		BIPHEP	40
16		dppf	32
17		DPEphos	22
18	$[Ru(COD)Cl_2]_n$	Xantphos	52
19		DPEphos	≤ 5
20		BIPHEP	≤ 5
21		dppf	≤ 5

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), and catalyst (5 mol-%) in toluene (1 mL) under nitrogen at 160 °C for 12–16 h. [b] Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; DPEphos = bis[(2-diphenylphosphino)phenyl] ether; dppf = 1,1′-bis(diphenylphosphino)ferrocene; BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl; COD = cyclooctadiene. [c] Isolated yields [%]. [d] In refluxing toluene.

High temperature (160 °C) was always necessary for these reactions, as only traces of product could be observed in refluxing toluene (Table 1, Entry 2). To improve the product yields, we focused on the Ru loading and the ligand/catalyst ratio (Table 2). With $[Ru(p\text{-cymene})Cl_2]_2$ and Xantphos as the catalytic system, several fine-tuning experiments indicated that a 1:1 ligand/Ru ratio is the optimum choice for obtaining TH-BDZ **5a**.

Table 2. Assessment of the reaction conditions.[a]

Entry	$[Ru(p\text{-cymene})Cl_2]_2$ [mol-%]	Xantphos [mol-%]	Time [h]	Yield [%][b]
1	2.5	2.5	15	42
2	5	5	15	69
3	5	10	15	55
4	10	10	15	60
5	5	5	3	25
6	5	5	6	51
7	5	5	48	51
8	5	5	15	32[c]
9	5	5	1 + 1	25[d]
10	5 (2.5 + 2.5)	5 (2.5 + 2.5)	15	36[e]

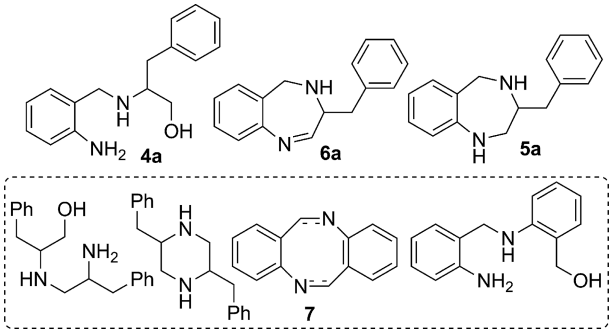
[a] Reaction conditions: under nitrogen, **1** (0.5 mmol), **2a** (0.5 mmol), catalyst (as stated) in toluene at 160 °C for the time indicated. [b] Isolated yields [%]. [c] In degassed toluene. [d] Reaction at 160 °C under microwave irradiation in the presence of an ionic liquid. [e] The catalyst was added in two portions: the first half at the beginning, and the remainder after an interval of 6 h.

Keeping this ratio constant, the catalyst loading was modified between 2.5 and 10 mol-%, and also the timing of the addition of the catalyst to the reaction mixture was examined. The best result was obtained starting with 5 mol-% of catalyst at the beginning of the process (69% yield; Table 2, Entry 2). The use of degassed toluene was also tried, but this had no influence on the yield (Table 2, Entry 8). Finally, microwave (MW) dielectric heating was applied, which was expected to speed up the reaction. However, when the reaction was carried out in toluene in the presence of one drop of $[bmim][BF_4]$ so that the required temperature could be reached, only 25% of **5a** was formed after 2 h of heating (Table 2, Entry 9). The influence of the solvent was also investigated. Switching from toluene to dioxane, THF, or 2-methyl-2-butanol (TAA) resulted in a decrease in the yield of **5a**. The cyclization was also attempted in the presence of various bases without any further improvement in the yield. On the basis of these experiments, the most efficient procedure was heating the reaction mixture at 160 °C in toluene (sealed vial) in the presence of 5 mol-% of a 1:1 mixture of $[Ru(p\text{-Cymene})Cl_2]_2$/Xanthphos for 15 h. This gave compound **5a** in 69% yield (Table 2, Entry 2).

The composition of the reaction mixture was analyzed at different times using TLC, HPLC–MS, and GC–MS, and the most significant components are reported in Table 3.

After 3 h, most of the starting materials (i.e., **1** and **2a**) had been consumed, with the exclusive formation of compounds **5a** (30%), **4a** (25%), and **6a** (35%). No trace of homocondensation products **7** (derived from the reaction of postulated amino aldehydes **3** or **3′**; see Scheme 1) was observed. As the reaction proceeded, intermediates **4a** and **6a** were slowly converted into **5a**, which was finally isolated with a maximum 69% yield after a reaction time of 15 h, together with a mixture containing unreduced diazepine **6a** and different amounts of oligomeric products (see the Supporting Information). Increasing the reaction time to 48 h resulted in a decrease in the yield of **5a** as a result of oligomer formation. To verify whether **4a** was an intermediate

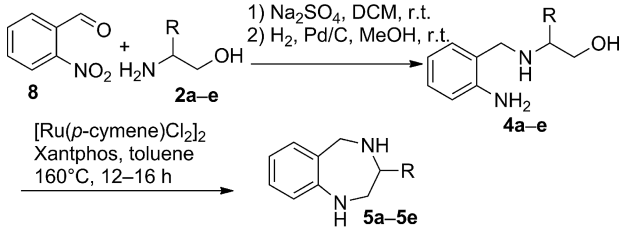
Table 3. Composition of the mixture at different reaction times.[a]



Time [h]	7 [%]	4a [%]	6a [%]	5a [%]	Oligomers[b] [%]
3	0	25	35	30	< 5
6	0	10	23	55	8
15	0	< 5	13	69	10
48	0	< 5	5	51	35

[a] Values determined by HPLC–MS (ESI) analysis using benzylamine as internal standard. [b] From HPLC–MS (ESI) analysis (see Supporting Information).

in the reaction, its preparation was undertaken by condensation of 2-nitrobenzaldehyde (**8**) with **2a**, followed by imine reduction with H_2 in the presence of Pd/C. The isolated **4a** was treated with $[Ru(p\text{-cymene})Cl_2]_2$ and Xantphos in toluene at 160 °C for 12 h, and TH-BDZ **5a** was formed in 45% yield (Scheme 2). This procedure was also extended to amino alcohols **2b**–**2e** to give the corresponding TH-BDZs (i.e., **5b**–**5e**) in moderate yields.

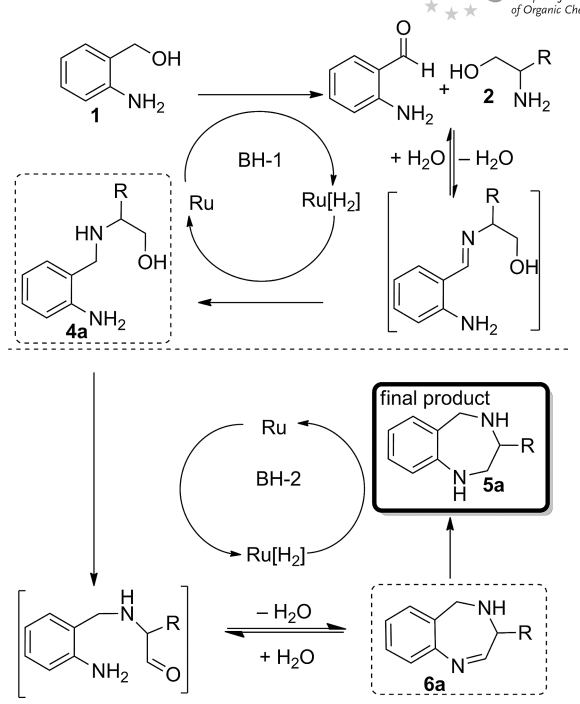


2a, **4a**, **5a**: R = –CH_2Ph (**5a**: Yield 45%)
2b, **4b**, **5b**: R = –Ph (**5b**: Yield 39%)
2c, **4c**, **5c**: R = –$CH_2CH(CH_3)_2$ (**5c**: Yield 33%)
2d, **4d**, **5d**: R= –CH_2CH_3 (**5d**: Yield 38%)
2e, **4e**, **5e**: R = –CH_3 (**5e**: Yield 37%)

Scheme 2. Multistep procedure to BDZ **5**. DCM = CH_2Cl_2.

Based on these results, a tentative reaction mechanism could be postulated (Scheme 3).

A first borrowing hydrogen process (BH-1) occurs with the formation of intermediate **4a** based on the fact that the benzylic alcohol is oxidized more quickly than the aliphatic one. The more nucleophilic amino group condenses with the aldehyde, and this is followed by imine reduction (BH-1). Then, a second borrowing hydrogen process starts (BH-2) with oxidation to the aldehyde followed by cyclocondensation to give dihydrodiazepine **6a**. A second hydrogen transfer completes the process to give the product (i.e., **5a**).[11]

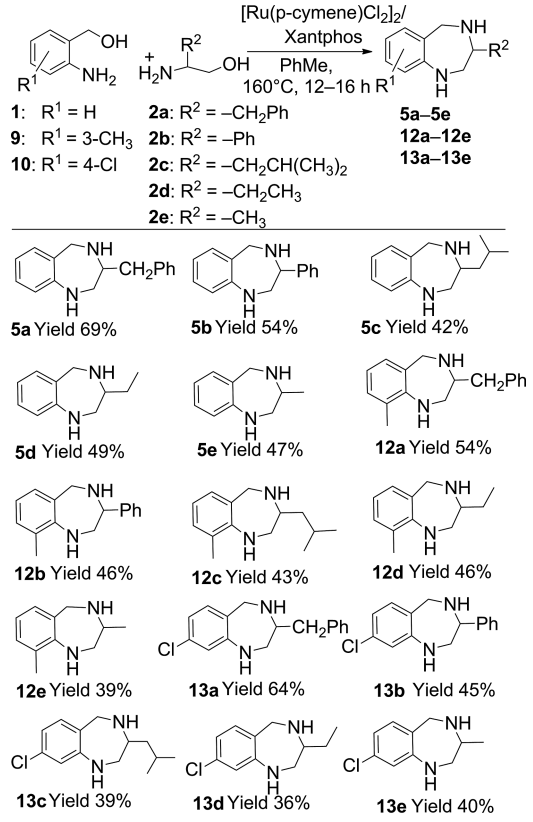


Scheme 3. Proposed mechanism for the TH-BDZ domino synthesis.

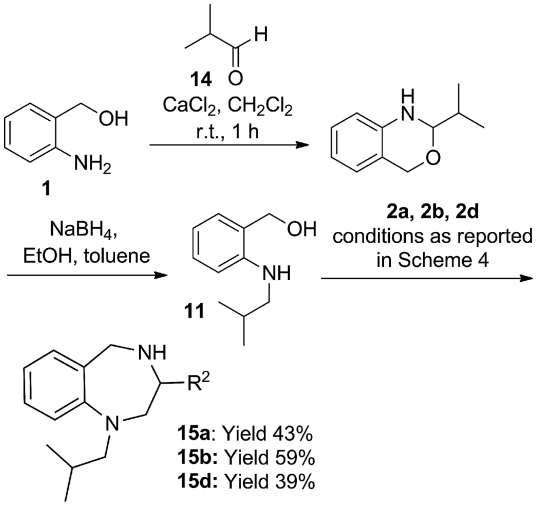
Having established a clarified picture of the reaction, we went on to examine the scope and generality of the process by treating different 2-aminobenzyl alcohols (**1**, **9**, **10**) with aromatic and aliphatic β-amino alcohols (**2a**–**2e**, Scheme 4).[12]

To our delight, in all the tested reactions, our procedure gave the desired products in good to moderate yields (69–36% based on the amount of starting benzyl alcohols). In the reaction of 2-aminobenzyl alcohol (**1**), all the aromatic and aliphatic β-amino alcohols (**2a**–**2e**) reacted smoothly, and a high yield of the product was obtained with phenylalaninol (**2a**). On the other hand, in the reactions with 2-amino-3-methylbenzyl alcohol (**9**), the moderate yields of **12a**–**12e** were probably due to a slight steric hindrance offered by the aromatic ring substituent. The reactions with 2-amino-4-chlorobenzyl alcohol (**10**) showed that the reaction conditions are compatible with electron-withdrawing substituents (Scheme 4). A comparison between the one-pot domino process and the multistep procedure, both developed in this work, was also possible. Comparing the yields obtained for compounds **5a**–**5e** in Schemes 2 and 4 shows that the one-pot tandem process was superior.

These reaction conditions were also used for the synthesis of 1,3-disubstituted TH-BDZs. Thus, starting from aminobenzyl alcohol (**1**), *N*-alkylated aminobenzyl alcohol **11** was obtained according to a reported procedure[13] (Scheme 5). Ru-mediated cyclocondensation with amino alcohols **2a**, **2b**, and **2d** gave products **15a**, **15b**, and **15d** in acceptable overall yields (Scheme 5). These products are more easily functionalizable on the single nucleophilic nitrogen atom using acyl chlorides or other standard electrophiles for diversity-oriented synthesis.



Scheme 4. Domino synthesis of 1,2,3,4-tetrahydro-1,4-benzodiazepines under Ru catalysis.



Scheme 5. Synthesis of TH-BDZs **15**.

Conclusions

The first example of cyclization of β-amino alcohols with 2-aminobenzyl alcohols to give TH-BDZs through a tandem borrowing hydrogen reaction is reported. Even though the TH-BDZs products were obtained in moderate to good yields, the direct formation of saturated benzodiazepines without using any external hydrogenation source is an eye-catching aspect of the reported method, which shows good efficiency and high atom economy. The method also gave consistent results with secondary aminobenzyl alcohols. Moreover, the final products could be isolated without any extractive workup, they were stable to silica gel purification, and they could be handled without extra precautions. Further studies on the extension of this method to the synthesis of unsaturated 1,4-benzodiazepines is currently underway.

Experimental Section

General Remarks: All reagents and solvents were used as purchased from commercial suppliers without further purification. Reactions were carried out in oven- or flame-dried vessels (vials) under nitrogen. Flash column chromatography was carried out with Merck silica gel 60, 0.040–0.063 mm (230–400 mesh). TLC plates were visualized by staining with a solution of Ninhydrin in EtOH then heating to develop the color. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded with an NMR spectrometer. Deuterated chloroform was used as the solvent, and chemical shift values (δ) are reported in parts per million (ppm). The residual signals of the solvent (δ = 7.26 ppm for ^{1}H, and δ = 77.16 ppm for ^{13}C) were used as an internal standard. The data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br. s = broad singlet), coupling constant (J) in Hz, and integration. Mass spectrometry data were collected with GC–MS or LC–MS ESI mass spectrometers. GC conditions: ion-trap detector equipped with a 30 m OV-101 capillary column, splitting injector at 280 °C, method: 45 °C, 5 min; 45–100 °C, 5 °C min^{-1}, 12 min at 100 °C; 100–280 °C, 50 °C min^{-1}, 13 min at 280 °C. LC–MS conditions: ESI ionization after passage through a C-18, 35 × 5 mm, 3 μm column; elution: mixture A (99.9% water, 0.1% HCOOH), mixture B (99.9% acetonitrile, 0.1% HCOOH); 0–20 min, 20–60% mixture B; 20–25 min 60% mixture B; 25–30 min 60–20% mixture B; flow 0.6 mL min^{-1}, room temperature. Reactions using MW dielectric heating were carried out with a microwave oven (Discover from CEM) under monomode irradiation in a 10 mL sealed vial. The internal temperature was monitored using an internal IR sensor, and the maximum internal pressure was monitored and kept under 300 psi. Compounds **1**, **2**, **8**, **9**, and **10** are commercially available. Compound **11** was prepared using the reported procedure.[13] Ru catalysts and ligands were purchased and used as received. Dry toluene purchased from Sigma–Aldrich was used for reactions.

3-(Phenylmethyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5a). General Procedure: Under nitrogen, 2-aminobenzyl alcohol (**1**; 61 mg, 0.5 mmol), β-amino alcohol **2a** (75 mg, 0.5 mmol), catalyst [Ru(*p*-cymene)Cl$_2$]$_2$ (16 mg, 0.025 mmol, 5 mol-%), and Xantphos (15 mg, 0.025 mmol, 5 mol-%) were added to a glass vial with a magnetic stirrer bar. Toluene (1.0 mL) was added, and the glass vial was sealed. The mixture was stirred at 160 °C in a sand bath for 16 h. Then, the mixture was cooled to room temperature, and the reaction was checked by TLC (CH_2Cl_2/MeOH, 9:1). Additional dichloromethane was added, and the reaction mixture was concentrated under reduced pressure. This crude reaction mixture was loaded directly onto a column for flash chromatographic purification (CH_2Cl_2 to CH_2Cl_2/MeOH, 97:3), which gave pure benzodiazepine **5a** (82 mg, 69%) as a yellowish waxy material. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.18 (m, 5 H), 7.07–7.03 (m, 2 H), 6.80 (t, J = 7.4 Hz, 1 H), 6.70 (d, J = 8.0 Hz, 1 H), 3.92, 3.83 (ABq, J = 14.5 Hz, 2 H), 3.32 (dd, J = 13.0, 2.0 Hz, 1 H), 3.19–3.13 (m, 1 H), 2.78–2.67 (m, 3 H), 1.78 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 139.1, 132.1, 130.1, 129.8, 129.0, 128.1, 127.0, 121.1, 119.1, 62.4, 54.6, 53.0, 41.0 ppm. MS (ESI): m/z = 239 [M +

H]$^+$. HRMS (ESI): calcd. for $C_{16}H_{19}N_2$ [M + H]$^+$ 239.1548; found 239.1544.

3-Phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5b): Yield 61 mg (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.21 (m, 5 H), 7.19–7.03 (m, 2 H), 6.86 (t, J = 7.4 Hz, 1 H), 6.77 (d, J = 7.8 Hz, 1 H), 4.14–3.86 (m, 3 H), 3.42 (dd, J = 13.0, 2.3 Hz, 1 H), 2.97 (dd, J = 13.0, 9.5 Hz, 1 H), 2.29 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 143.0, 132.3, 129.8, 128.6, 128.3 127.9, 127.5, 127.1, 126.8, 121.0, 118.9, 66.5, 56.7, 53.8 ppm. MS (ESI): m/z = 225 [M + H]$^+$. HRMS (ESI): calcd. for $C_{15}H_{17}N_2$ [M + H]$^+$ 225.1392; found 225.1389.

3-Isobutyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5c): Yield 43 mg (42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.06 (m, 2 H), 6.82 (t, J = 7.1 Hz, 1 H), 6.74 (d, J = 7.6 Hz, 1 H), 4.03, 3.90 (ABq, J = 14.8 Hz, 2 H), 3.53 (br. s, 2 H), 3.35 (dd, J = 13.3, 2.5 Hz, 1 H), 3.0 (td, J = 9.0, 2.4 Hz, 1 H), 2.71–2.65 (m, 1 H), 1.81–1.65 (m, 1 H), 1.37 (m, 1 H), 1.25 (m, 1 H), 0.95 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 132.1, 129.6, 127.7, 120.6, 118.6, 58.7, 55.3, 52.5, 43.5, 24.9, 23.2, 22.7 ppm. MS (ESI): m/z = 205 [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{21}N_2$ [M + H]$^+$ 205.1705; found 205.1700.

3-Ethyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5d): Yield 44 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.08 (m, 2 H), 6.83 (t, J = 7.4 Hz, 1 H), 6.74 (d, J = 7.8 Hz, 1 H), 5.15 (br. s, 2 H), 4.19, 3.94 (ABq, J = 14.5 Hz, 2 H), 3.39 (dd, J = 13.8, 1.9 Hz, 1 H), 3.03 (dd, J = 13.9, 6.0 Hz, 1 H), 2.91–2.85 (m, 1 H), 1.85–1.58 (m, 2 H), 1.01 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 131.0, 129.3, 126.5, 121.5, 119.2, 62.6, 51.3, 50.8, 25.2, 10.9 ppm. MS (ESI): m/z = 177 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{17}N_2$ [M + H]$^+$ 177.1392; found 177.138.

3-Methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5e): Yield 38 mg (47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (m, 2 H), 6.87 (t, J = 7.4 Hz, 1 H), 6.78 (d, J = 7.6 Hz, 1 H), 4.08, 3.95 (ABq, J = 14.6 Hz, 2 H), 3.36 (dd, J = 13.4, 2.4 Hz, 1 H), 3.23–3.12 (m, 1 H), 2.90 (br. s, 2 H), 2.76 (dd, J = 13.3, 8.8 Hz, 1 H), 1.38–1.17 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0, 130.4, 128.9, 128.5, 121.2, 119.0, 56.5, 54.6, 51.3, 18.8 ppm. MS (ESI): m/z = 163 [M + H]$^+$. HRMS (ESI): calcd. for $C_{10}H_{15}N_2$ [M + H]$^+$ 163.1235; found 163.1232.

3-Benzyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (12a): Yield 68 mg (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.18 (m, 5 H), 6.97 (m, 2 H), 6.72 (m, 1 H), 3.95, 3.85 (ABq, J = 14.5 Hz, 2 H), 3.40 (dd, J = 13.1, 2.3 Hz, 1 H), 3.18 (qd, J = 7.3, 2.5 Hz, 1 H), 2.79 (m, 1 H), 2.68 (m, 2 H), 2.19 (s, 3 H), 1.94 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.1, 138.9, 131.6, 129.5, 129.3, 128.7 (2 C), 128.0 (2 C), 126.5, 125.0, 120.1, 61.9, 53.6, 52.6, 40.6, 17.7 ppm. MS (ESI): m/z = 253 [M + H]$^+$. HRMS (ESI): calcd. for $C_{17}H_{21}N_2$ [M + H]$^+$ 253.1705; found 253.170.

9-Methyl-3-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (12b): Yield 55 mg (46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.17 (m, 5 H), 7.04 (d, J = 7.4 Hz, 2 H), 6.78 (t, J = 7.5 Hz, 1 H), 4.10–3.97 (m, 3 H), 3.52 (dd, J = 13.1, 2.5 Hz, 1 H), 2.95 (dd, J = 13.1, 9.4 Hz, 1 H), 2.23 (s, 3 H), 2.0 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 143.0, 132.1, 129.4, 128.6, 128.1, 127.5, 127.1, 125.2, 120.4, 66.3, 56.1, 53.6, 17.8 ppm. MS (ESI): m/z = 239 [M + H]$^+$. HRMS (ESI): calcd. for $C_{16}H_{19}N_2$ [M + H]$^+$ 239.1548; found 239.1544.

3-Isobutyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (12c): Yield 47 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–6.87 (m, 2 H), 6.81–6.59 (m, 1 H), 4.03, 3.89 (ABq, J = 14.8 Hz, 2 H), 3.42 (dd, J = 13.4, 2.2 Hz, 1 H), 3.01 (d, J = 6.3 Hz, 1 H), 2.67 (dd, J = 13.4, 8.3 Hz, 1 H), 2.18 (s, 3 H), 1.87–1.62 (m, 1 H), 1.38 (dt, J = 13.7, 6.9 Hz, 1 H), 1.30–1.15 (m, 1 H), 2.0–1.6 (br. s, 2 H), 0.93 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.1, 130.1, 129.5, 128.2, 124.9, 120.1, 58.4, 53.6, 51.7, 42.6, 24.9, 22.97, 22.89, 17.7 ppm. MS (ESI): m/z = 219 [M + H]$^+$. HRMS (ESI): calcd. for $C_{14}H_{23}N_2$ [M + H]$^+$ 219.1861; found 219.185.

3-Ethyl-9-methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (12d): Yield 45 mg (46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.99–6.64 (m, 2 H), 6.71 (t, J = 7.4 Hz, 1 H), 4.05, 3.90 (ABq, J = 14.6 Hz, 2 H), 3.68 (br. s, 2 H), 3.46 (dd, J = 13.4, 1.9 Hz, 1 H), 2.88 (d, J = 6.8 Hz, 1 H), 2.73 (dd, J = 13.4, 8.4 Hz, 1 H), 2.18 (s, 3 H), 1.68–1.38 (m, 2 H), 0.98 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.2, 129.7, 129.4, 128.3, 125.0, 120.2, 62.1, 52.5, 51.6, 26.1, 17.7, 10.9 ppm. MS (ESI): m/z = 191 [M + H]$^+$. HRMS (ESI): calcd. for $C_{12}H_{19}N_2$ [M + H]$^+$ 191.1548; found 191.1544.

3,9-Dimethyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (12e): Yield 36 mg (39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (dd, J = 21.9, 7.4 Hz, 2 H), 6.72 (t, J = 7.4 Hz, 1 H), 4.02, 3.89 (ABq, J = 14.6 Hz, 2 H), 3.78 (br. s, 2 H), 3.39 (dd, J = 13.5, 2.5 Hz, 1 H), 3.27–2.99 (m, 1 H), 2.70 (dd, J = 13.5, 8.7 Hz, 1 H), 2.19 (s, 3 H), 1.20 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 130.6, 129.6, 128.1, 124.6, 121.3, 56.4, 55.5, 51.7, 19.3, 17.9 ppm. MS (ESI): m/z = 177 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{17}N_2$ [M + H]$^+$ 177.1392; found 177.1387.

3-Benzyl-8-chloro-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (13a): Yield 87 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.12 (m, 5 H), 6.95 (d, J = 8.0 Hz, 1 H), 6.83–6.63 (m, 2 H), 3.87, 3.75 (ABq, J = 14.6 Hz, 2 H), 3.30 (d, J = 11.7 Hz, 1 H), 3.15–3.09 (m, 1 H), 2.84–2.58 (m, 3 H), 2.0–1.5 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.9, 138.6, 132.7, 130.8, 130.3, 129.4, 128.7, 126.6, 120.4, 118.5, 61.9, 54.2, 52.1, 40.6 ppm. MS (ESI): m/z = 273 [M + H]$^+$. HRMS (ESI): calcd. for $C_{16}H_{18}ClN_2$ [M + H]$^+$ 273.1158; found 273.1155.

8-Chloro-3-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (13b): Yield 60 mg (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.15 (m, 5 H), 7.04 (d, J = 8.0 Hz, 1 H), 6.91–6.69 (m, 2 H), 4.04–3.88 (m, 3 H), 3.39 (d, J = 12.4 Hz, 1 H), 2.96 (dd, J = 13.1, 9.4 Hz, 1 H), 2.05 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 142.7, 132.8, 130.9, 130.5, 128.6, 127.6, 127.0, 120.6, 118.7, 66.2, 56.4, 53.1 ppm. MS (ESI): m/z = 259 [M + H]$^+$. HRMS (ESI): calcd. for $C_{15}H_{16}ClN_2$ [M + H]$^+$ 259.1002; found 259.1097.

8-Chloro-3-isobutyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (13c): Yield 48 mg (39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, J = 8.0 Hz, 1 H), 6.83–6.59 (m, 2 H), 3.93, 3.79 (ABq, J = 14.9 Hz, 2 H), 3.30 (dd, J = 13.2, 2.5 Hz, 1 H), 2.93–2.87 (m, 1 H), 2.63–2.58 (m, 1 H), 1.71 (br. s, 2 H), 1.40–1.07 (m, 3 H), 0.91 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 132.7, 130.7, 130.3, 120.3, 118.4, 58.5, 55.0, 51.9, 43.3, 24.9, 23.2, 22.7 ppm. MS (ESI): m/z = 239 [M + H]$^+$. HRMS (ESI): calcd. for $C_{13}H_{20}ClN_2$ [M + H]$^+$ 239.1315; found 239.1312.

8-Chloro-3-ethyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (13d): Yield 38 mg (36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, J = 7.9 Hz, 1 H), 6.77–6.62 (m, 2 H), 3.94, 3.80 (ABq, J = 14.8 Hz, 2 H), 3.34 (dd, J = 13.0, 1.7 Hz, 1 H), 2.78–2.73 (m, 1 H), 2.66–2.61 (m, 1 H), 1.87 (br. s, 2 H), 1.44–1.39 (m, 2 H), 0.96 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 130.8, 130.2, 128.9, 120.3, 118.4, 62.2, 54.3, 51.9, 27.1, 11.0 ppm. MS (ESI): m/z = 211 [M + H]$^+$. HRMS (ESI): calcd. for $C_{11}H_{16}ClN_2$ [M + H]$^+$ 211.1002; found 211.1000.

8-Chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (13e): Yield 40 mg (40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, J =

7.6 Hz, 1 H), 6.83–6.60 (m, 2 H), 3.94, 3.81 (ABq, J = 14.5 Hz, 2 H), 3.29 (d, J = 12.8 Hz, 1 H), 3.10–3.01 (m, 1 H), 2.79–2.54 (m, 1 H), 1.12 (d, J = 5.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 133.0, 131.0, 120.6 (2 C), 118.6, 56.1, 55.5, 51.6, 29.8 ppm. MS (ESI): m/z = 197 $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{14}ClN_2$ $[M + H]^+$ 197.0845; found 197.0841.

3-Benzyl-1-isobutyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (15a): Yield 63 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.07 (m, 7 H), 6.97–6.75 (m, 2 H), 3.95–3.85 (m, 1 H), 3.13–3.09 (m, 3 H), 2.83–2.33 (m, 6 H), 1.71–1.64 (m, 1 H), 0.91 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 138.6, 133.8, 129.8, 129.4, 128.7, 127.9, 126.6, 121.2, 117.5, 62.5, 61.1, 60.8, 52.3, 40.3, 27.0, 20.8, 20.6 ppm. MS (ESI): m/z = 295 $[M + H]^+$. HRMS (ESI): calcd. for $C_{20}H_{27}N_2$ $[M + H]^+$ 295.2174; found 295.2170.

1-Isobutyl-3-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (15b): Yield 83 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.15 (m, 7 H), 7.01–6.85 (m, 2 H), 4.11–3.90 (m, 1 H), 3.15 (m, 2 H), 2.91–2.70 (m, 2 H), 1.96 (br. s, 1 H), 1.90–1.76 (m, 2 H), 1.38–1.17 (m, 1 H), 1.0 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 142.3, 134.1, 129.2, 128.1, 127.3, 127.0, 126.6, 120.7, 117.1, 64.7, 62.8, 62.0, 52.8, 26.7, 20.3, 20.1 ppm. MS (ESI): m/z = 281 $[M + H]^+$. HRMS (ESI): calcd. for $C_{19}H_{25}N_2$ $[M + H]^+$ 281.2018; found 281.2015.

3-Ethyl-1-isobutyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (15d): Yield 45 mg (39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.04 (m, 2 H), 6.98–6.80 (m, 2 H), 4.08, 3.95 (ABq, J = 13.7 Hz, 2 H), 3.78 (br. s, 1 H, NH), 3.14–2.84 (m, 3 H), 2.64 (dd, J = 13.9, 9.6 Hz, 2 H), 1.90–1.73 (m, 1 H), 1.66–1.32 (m, 2 H), 1.08–0.74 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 130.2, 128.5, 121.4, 117.5, 62.5, 60.8, 60.1, 51.3, 27.0, 26.1, 20.8, 20.6, 10.8 ppm. MS (ESI): m/z = 233 $[M + H]^+$. HRMS (ESI): calcd. for $C_{15}H_{25}N_2$ $[M + H]^+$ 233.2018; found 233.2016.

Multistep Procedure for the Synthesis of Benzodiazepines 5a–e

Step 1: Under nitrogen, β-amino alcohol **2a**–**2e** (0.66 mmol) and 2-nitrobenzaldehyde (**8**; 0.66 mmol) were dissolved in dry dichloromethane (8 mL), and then Na_2SO_4 (2.5 equiv.) was added. The mixture was stirred at room temperature for 12 h, then it was filtered, and the Na_2SO_4 was washed with CH_2Cl_2. The solvent was evaporated to dryness to give the crude imine, which was used in the next step without further purification. The formation of the product was confirmed by TLC, MS, and ^{1}H NMR spectroscopic analysis of the crude material. The imine was dissolved in methanol under nitrogen, and then Pd/C (catalytic amount) was added. The reaction mixture was stirred at room temperature under hydrogen (1 atm) for 16 h. The reaction mixture was then filtered through Celite, and the solvent was evaporated. The crude material was purified by flash column chromatography on silica gel (eluent CH_2Cl_2/MeOH) to give pure amine **4a**–**4e**.

Step 2: Amine **4a**–**4e** (0.3 mmol) was mixed with $[Ru(p\text{-cymene})Cl_2]_2$ (9.5 mg, 0.05 equiv.) and Xantphos (9 mg, 0.05 equiv.) in toluene (1 mL) under nitrogen in a pressure-resistant glass tube containing a magnetic stirrer bar, and then the glass tube was sealed. The reaction mixture was stirred at 160 °C in a sand bath for 12 h. The mixture was cooled to room temperature, and then it was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH) to give pure product **5a**–**5e**.

2-[(2-Aminobenzyl)amino]-3-phenylpropan-1-ol (4a): Yield 93 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.12 (m, 5 H), 7.06 (t, J = 7.6 Hz, 1 H), 6.96 (d, J = 7.4 Hz, 1 H), 6.75–6.47 (m, 2 H), 3.77 (s, 2 H), 3.63 (dd, J = 10.9, 4.0 Hz, 1 H), 3.54–3.30 (m, 1 H), 3.13–2.60 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 138.2, 129.4, 128.8, 128.1, 125.9, 123.5, 117.6, 115.5, 63.0, 59.4, 49.7, 37.5 ppm. MS (ESI): m/z = 257.16 $[M + H]^+$. HRMS (ESI): calcd. for $C_{16}H_{21}N_2O$ $[M + H]^+$ 257.1654; found 257.1651.

2-[(2-Aminobenzyl)amino]-2-phenylethanol (4b): Yield 102 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.25 (m, 5 H), 7.13–7.03 (m, 1 H), 6.92 (dd, J = 7.9, 6.9 Hz, 1 H), 6.73–6.58 (m, 2 H), 3.87–3.65 (m, 3 H), 3.65–3.50 (m, 2 H), 3.48–2.81 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 140.0, 129.7, 128.3, 128.1, 127.3, 127.1, 126.9, 123.6, 117.7, 115.5, 66.4, 63.8, 49.6 ppm. MS (ESI): m/z = 243.15 $[M + H]^+$. HRMS (ESI): calcd. for $C_{15}H_{19}N_2O$ $[M + H]^+$ 243.1497; found 243.1491.

2-[(2-Aminobenzyl)amino]-4-methylpentan-1-ol (4c): Yield 85 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15–6.92 (m, 2 H), 6.80–6.48 (m, 2 H), 4.55 (br. s, 2 H), 3.94–3.84 (m, 2 H), 3.70 (dd, J = 11.3, 3.0 Hz, 1 H), 3.45–3.40 (m, 1 H), 2.87–2.75 (m, 1 H), 1.70–1.51 (m, 1 H), 1.44–1.23 (m, 2 H), 0.83 (d, J = 6.5 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 130.3, 128.8, 121.3, 118.0, 116.1, 62.5, 56.1, 48.2, 39.2, 24.5, 22.5, 22.0 ppm. MS (ESI): m/z = 223.18 $[M + H]^+$. HRMS (ESI): calcd. for $C_{13}H_{23}N_2O$ $[M + H]^+$ 223.1810; found 223.1807.

2-[(2-Aminobenzyl)amino]butan-1-ol (4d): Yield 90 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–6.95 (m, 2 H), 6.76–6.55 (m, 2 H), 3.91–3.65 (m, 5 H), 3.43 (dd, J = 11.3, 6.3 Hz, 1 H), 2.66–2.61 (m, 1 H), 1.65–1.36 (m, 2 H), 0.89 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 130.0, 128.5, 122.2, 117.9, 115.9, 62.2, 59.5, 48.7, 22.9, 9.9 ppm. MS (ESI): m/z = 195 $[M + H]^+$. HRMS (ESI): calcd. for $C_{11}H_{19}N_2O$ $[M + H]^+$ 195.1497; found 195.1495.

2-[(2-Aminobenzyl)amino]propan-1-ol (4e): Yield 80 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–6.93 (m, 2 H), 6.75–6.58 (m, 2 H), 3.94 (d, J = 12.7 Hz, 1 H), 3.76 (d, J = 12.7 Hz, 1 H), 3.71 (s, 2 H), 3.60 (dd, J = 11.1, 3.9 Hz, 1 H), 3.40–3.35 (m, 1 H), 2.93–2.77 (m, 1 H), 1.11 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 129.7, 128.3, 123.0, 117.8, 115.8, 65.4, 53.7, 48.9, 16.0 ppm. MS (ESI): m/z = 181.13 $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{17}N_2O$ $[M + H]^+$ 181.1341; found 181.1337.

Supporting Information (see footnote on the first page of this article): General, HPLC MS (ESI) analysis, ^{1}H and ^{13}C NMR spectra.

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[11] The presence of unsaturated compound **6a** in the reaction mixture, even after 15 h, suggests that the Ru-mediated hydrogenation of BDZ is slower than the oxidation/condensation step. We cannot exclude the possibility that this sluggish reactivity could also be due to degradation of the catalyst after a long time at 160 °C. Attempts to promote the hydrogenation by the addition of hydrogen donors (such as *i*PrOH, HCOOH, triethylsilane, or the Hantzsch ester) were unsuccessful.

[12] When (*S*)-**2a** was submitted to these reaction conditions, product **5a** was recovered as a racemic mixture. All the products prepared in this work were obtained as mixtures of enantiomers.

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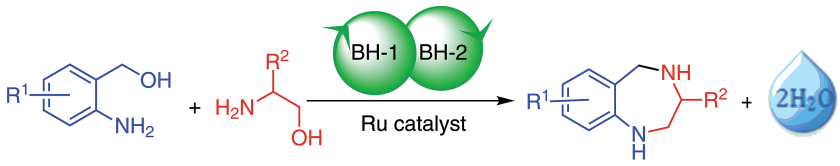

* one-pot BDZ synthesis
* high atom economy
* 18 examples reported

Two consecutive Ru-catalyzed borrowing hydrogen processes offer an efficient method for benzodiazepine synthesis.

Hydrogen Transfer

Keywords: Hydrogen transfer / Homogeneous catalysis / Ruthenium / Cyclization / Domino reactions

