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Solid supported Hayashi–Jørgensen catalyst as an efficient and recyclable organocatalyst for asymmetric Michael addition reactions

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Dedicated to Prof. Marek Chmielewski on his 75th birthday

ABSTRACT

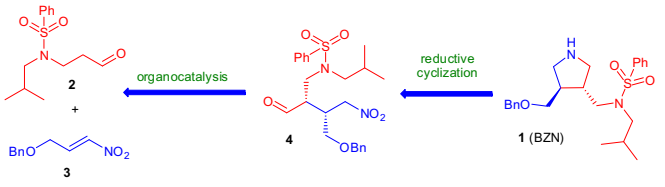
A comparison of three different catalytic systems for the efficient, asymmetric synthesis of *N*-({(3*R*,4*R*)-4-[(benzyloxy)methyl]pyrrolidin-3-yl}methyl)-*N*-(2-methylpropyl)benzenesulfonamide **1** (BZN) is described. The presented strategy is based on the organocatalytic Michael addition of aldehyde **2** to *trans*-nitroalkene **3**, and subsequent reductive cyclization. High yields, enantio-, and diastereoselectivities were achieved in the Michael addition by application of a POSS- or Wang resin-supported Hayashi–Jørgensen catalyst.

1. Introduction

Pyrrolidine-derived compound **1**, known as *N*-({(3*R*,4*R*)-4-[(benzyloxy)methyl]pyrrolidin-3-yl}methyl)-*N*-(2-methylpropyl) benzenesulfonamide (BZN), exhibits interesting binding to HIV-1 protease.[1] The pharmacological activity of BZN is still unknown, while no synthetic pathway has been reported so far, either. Substituted pyrrolidines are an important framework by virtue of their frequent appearance in a large number of biologically active natural products and pharmaceuticals.[2] Common methods for the synthesis of optically active pyrrolidines typically involve relatively long synthetic sequences starting from different natural chiral pool compounds.[3] The main drawback of these approaches lies in the presence of only oxygen functionalities in the pyrrolidine scaffold. However, many bioactive pyrrolidine derivatives, such as BZN, possess substituents of a different nature. For these reasons, appropriately substituted γ-nitroaldehydes, which can be easily obtained via organocatalytic Michael reactions, seem to be interesting precursors in the synthesis of functionalized pyrrolidines. Although the organocatalytic asymmetric Michael addition of aldehydes to nitroolefins leading to γ-nitroaldehydes is a key transformation in organic synthesis,[4] only a few strategies based on organocatalysis en route to pyrrolidines have been developed.[5] Herein, we propose a simple and efficient approach to the asymmetric synthesis of compound **1** (BZN). The synthetic strategy involves sequential organocatalytic Michael addition of aldehyde **2** to nitroolefin **3** in the presence of homogenous or heterogenous Hayashi–Jørgensen-type catalysts, and reductive cyclization of the obtained γ-nitroaldehyde **4** (Scheme 1).

High efficiency, selectivity, and robustness in asymmetric reactions make the Hayashi–Jørgensen catalyst one of the most important organocatalysts.[6] However, its practical application suffers from some limitations, such as high catalyst loading and difficulties in separating the catalyst from the product. It is also noteworthy that α-substituted γ-nitroaldehydes can undergo epimerization in the presence of the catalyst. This situation occurs when the products remain in contact with the catalyst for an extended period of time, after turnover is completed. When the γ-nitroaldehydes with a high *syn:anti* ratio react with the catalyst, a low steady-state concentration of the enamine is rapidly established, and the equilibration between *syn* and *anti* continues until thermodynamic ratio is reached (Scheme 2).

This effect, intensively studied and explained by Blackmond et al.[7] has been confirmed by our group.[8] Bearing in mind that in order to maintain the high diastereomeric ratio, the catalyst has to be removed from the reaction mixture immediately after complete conversion of substrates, we proposed three various



Scheme 1. Retrosynthetic approach to BZN via organocatalytic Michael addition and subsequent reductive cyclization.

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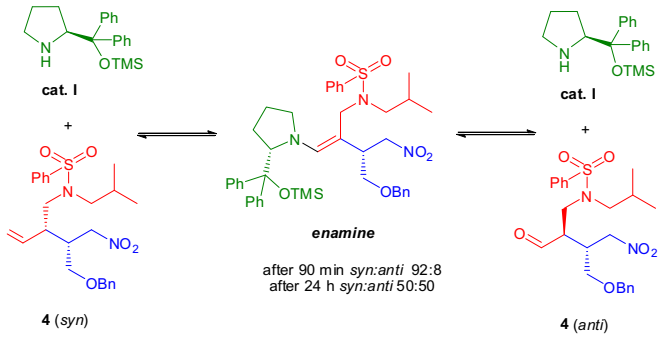


Scheme 2. Reversible enamine formation between **cat. 1**, **4** (*syn*), and **4** (*anti*).

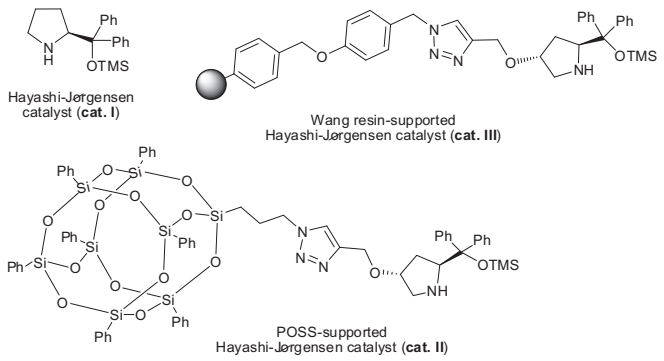


Figure 1. Hayashi–Jørgensen-type catalysts examined in this work.

homogenous and heterogenous catalytic systems based on a Hayashi–Jørgensen-type catalyst, which can be easily removed from the reaction mixture, thus overcoming the mentioned drawback (Fig. 1).

The first approach is based on complexing the pyrrolidine moiety with copper salts. We observed that the Hayashi–Jørgensen catalyst **cat. I** could be easily removed after turnover was completed by simple extraction with saturated aqueous $CuSO_4$. The other two approaches involve homogenous and heterogenous catalysis based on immobilized Hayashi–Jørgensen-type catalysts **cat. II** and **cat. III**.

Several research groups have immobilized the Hayashi–Jørgensen catalyst on a variety of solid supports including polymers,[9] ionic liquids,[10] magnetic nanoparticles,[11] porous materials,[12] dendrimers,[13] and fluorous phases[14] to exploit the inherent advantages derived from simple purification of the product, the possibility of straightforward recycling, reuse of the catalyst, and the potential for its use in flow chemistry.

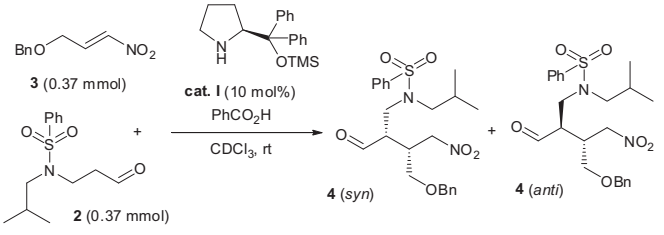
Herein, we propose an efficient and easily recoverable homogenous catalyst based on POSS (polyhedral oligomeric silsesquioxane)-supported Hayashi–Jørgensen-type catalyst **cat. II**. POSS are a new class of organic–inorganic hybrid materials consisting of a silicon-oxygen framework. Due to marked differences in solubilities in various solvents, making it possible to separate these compounds by simple precipitation, POSS are ideal soluble supports for homogenous catalysis.[15] Despite that, only one literature precedent for the application of a POSS-supported Hayashi–Jørgensen catalyst in organocatalytic Michael addition has appeared.[16]

Beside homogenous catalysis, we propose heterogenous catalysis as an alternative approach, based on the application of insoluble Wang resin as a solid support for the Hayashi–Jørgensen catalyst **cat. III**. Despite insoluble polymers being common support for various types of heterogenous catalysts,[17] to the best of our knowledge, Wang resin-supported Hayashi–Jørgensen catalyst has not been used for Michael addition so far. We also found that the POSS- or Wang resin-supported Hayashi–Jørgensen catalysts do not cause epimerization of α-substituted γ-nitroaldehydes, which bolsters the practicality of this approach.

2. Results and discussion

We began our investigations by exploring the isomerization process in the aforementioned Michael addition. Towards this purpose, we conducted a ^{1}H NMR experiment in which we expected to observe the diastereomeric ratio decreasing in time during the Michael addition of aldehyde **2** to β-nitrostyrene **3** catalyzed by the Hayashi–Jørgensen catalyst **cat. I** (Scheme 3). The reaction was performed in deuterated chloroform in the presence of 10 mol% of the Hayashi–Jørgensen catalyst **cat. I** and benzoic acid (0.5 equiv) as an additive, at ambient temperature. After 35 min, we observed 87% conversion to the desired product **4** with a *syn*/*anti* ratio of 94:6. After an additional 35 min, the conversion increased to 97%, without changes in the *syn*/*anti* ratio. However, after complete conversion of the starting aldehyde **2** (110 min), we began to observe a slight decrease in the *syn*/*anti* ratio to 92:8, and the equilibration between *syn* and *anti* continued until the *syn*/*anti* ratio reached equilibrium at 50:50, and did not change with additional time.

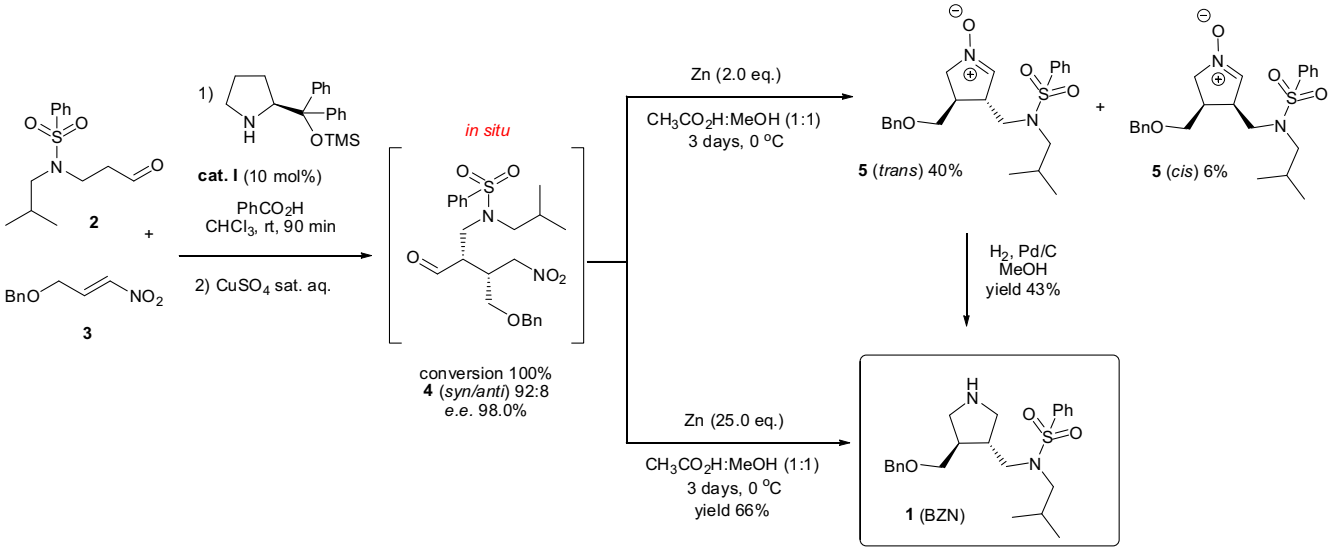
Having confirmed that the isomerization process shown in Scheme 2 occurs in the discussed Michael addition, we decided that all subsequent reactions would be monitored by ^{1}H NMR and after complete conversion, the catalyst would be removed by simple column chromatography, as it was done in our previous report.[8] For this purpose, the Michael addition of aldehyde **2** to β-nitrostyrene **3** was performed under the same conditions as described above. After complete conversion (90 min, determined by ^{1}H NMR, **4** *syn*/*anti* ratio 92:8), and further purification by column chromatography, the corresponding γ-nitroaldehyde **4** was obtained in 93% yield, and with high enantioselectivity (98% e.e.). However, the *syn*/*anti* ratio was only 67:33. The observed changes in the diastereomeric ratio (**4** *syn*/*anti* 92:8 *vs* 67:33) indicate that the isomerization progresses not only after turnover is completed, but also during purification by column chromatography. Bearing in mind these drawbacks, in the next step we decided to perform the reaction as a *one-pot* procedure without isolation of the product, but with immediate isolation of the catalyst. To achieve this goal, we first utilized the propensity of copper salts to complex the pyrrolidine moiety. Proceeding as in the previous example, after turnover completed (90 min, determined by ^{1}H NMR, **4** *syn*/*anti* ratio 92:8), the reaction mixture was washed with saturated aqueous $CuSO_4$ to remove the catalyst and left for 24 h. After that time, the ^{1}H NMR analysis showed only small changes in the *syn*/*anti* ratio (**4** *syn*/*anti* 92:8 *vs* 94:6). After determining suitable conditions, we were ready to exploit the discussed Michael reaction in the synthesis of compound **1** (BZN). Another purpose of the study was to confirm the configuration of the major diastereomer **4** (*syn*) by converting it into a cyclic nitrone. Following the example



Scheme 3. ^{1}H NMR analysis of *syn*/*anti* equilibration in the Michael addition of aldehyde **2** to (*E*)-β-nitrostyrene **3** catalyzed by 10 mol% of the Hayashi–Jørgensen catalyst **cat. I**; selected signals corresponding to the carbonyl groups are presented.

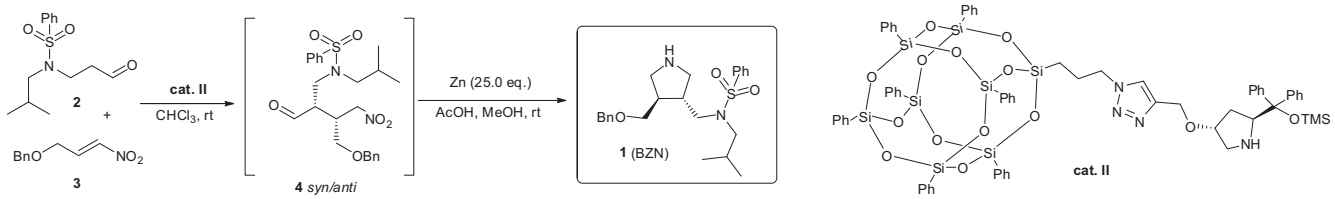
described above, after complete conversion of starting materials (90 min), and washing with saturated aqueous $CuSO_4$, the solvent was evaporated, and the crude product **4** with a *syn*/*anti* ratio of 92:8 was used in the next step. The subsequent reductive cyclization was performed with Zn powder (2.0 equiv) and acetic acid in methanol (1:1). The reaction mixture was stirred for 3 days at 0 °C. After work-up and further purification by column chromatography, nitrone **5** (*trans*) and **5** (*cis*) was obtained in moderate yield (46%), in a 87:13 ratio (Scheme 4). The relative configuration of **5** (*trans*) and **5** (*cis*) nitrone was confirmed on the basis of the analysis of NOE experiments. As described previously, cyclic nitrones are valuable building blocks in the synthesis of many biologically active nitrogen heterocycles, due to their various possibilities of functionalization.[8] In order to obtain compound **1** (BZN), a simple reduction in standard conditions (H_2, Pd/C in methanol at ambient temperature) proved efficient for nitrone **5** (*trans*) reduction. The corresponding amine **1** (BZN) was obtained in 43% yield (Scheme 4). The relative configuration of **1** (BZN) was also confirmed through the analysis of NOE experiments. Further investigations revealed that amine **1** (BZN) could be obtained in a more efficient manner via direct reduction of γ-nitroaldehyde **4**. When the crude product **4** with *syn*/*anti* ratio 92:8, washed with saturated aqueous $CuSO_4$, was treated with a large excess of Zn powder (25 equiv *vs* 2.0 eq uiv) in a mixture of acetic acid and methanol for 3 days at 0 °C, after work-up and further purification by column chromatography, only the desired amine **1** (BZN) (*trans*) diastereomer was isolated in 66% yield (Scheme 4).

Despite these promising results, we realized that for a more attractive and efficient synthesis of compound **1** (BZN), the catalyst used in the Michael reaction should be easily separated and reused in the next catalytic cycle. To achieve the intended purpose, in the next step, we decided to examine the POSS-supported Hayashi–Jørgensen catalyst **cat. II** developed by Nie et al.[16] POSS-supported **cat. II** was employed by Nie et al. in the asymmetric Michael addition reaction of various aldehydes and arylnitroalkenes, providing the corresponding γ-nitroaldehydes in good yields, and with excellent enantioselectivities and good diastereoselectivities. Moreover, the catalyst was readily recovered and reused for further transformations.[16] A characteristic feature of the POSS-supported catalyst **cat. II** is that it dissolves in typical organic solvents, such as CH_2Cl_2, $CHCl_3$, toluene, AcOEt, and is insoluble in Et_2O and MTBE, which allows for simple recovery of the catalyst by precipitation. To evaluate the catalytic efficiency of the POSS-supported catalyst **cat. II**, we carried out the Michael addition of aldehyde **2** with β-nitrostyrene **3**. The reaction was performed in chloroform in the presence of 10 mol% of the POSS-supported catalyst **cat. II**, at ambient temperature. However, the reaction catalyzed by **cat. II** was found to be significantly slower than the reaction catalyzed by **cat. I** under the same conditions (8 days *vs* 90 min). After 8 days, ^{1}H NMR analysis indicated that the conversion to the corresponding γ-nitroaldehyde **4** was only 81%, with a *syn*/*anti* ratio 85:15 (Table 1, Entry 1). Despite incomplete conversion, we decided to ascertain if **cat. II** could be easily isolated from the reaction mixture. After evaporation of the solvent and precipitation with an excess of MTBE, **cat. II** was recovered in 76% yield. The crude γ-nitroaldehyde **4** was subjected to reductive cyclization by employing the same reducing system (Zn/AcOH in MeOH), leading to amine **1** (BZN) in 39% yield (Table 1, Entry 1). Next, we examined the influence of catalyst amount on the discussed Michael addition. The best result was obtained when the reaction was carried out with 20 mol% of **cat. II**. After 3 days, we observed complete conversion to γ-nitroaldehyde **4** with a high *syn*/*anti* ratio (91:9) and stereoselectivity (95% *e.e.*). The catalyst was recovered in 81% yield. After subsequent reductive cyclization reaction and purification, amine **1** (BZN) was isolated in good yield (62%; Table 1, Entry 2). Increasing the amount of catalyst loading to 50 mol% led to decrease in reaction time to 1 day, but the diastereoselectivity was slightly lower (*syn*/*anti* ratio 87:13 *vs* 91:9), and **cat. II** was recovered in 79% yield. In the next step, amine **1** (BZN) was obtained in a similar, 61% yield (Table 1, Entry 3). Having optimized the reaction conditions, we continued our studies by exploring the recyclability of **cat. II**. As shown in Table 1 (Entry 4), no significant decrease in catalytic activity was observed when 20 mol% of the recovered **cat. II** was used in the second catalytic cycle. The reaction proceeded with similar diastereo- and enantioselectivities (*syn*/*anti* ratio 92:8, *e.e.* 92% *vs* *syn*/*anti* ratio 91:9, *e.e.* 95%). The recovery of the catalyst was the same (78%), and amine **1** (BZN) was obtained in a similar yield (59%; Table 1, Entry 2 *vs* 4). However, in the third catalytic cycle, we observed a significant deterioration of the catalyst activity, which proved partial decomposition of **cat. II**. After 13 days, the conversion to the corresponding γ-nitroaldehyde **4** was only 55%. The diastereo- and enantioselectivity was still on



Scheme 4. Optimization of the sequential Michael addition of aldehyde **2** to (*E*)-β-nitrostyrene **3** catalyzed by the Hayashi–Jørgensen catalyst **cat. I** and reductive cyclization to the corresponding pyrrolidine **1** (BZN).

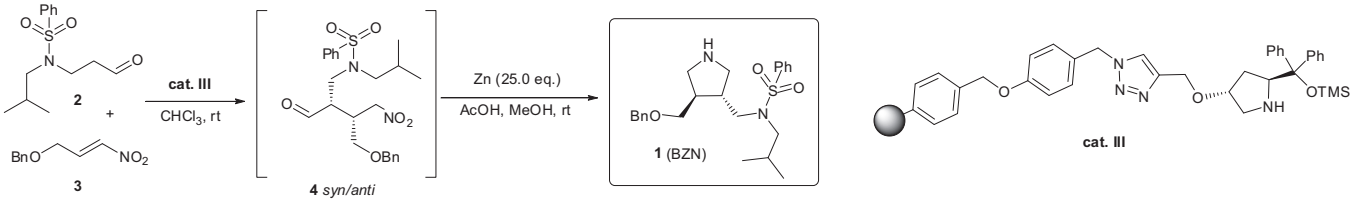
Table 1
The homogenous Michael addition reaction of aldehyde **2** to β-nitrostyrene **3** catalyzed by POSS-supported catalyst **cat. II**, and subsequent reductive cyclization to amine **1** (BZN)[a]



Entry	Catalyst [%mol]	Catalytic cycle	Catalyst recovery	Conversion[b] [%]	Time [days]	**4** (*syn*/*anti*)[b]	**4** (*e.e.*)[c] [%]	Yield **1**[d] [%]
1	10	1	76	81	8	85:15	95.9	39
2	20	1	81	100	3	91:9	95.0	62
3	50	1	79	100	1	87:13	94.8	61
4	20	2	78	100	3	92:8	92.0	59
5	20	3	85	55	13	93:7	96.5	22

[a] Reaction conditions for the Michael addition: aldehyde **2** (0.37 mmol), nitroalkene **3** (0.37 mmol), $CHCl_3$, rt; the reaction was monitored by TLC and ^1H NMR, **cat. II** was removed from the reaction mixture by precipitation with an excess of MTBE; Reaction conditions for reductive cyclization: Zn powder (25.0 equiv), AcOH:MeOH (1:1), 0 °C, 3 days.
[b] Determined by ^1H NMR of the crude reaction mixture.
[c] Determined by HPLC of the crude reaction mixture.
[d] Yield of isolated product, configuration established by NOE experiments.

Table 2
The heterogenous Michael addition of aldehyde **2** to β-nitrostyrene **3** catalyzed by Wang resin-supported catalyst **cat. III**, and subsequential reductive cyclization to amine **1** (BZN)[a]



Entry	Catalyst [%mol]	Catalytic cycle	Catalyst recovery	Conversion[b] [%]	Time [h]	**4** (*syn*/*anti*)[b]	**4** (*e.e.*)[c] [%]	Yield **1**[d] [%]
1	10	1	100	100	21	92:8	94.2	64
2	20	1	100	100	15	93:7	93.2	65
3	50	1	100	100	5	94:6	92.8	64
4	20	2	99	100	20	92:8	93.6	55
5	20	3	97	87	7 days	92:8	93.8	43

[a] Reaction conditions for the Michael addition: aldehyde **2** (0.37 mmol), nitroalkene **3** (0.37 mmol), $CHCl_3$, rt; the reaction was monitored by TLC and ^1H NMR, **cat. III** was removed from the reaction mixture by filtration; Reaction conditions for reductive cyclization: Zn powder (25.0 equiv), AcOH:MeOH (1:1), 0 °C, 3 days.
[b] Determined by ^1H NMR of the crude reaction mixture.
[c] Determined by HPLC of the crude reaction mixture.
[d] Yield of isolated product, configuration established by NOE experiments.

the same level (*syn*/*anti* ratio 93:7, *e.e.* 96%), but amine **1** (BZN) was obtained in lower yield (22%; Table 1, Entry 5).

Although the Michael addition catalyzed by **cat. II** provided the corresponding γ-nitroaldehyde **4** in high yield and with high enantioselectivity, without a significant deterioration of diastereoselectivity, the catalyst recovery was in the range of 80%. To achieve higher catalyst recovery, in the next step, we investigated a heterogenous catalytic system based on insoluble Wang resin-supported Hayashi–Jørgensen catalyst **cat. III**, which, to the best of our knowledge, has not been used for Michael addition so far. We examined the catalytic efficiency of **cat. III** in the Michael addition of aldehyde **2** to β-nitrostyrene **3**. The reaction was performed under the same conditions as in the previous example, in chloroform in the presence of 10 mol% of **cat. III**, at ambient temperature. In comparition to the POSS-supported **cat. II**, 10 mol% of **cat. III** turned out to be sufficient to achieve complete conversion after 21 h. γ-Nitroaldehyde **4** was obtained with high enantioselectivity (94%) as an inseparable mixture of diastereomers in *syn*/*anti* ratio 92:8. After simple filtration, **cat. III** was recovered in 100% yield, and the crude product **4** was subjected to reductive cyclization to obtain amine **1** (BZN) in 64% yield (Table 2, Entry 1). Next, we investigated the influence of catalyst amount on the discussed Michael addition. Increasing the catalyst loading to 20 mol% or 50 mol% resulted only in a decrease in the reaction time, without changing the enantio- and diastereoselectivity (Table 2, Entries 1–3). Encouraged by the results, we endeavored to apply **cat. III** in the next catalytic cycle. To our satisfaction, no significant decrease in catalytic activity was observed, when 20 mol% of the recovered catalyst **cat. III** was used in the second cycle of the Michael addition (Table 2, Entry 4). However, the catalytic activity dropped markedly in the third cycle. After 7 days, ^1H NMR analysis indicated that the conversion to the corresponding γ-nitroaldehyde **4** was 87%. However, the stereoselectivity was unaffected throughout all catalytic cycles (Table 2, Entry 5). These results demonstrate that **cat. III** is the best recyclable organocatalyst for the discussed Michael addition among the ones examined here, exhibiting high activity as well as a very simple procedure for catalyst recovery.

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3. Conclusion

In conclusion, an attractive method for the formation of optically active pyrrolidine **1** (BZN) has been developed. The presented strategy is based on organocatalytic Michael addition of aldehyde **2** to *trans*-nitroalkene **3**, and subsequent Zn-promoted reductive cyclization process. As it was demonstrated, three catalytic systems based on a Hayashi–Jørgensen-type catalyst were applied to the efficient and highly stereoselective Michael addition reaction. The presented homogenous and heterogenous catalytic systems could be easily recovered and reused (POSS- or Wang resin-supported catalyst) in the next catalytic cycle without a significant loss of catalytic activities and stereoselectivities. One great advantage for the presented immobilized catalysts are that they do not cause epimerization of α-substituted γ-nitroaldehydes. Further studies, focusing on the preparation of more stable solid phase-supported Hayashi–Jørgensen catalysts, and their application to different biologically active pyrrolidine synthesis are currently under investigation and will be reported in due course.

4. Experimental

4.1. Synthesis of aldehyde 2

4.1.1. *N*-Isobutylbenzenesulfonamide 6

To a solution of 2-methylpropan-1-amine (4 mL, 40.25 mmol) in dry CH_2Cl_2 (40 mL), *N*,*N*-diisopropylethylamine (7.0 mL, 40.25 mmol, 1.0 equiv) was added under argon at −25 °C, the mixture was stirred for 15 min, then benzenosulfonylchloride (5.12 mL, 40.25 mmol, 1.0 equiv) was added. The resulting solution was warmed gradually to room temperature and stirred overnight. The reaction was quenched with 1 M aq HCl (10 mL). After phase separation, the organic layer was washed with H_2O (20 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. Further evaporation under high vacuum gave 8.568 g (quant yield) of sulfonoamide **6** as a white solid. R_f = 0.51 (1:2 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.80 (m, 2H), 7.56–7.43 (m, 3H), 4.75 (t, *J* 6.2 Hz, 1H), 2.71 (t, *J* 6.6 Hz, 2H), 1.66 (dp, *J* 13.4, 6.7 Hz, 1H), 0.82 (d, *J* 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 133.2, 129.7, 127.6, 51.2, 29.1, 20.5; IR (film) *v*: 3286, 2960, 1447, 1323, 1182, 1093, 754, 718, 689, 585 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{15}NNaO_2S$ [M+Na$^+$] 236.0721. Found 236.0725.

4.1.2. *N*-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-*N*-isobutylbenzenesulfonamide 7

To a solution of sulfonoamide **6** (4.505 g, 21.1 mmol) in dry THF (300 mL), triphenylfosfine (16.6 g, 63.4 mmol, 3.0 equiv), a solution of 3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol **9** (12.06 g, 63.4 mmol, 3.0 equiv) in dry THF (50 mL), and diisopropyl azodicarboxylate (12.48 mL, 63.4 mmol, 3.0 equiv) were added under argon at 0 °C. The resulting solution was warmed gradually to room temperature and stirred overnight. Then solvent was then evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (1:15 AcOEt/hexanes) to afford 5.45 g (67%) of product **7** as a yellow oil. R_f = 0.32 (1:9 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.79 (m, 2H), 7.59–7.46 (m, 3H), 3.57 (t, *J* 5.9 Hz, 2H), 3.24–3.16 (m, 2H), 2.92 (d, *J* 7.5 Hz, 2H), 1.99–1.86 (m, 1H), 1.77–1.67 (m, 2H), 0.92 (d, *J* 6.6 Hz, 6H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 132.9, 129.5, 127.8, 61.0, 57.0, 46.7, 32.4, 27.6, 26.5, 20.6, 18.8, −4.8; IR (film) *v*: 2956, 2928, 2856, 1720, 1470, 1345, 1256, 1158, 1091, 1005, 964, 836, 776, 748, 691, 583 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{35}NNaO_3SSi$ [M+Na$^+$] 408.2005. Found 408.2000.

4.1.3. *N*-(3-Hydroxypropyl)-*N*-isobutylbenzenesulfonamide 8

To a solution of **7** (5.4 g, 14.0 mmol) in dry THF (150 mL), a 1 M solution of tetrabutylammonium fluoride in THF (18.2 mL, 18,2 mmol, 1.3 equiv) was added under argon at 0 °C. The resulting solution was warmed gradually to room temperature and stirred overnight. The solvent was then evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (1:1 AcOEt/hexanes) to afford 3.04 g (80%) of alcohol **8** as a colorless oil. R_f = 0.18 (1:1 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.79 (m, 2H), 7.63–7.48 (m, 3H), 3.74 (dd, *J* 10.4, 5.1 Hz, 2H), 3.24 (t, *J* 6.8 Hz, 2H), 2.92 (d, *J* 7.6 Hz, 2H), 2.36–2.23 (m, 1H), 1.98–1.82 (m, 1H), 1.81–1.71 (m, 2H), 0.90 (d, *J* 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 133.1, 129.7, 127.8, 59.7, 57.9, 46.6, 32.3, 27.9, 20.7; IR (film) *v*: 3533, 2961, 1666, 1446, 1331, 1156, 1091, 994, 781, 743, 691, 583 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{21}NNaO_3S$ [M+Na$^+$] 294.1140. Found 294.1136.

4.1.4. *N*-Isobutyl-*N*-(3-oxopropyl)benzenesulfonamide 2

To a cooled (−78 °C) mixture of dry DMSO (3.09 mL, 43.52 mmol, 4.0 equiv) and dry CH_2Cl_2 (30 mL), oxalyl chloride (1.84 mL, 21.76 mmol, 2.0 equiv) was added dropwise under argon. The reaction mixture was stirred for 90 min at the same temperature, and then a solution of alcohol **8** (2.952 g, 10.88 mmol) in dry CH_2Cl_2 (50 ml) was added dropwise. The reaction was stirred for an additional 2 h, at −78 °C, and then dry Et_3N (12 mL, 87.04 mmol, 8.0 equiv) was added. The resulting solution was warmed gradually to room temperature and stirred overnight. The reaction was quenched with satd aq NH_4Cl (30 ml), and H_2O (30 mL). After phase separation, the aqueous layer was washed with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with satd aq NH_4Cl (30 ml), H_2O (30 mL), brine (30 ml), and then dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (1:4 AcOEt/hexanes); to afford 2.392 g (82%) of aldehyde **2** as a yellow oil. R_f = 0.63 (1:1 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, *J* 0.9 Hz, 1H), 7.84–7.79 (m, 2H), 7.64–7.50 (m, 3H), 3.44–3.36 (m, 2H), 2.90 (d, *J* 7.5 Hz, 2H), 2.88–2.82 (m, 2H), 1.92–1.77 (m, 1H), 0.92 (d, *J* 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 139.6, 133.3, 129.8, 127.8, 57.7, 44.5, 43.0, 27.8, 20.54; IR (film) *v*: 2963, 1723, 1447, 1336, 1158, 1092, 997, 753, 692, 582 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{19}NNaO_3S$ [M+Na$^+$] 292.0983. Found 292.0977.

4.1.5. 3-((*tert*-Butyldimethylsilyl)oxy)propan-1-ol 9

To a solution of sodium hydride (2.1 g, 60% disp. in mineral oil, 52.6 mmol) in dry THF (60 mL), a solution of propane-1,3-diol (3.9 mL, 52.6 mmol) in dry THF (20 mL) was added under argon at 0 °C. The reaction mixture was stirred for 120 min at the same temperature, and then a solution of *tert*-butyldimethylsilyl chloride (7.9 g, 52.6 mmol) in dry THF (20 ml) was added dropwise. After stirring overnight, the reaction was quenched with satd aq $NaHCO_3$ (50 ml). The aqueous layer was washed with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (30 ml), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give 9.81 g (98%) of alcohol **9** as a yellow oil, which was pure enough to be used for Mitsunobu reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84–3.76 (m, 4H), 2.60 (s, 1H), 1.82–1.73 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.4, 62.8, 34.9, 26.5, 18.8, −4.9.

4.2. Synthesis of *trans*-nitroalkene 3

4.2.1. (*Z*)-1,4-Bis(benzyloxy)but-2-ene 10

To a solution of sodium hydride (2.4 g, 60% disp. in mineral oil, 59.0 mmol, 2.6 equiv) in dry DMF (50 mL), a solution of (*Z*)-but-2-

ene-1,4-diol (1.87 mL, 22.7 mmol) in dry DMF (10 mL) was added under argon at 0 °C. The resulting solution was warmed gradually to room temperature and stirred for 1 h. Then benzyl bromide (9.4 mL, 79.5 mmol, 3.5 equiv) was added dropwise. After stirring overnight, the reaction was quenched with satd aq NH_4Cl (30 ml). The aqueous layer was washed with Et_2O (3 × 20 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 ml), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (1:15 AcOEt/hexanes); to afford 5.97 g (98%) of **10** as a yellow oil. R_f = 0.52 (1:6 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.31 (m, 10H), 5.88–5.83 (m, 2H), 4.55 (s, 4H), 4.14–4.11 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 130.2, 129.1, 128.5, 128.3, 72.9, 66.5.

4.2.2. 2-(Benzyloxy)acetaldehyde 11

Ozone was passed through a stirred solution of **10** (5.9 g, 22.0 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C. The progress of the reaction was followed by TLC (1:6 AcOEt/hexanes). After 45 min, slightly green solution occurred. At this point, oxygen was bubbled through reaction mixture for 20 min, and the same procedure was repeated with argone. Than Me_2S (3.5 mL, 2.0 equiv) was added. Resulting mixture was warmed slowly to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (1:6 AcOEt/hexanes); to afford 3.24 g (98%) of **11** as a colorless oil; R_f = 0.26 (1:4 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75–9.73 (m, 1H), 7.40–7.30 (m, 5H), 4.64 (s, 2H), 4.11 (d, *J* 0.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 137.5, 129.2, 128.8, 128.7, 75.9, 74.3.

4.2.3. (*E*)-(((3-Nitroallyl)oxy)methyl)benzene 3

To a solution of aldehyde **11** (3.0 g, 20 mmol) in 70 mL of dry toluene, nitromethane (10.8 ml, 200 mmol, 10.0 equiv) and *N,N,N,N*-tetramethylguanidine (253 μL, 2.0 mmol, 10 mol%) were added at 0 °C under argon. The resulting solution was stirred at the same temperature for 90 min, until complete conversion of the starting aldehyde **11** (TLC control, 1:1 AcOEt/hexanes). Next MsCl (2.32 mL, 30 mmol, 1.5 equiv) and Et_3N (4.18 mL, 30 mmol, 1.5 equiv) were added at 0 °C and the reaction mixture was stirred for an additional 40 min at the same temperature (TLC control, 1:1 AcOEt/hexanes). The reaction mixture was quenched with sat d aq $NaHCO_3$ (20 mL) and diluted with Et_2O (20 mL). After phase separation, the aqueous layer was washed with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydr. Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (1:6 AcOEt/hexanes) to give 2.86 g (74%) nitroalkene **3** as a yellow oil. R_f = 0.77 (1:1 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.31 (m, 6H), 7.29–7.26 (m, 2H), 4.62 (s, 2H), 4.29–4.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 139.1, 137.7, 129.3, 128.8, 128.4, 73.9, 66.2; IR (film) *v*: 3032, 2864, 1658, 1525, 1435, 1356, 1121, 1025, 932, 825, 740, 699 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{11}NNaO_3$ [M+Na$^+$] 216.0637. Found 216.0631.

4.3. Synthesis of Hayashi–Jørgensen catalyst (cat. I)

The Hayashi–Jorgensen catalyst **cat. II** was obtained according to the literature procedure.[8]

4.4. Synthesis of POSS-supported Hayashi–Jørgensen catalyst (cat. II)

The POSS-supported Hayashi–Jorgensen catalyst **cat. II** was obtained according to the literature procedure.[16,18]

4.5. Synthesis of Wang resin-supported Hayashi–Jørgensen catalyst (cat. III)

4.5.1. 1-Ethyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate 12

To a suspension of *trans*-4-hydroxy-L-proline (2.38 g, 18.1 mmol) in 30 mL of methanol, anhydrous K_2CO_3 (2.5 g, 18.1 mmol, 1.0 equiv) was added followed by the addition of ethyl chloroformate (3.8 mL, 39.8 mmol, 2.2 equiv) in 7 mL of methanol. After being stirred at ambient temperature for 18 h methanol was removed in vacuo. The remaining residue was dissolved in CH_2Cl_2, washed with water and dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give 3.047 g (78%) of product **12** as a colorless oil, which was used for the next step without further purification. Spectroscopic data was complementary with literature data.[19] $[\alpha]_D^{24}$ = −70 (*c* 2.5, $CHCl_3$); mixture of rotamers 1:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58–4.44 (m, 2H), 4.14 (q, *J* 7.1 Hz, 2H), 3.74 (d, *J* 5.7 Hz, 3H), 3.66 (dd, *J* 11.6, 4.2 Hz, 1H), 3.52 (d, *J* 11.5 Hz, 1H), 2.46–2.21 (m, 2H), 2.11 and 2.06 (dd, *J* 8.0, 5.0 Hz, 1H), 1.26 and 1.20 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0 and 173.8, 155.9 and 155.5, 70.8 and 70.0, 62.2, 58.4 and 58.3, 55.7 and 55.2, 52.9 and 52.8, 39.8 and 39.1; 15.2 and 15.1; IR (film) *v*: 3443, 2984, 2954, 1749, 1685, 1435, 1384, 1351, 1205, 1174, 1127, 1087, 1025, 783 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_9H_{15}NNaO_5$ [M+Na$^+$] 240.0848. Found 240.0843.

4.5.2. Ethyl (2*S*,4*R*)-4-hydroxy-2-(hydroxydiphenylmethyl) pyrrolidine-1-carboxylate 13

To a solution of **12** (3.02 g, 13.9 mmol) in 10 mL of dry THF, phenyl magnesium bromide solution (1M in THF) (41.7 mL, 41.7 mmol, 3.0 equiv) was added dropwise at 0 °C under argon. The resulting solution was warmed gradually to room temperature and stirred overnight. The reaction was quenched with satd aq NH_4Cl (5 ml), and H_2O (5 mL). After phase separation, the aqueous layer was washed with Et_2O (4 × 10 mL). The combined organic layers were washed with brine (30 ml), and then dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was recrystallized from Et_2O. Further evaporation under high vacuum gave 1.879 g (40%) of **13** as a white solid. Spectroscopic data was complementary with literature data.[19] Mp 175–176 °C; $[\alpha]_D^{24}$ = −46.1 (*c* 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.21 (m, 10H), 5.10 (dd, *J* 8.5, 6.6 Hz, 1H), 4.15–4.01 (m, 1H), 4.01–3.86 (m, 2H), 3.55 (d, *J* 12.0 Hz, 1H), 3.01 (dd, *J* 12.0, 4.1 Hz, 1H), 2.15 (dt, *J* 14.0, 6.0 Hz, 1H), 2.10–1.99 (m, 1H), 1.77 (s, 1H), 1.16 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 146.0, 143.9, 128.6, 128.4, 128.3, 128.0, 127.9, 127.8, 82.1, 70.4, 66.1, 62.6, 56.7, 39.8, 15.1; IR (film) *v*: 3410, 2984, 1668, 1428, 1382, 1345, 1199, 768, 702 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{23}NNaO_4$ [M+Na$^+$] 364.1525. Found 364.1519.

4.5.3. (6*R*,7a*S*)-1,1-Diphenyl-6-(prop-2-yn-1-yloxy)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 14

To a solution of sodium hydride (440 mg, 60% disp. in mineral oil, 11 mmol, 2.0 equiv) in dry DMF (10 mL), a solution of **13** (1.879 g, 5.5 mmol) in dry DMF (10 mL) was added under argon at 0 °C. The reaction mixture was stirred for 15 min at the same temperature, and then a solution of propargyl bromide (80% in toluene) (1.2 mL, 5.5 mmol, 2.0 equiv) was added dropwise. The resulting solution was warmed to room temperature and stirred for 90 min, until complete conversion of the starting **13** (TLC control, 1:2 AcOEt/hexanes). Then the reaction was quenched with sat d aq NH_4Cl (10 ml). After phase separation, the aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (30 ml), and then dried over Na_2SO_4, and

filtered. The filtrate was concentrated under reduced pressure to give 1.804 g (98%) of product **14** as an orange oil, which was used for the next step without further purification. Spectroscopic data was complementary with literature data.[19] R_f = 0.41 (1:2 AcOEt/hexanes); $[\alpha]_D^{22}$ = −200.1 (*c* 2.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.51 (m, 2H), 7.42–7.28 (m, 8H), 4.85 (dd, *J* 11.2, 5.0 Hz, 1H), 4.30 (t, *J* 5.6 Hz, 1H), 4.13 (d, *J* 2.4 Hz, 2H), 4.05 (dd, *J* 12.9, 5.9 Hz, 1H), 3.30 (dd, *J* 12.9, 1.0 Hz, 1H), 2.44 (t, *J* 2.4 Hz, 1H), 1.90 (dd, *J* 13.5, 5.0 Hz, 1H), 1.21 (ddd, *J* 13.6, 11.3, 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 143.5, 140.7, 129.24, 129.10, 129.05, 128.5, 126.7, 126.0, 86.4, 78.8, 75.5, 67.9, 57.3, 54.2, 36.6; IR (film) *v*: 3286, 2954, 1758, 1494, 1449, 1374, 1246, 1226, 1093, 1003, 783, 704 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{19}NNaO_3$ [M+Na$^+$] 356.1263. Found 356.1257.

4.5.4. Diphenyl((2*S*,4*R*)-4-(prop-2-yn-1-yloxy)pyrrolidin-2-yl) methanol 15

To a solution of **14** (1.8 g, 5.4 mmol) in 15 mL of EtOH, potassium hydroxide (1.5 g, 27.0 mmol, 5.0 equiv) in H_2O (3 mL) was added, and the reaction mixture was refluxing for overnight, until complete conversion of the starting **14** (TLC control, 1:2 AcOEt/hexanes). Then the reaction was cooled to room temperature, and diluted with AcOEt (10 mL) and H_2O (15 mL). After phase separation, the aqueous layer was washed with AcOEt (3 × 10 mL). The combined organic layers were washed with brine (30 ml), and then dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give 1.611 g (97%) of product **15** as a brown waxy solid, which was used for the next step without further purification. Spectroscopic data was complementary with literature data.[19] R_f = 0.15 (1:2 AcOEt/hexanes); $[\alpha]_D^{24}$ = −111.1 (*c* 3.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–7.56 (m, 2H), 7.52–7.46 (m, 2H), 7.36–7.24 (m, 4H), 7.24–7.13 (m, 2H), 4.57 (dd, *J* 9.8, 6.6 Hz, 1H), 4.16 (ddt, *J* 3.5, 2.8, 1.7 Hz, 1H), 4.10 (d, *J* 1.8 Hz, 1H), 4.09 (d, *J* 1.8 Hz, 1H), 3.17 (dd, *J* 11.5, 4.3 Hz, 1H), 3.11 (ddd, *J* 4.0, 3.0, 1.6 Hz, 1H), 1.80 (ddd, *J* 13.8, 9.8, 5.3 Hz, 1H), 1.70–1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 145.5, 128.9, 128.7, 127.3, 127.1, 126.6, 126.0, 80.5, 80.1, 77.5, 74.8, 64.0, 56.7, 52.9, 33.4; IR (film) *v*: 3362, 3286, 2939, 1598, 1491, 1448, 1356, 1174, 1080, 986, 750, 701, 664, 636 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{22}NO_2$ [M+H$^+$] 308.1651. Found 308.1653.

4.5.5. (2*S*,4*R*)-2-(Diphenyl((trimethylsilyl)oxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine 16

To a solution of **15** (1.504 g, 4.89 mmol) in dry CH_2Cl_2 (20 mL), Et_3N (887 μL, 6.36 mmol, 1.3 equiv) was added under argon. The resulting solution was stirred for 15 min, and then cooled to 0 °C. Trimethylsilyltriflate (974 μL, 5.38 mmol, 1.1 equiv) was added dropwise, and the resulting mixture was warmed gradually to room temperature and stirred for overnight, until complete conversion of the starting **15** (TLC control, 1:2 AcOEt/hexanes). Then the reaction was quenched with H_2O (10 ml). After phase separation, the aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (30 ml), and then dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (1:2 AcOEt/hexanes); to afford 1.628 g (88%) of **16** as a yellow oil. Spectroscopic data was complementary with literature data.[19] R_f = 0.64 (1:2 AcOEt/hexanes); $[\alpha]_D^{24}$ = −42.4 (*c* 3.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.45 (m, 2H), 7.38–7.32 (m, 2H), 7.32–7.19 (m, 6H), 4.33 (t, *J* 7.9 Hz, 1H), 4.07 (d, *J* 0.7 Hz, 1H), 4.06 (d, *J* 0.7 Hz, 1H), 3.98–3.91 (m, 1H), 2.97 (dd, *J* 11.8, 2.4 Hz, 1H), 2.81 (dd, *J* 11.8, 4.8 Hz, 1H), 2.37 (td, *J* 2.4, 0.7 Hz, 1H), 1.83 (s, 1H), 1.72 (d, *J* 4.0 Hz, 1H), 1.69 (d, *J* 3.9 Hz, 1H), −0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 146.0, 129.1, 128.3, 128.2, 128.1, 127.53, 127.45, 83.5, 80.7, 79.9, 74.6, 64.2, 56.7, 53.3, 34.7, 2.8; IR (film) *v*: 3303, 2952, 1492, 1446, 1250, 1071, 876, 838, 757, 701 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{30}NO_2Si$ [M+H$^+$] 380.2046. Found 380.2049.

4.5.6. *p*-Alkoxybenzyl chloride resin 17

p-Alkoxybenzyl alcohol resin (2.0 g, 2.0 mmol, 1.0 mmol/g loading, 75–100 mesh) was chlorinated with thionyl chloride (1.46 mL, 20 mmol; 10 equiv) in toluene (40 mL) at 70 °C for 2 h. The resin was filtered and washed with toluene (3 × 10 mL), DMF (3 × 10 mL), THF (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL) and dried in a high vacuum to afford (2.141 g) (99%) of resin **17**.

4.5.7. *p*-Alkoxybenzyl azide resin 18

Resin **17** (2.141 g) was treated with sodium azide (696 mg, 10.71 mmol; 5.0 equiv) under argon in dry DMF (10 mL) at 70 °C for 24 h. Thereafter, the resin was filtered; washed with DMF (3 × 10 mL), water (3 × 10 mL),(3 × 10 mL), MeOH (3 × 10 mL), THF (3 × 10 mL), CH_2Cl_2 (3 × 10 mL); and dried in a high vacuum to afford (2.145 g) (97%) of resin 18. IR (KBr) *v*: 3025, 2922, 2097 (azide), 1602, 1511, 1493, 1452, 1243, 1029, 759, 698, 538 cm^{-1}.

4.5.8. Wang resin-supported Hayashi–Jørgensen catalyst (cat. III)

To a solution of acetylenic proline **16** (100 mg, 0.263 mmol, 1.0 equiv) in dry CH_2Cl_2 (2 mL), azide resin **18** (263 mg), copper iodide (2.5 mg, 0.013 mmol, 5 mol%) and *N,N*-diisopropylethylamine (46 μL, 0.263 mmol, 1.0 equiv) were added under argon, and the mixture was left at room temperature for overnight. Thereafter, the resin was filtered; washed with: water (3 × 10 mL), MeOH (3 × 10 mL), CH_2Cl_2 (3 × 10 mL); and dried in a high vacuum to afford (357 mg) (54%) of **cat. III**. IR (KBr) *v*: 3025, 2922, 1601, 1513, 1493, 1452, 1250, 1069, 838, 758, 698, 537 cm^{-1}.

4.5.9. Synthesis of nitrone 7 via organocatalytic Michael addition catalyzed by Hayashi–Jørgensen catalyst (cat. I) and subsequent reductive cyclization (Strategy I)

To a solution of nitroalkene **3** (72 mg, 0.37 mmol, 1.0 equiv) in 1 mL of $CHCl_3$, Hayashi–Jørgensen catalyst **cat. I** (12 mg, 0.037 mmol, 10 mol%) and benzoic acid (22 mg, 0.185 mmol, 0.5 equiv) were added, and the mixture was stirred at room temperature for 10 min, then solution of aldehyde 2 (2.0 mmol, 2.0 equiv.) in 1 mL of $CHCl_3$ was added. The resulting mixture was stirred for 90 min, at the same temperature until complete conversion of the starting substrate (reaction progress was monitored by TLC and ^{1}H NMR). At the moment of complete conversion, the reaction was quenched with satd aq $CuSO_4$ (2 ml), and stirred for 15 min. After phase separation, the aqueous layer was washed with $CHCl_3$ (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure at 20 °C (without bath hitting) to give 161 mg of crude γ-nitroaldehydes **4** as a yellow oil, which was used for the next step without further purification.

4.5.10. *N*-((2*S*,3*R*)-4-(Benzyloxy)-2-formyl-3-(nitromethyl) butyl)-*N*-isobutylbenzenesulfonamide 4 (*syn*) and 4 (*anti*)

Inseparable mixture of diastereomers; $[\alpha]_D^{24}$ = −4.9 (*c* 15.9, $CHCl_3$); *syn/anti* 92:8 (determined by ^{1}H NMR of crude reaction mixture); *e.e.* 97.2% (determined by HPLC of crude reaction mixture); R_f = 0.33 (1:4 AcOEt/hexanes); major isomer **4** (*syn*) selected signals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (d, *J* 1.3 Hz, 1H), 4.60–4.55 (m, 2H), 4.48 (d, *J* 1.3 Hz, 2H), 3.57 (d, *J* 4.5 Hz, 2H), 3.46 (dd, *J* 14.8, 8.0 Hz, 1H), 3.25 (dd, *J* 14.8, 5.4 Hz, 1H), 3.14–3.02 (m, 2H), 2.84 (d, *J* 7.6 Hz, 2H), 1.91–1.76 (m, 1H), 0.84 (d, *J* 4.5 Hz, 3H), 0.82 (d, *J* 4.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.3, 138.8, 137.8, 133.6, 129.9, 129.2, 128.7, 128.4, 128.0, 74.6, 74.2, 68.8, 58.7, 51.8, 47.5, 37.9, 27.6, 2×20.7; minor isomer **4** (*anti*) selected signals: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.5 Hz,

1H), 3.65 (dd, *J* = 10.1, 4.1 Hz, 1H), 3.55–3.49 (m, 2H), 3.34–3.28 (m, 1H), 3.00–2.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 139.0, 137.7, 128.6, 76.1, 67.2, 58.4, 50.8, 47.9, 38.7; IR (film) *v*: 2963, 2871, 1720, 1554, 1338, 1160, 1091, 751, 692, 582 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{30}N_2NaO_6S$ [M+Na$^+$] 485.1722. Found 485.1713; HPLC (Chiralcel OZ-H, 40% *i*-PrOH 60% *n*–hexane, flow rate: 1.0 mL min^{-1}, λ = 210 nm, Tem. 21 °C); major isomer **4** (*syn*) 29.6 min, 36.4 min; minor isomer **4** (*anti*) 16.3 min, 96.0 min.

To a solution of crude γ-nitroaldehyde **4** (*syn/anti* 92:8) (161 mg, 1.0 mmol, 1.0 equiv.) in 2 mL of MeOH, Zn powder (48 mg, 0.74 mmol, 2.0 equiv) was added, the mixture was cooled to 0 °C, and acetic acid (2.0 mL) was added. The reaction was stirred at 0 °C for 3 days. Then the reaction was quenched with 4 M aq NaOH to pH = 7, and diluted with CH_2Cl_2 (5 mL). After phase separation, the aqueous layer was washed with $CHCl_3$ (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude mixture of nitrones which was purified by silica gel column chromatography (1:4 MeOH/AcOEt); to afford 63 mg (40%) of nitrone **5** (*trans*), and 10 mg (6%) of nitrone **5** (*cis*).

4.5.11. (3*R*,4*S*)-3-((Benzyloxy)methyl)-4-((*N*-isobutylphenylsulfonamido)methyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (5 *trans*)

Colorless oil; $[\alpha]_D^{20}$ = +57.7 (*c* 5.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78–7.76 (m, 2H, Ph), 7.60–7.57 (m, 1H, Ph), 7.50 (t, *J* 7.8 Hz, 2H, Ph), 7.38–7.34 (m, 2H, Ph), 7.33–7.29 (m, 3H, Ph), 7.00–6.99 (m, 1H, C*H*═NO), 4.54 (d, *J* 12.0 Hz, 1H, PhC*H*HO), 4.52 (d, *J* 11.9 Hz, 1H, PhCH*H*O), 4.21–4.16 (m, 1H, C*H*HNO), 3.88 (dd, *J* 14.3, 6.2 Hz, 1H, CH*H*NO), 3.54 (d, *J* 9.6 Hz, 1H, C*H*HOBn), 3.52 (d, *J* 9.7 Hz, 1H, CH*H*OBn), 3.38–3.28 (m, 1H, C*H*CH$_2$NSO$_2$Ph), 3.26 (dd, *J* 14.2, 6.6 Hz, 1H, C*H*HNSO$_2$Ph), 3.10 (dd, *J* 14.2, 8.0 Hz, 1H, CH*H*NSO$_2$Ph), 2.87 (dd, *J* 13.7, 8.0 Hz, 1H, C*H*H-*i*-Pr), 2.84 (dd, *J* 13.8, 7.3 Hz, 1H, CH*H*-*i*-Pr), 2.66 (qd, *J* 11.8, 5.9 Hz, 1H, C*H*CH$_2$OBn), 1.79 (tt, *J* 13.8, 6.8 Hz, 1H, C*H*(CH$_3$)$_2$), 0.85 (d, *J* 6.6 Hz, 3H, CH$_3$), 0.84 (d, *J* 6.6 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.17, 138.18, 136.22, 133.48, 129.82, 129.16, 128.57, 128.41, 127.92, 74.04, 71.26, 64.96, 58.62, 52.51, 45.97, 38.28, 27.74, 20.62, 20.56; IR (film) *v*: 3403, 2959, 2925, 2870, 1583, 1446, 1336, 1246, 1158, 1091, 996, 776, 751, 693, 582 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{30}N_2NaO_4S$ [M+Na$^+$] 453.1824. Found 453.1819.

4.5.12. (3*R*,4*R*)-3-((Benzyloxy)methyl)-4-((*N*-isobutylphenylsulfonamido)methyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (5 *cis*)

Colorless oil; $[\alpha]_D^{20}$ = −30.5 (*c* 2.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (dd, *J* 8.4, 1.2 Hz, 2H, Ph), 7.61–7.57 (m, 1H, Ph), 7.51–7.47 (m, 2H, Ph), 7.34–7.29 (m, 3H, Ph), 7.26–7.24 (m, 2H, Ph), 6.91–6.88 (m, 1H, C*H*═NO), 4.50–4.45 (m, 2H, PhC*H*$_2$O), 4.06 (dd, *J* 14.0, 8.7 Hz, 1H, C*H*HNO), 3.89 (dd, *J* 13.9, 5.9 Hz, 1H, CH*H*NO), 3.60–3.54 (m, 1H, C*H*CH$_2$NSO$_2$Ph), 3.55–3.50 (m, 2H, C*H*$_2$-OBn), 3.31 (dd, *J* 14.3, 4.7 Hz, 1H, C*H*HNSO$_2$Ph), 3.19 (dd, *J* 14.3, 11.0 Hz, 1H, CH*H*NSO$_2$Ph), 2.97–2.90 (m, 1H, C*H*CH$_2$OBn), 2.84 (dd, *J* 13.7, 8.2 Hz, 1H, C*H*H-*i*-Pr), 2.80 (dd, *J* 13.7, 6.9 Hz, 1H, CH*H*-*i*-Pr), 1.78 (tt, *J* 13.5, 6.7 Hz, 1H, C*H*(CH$_3$)$_2$), 0.89 (d, *J* 6.6 Hz, 3H, CH$_3$), 0.87 (d, *J* 6.6 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.99, 137.89, 136.97, 133.47, 129.82, 129.17, 128.63, 128.36, 127.96, 74.05, 68.38, 65.23, 58.67, 48.96, 44.07, 36.81, 30.30, 27.89, 20.65, 20.59; IR (film) *v*: 3386, 2960, 2925, 2870, 1585, 48, 337, 45, 1159, 1091, 751, 694, 582 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{30}N_2NaO_4S$ [M+Na$^+$] 453.1824. Found 453.1805.

4.5.13. Synthesis of amine 1 (BZN) via reduction of nitrone (5 *trans*)

To a methanolic solution (2 mL) of nitrone **5** (*trans*) catalytic amount of Pd/C (10 wt.%) was added. The mixture was saturated with hydrogen at ambient temperature for 24 h. Then the catalyst was removed by filtration and the reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (108:8:1 AcOEt/MeOH/30–33% NH_3 aq) to give 21 mg (43%) of amine **1** (BZN) as a waxy solid. $[\alpha]_D^{20}$ = +31.7 (c = 5.8; $CHCl_3$); R_f = 0.15 (100% MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* 7.4 Hz, 2H, Ph), 7.52 (t, *J* 7.4 Hz, 1H, Ph), 7.45 (t, *J* 7.7 Hz, 2H, Ph), 7.32–7.22 (m, 4H, Ph), 4.46 (s, 2H, PhC*H*$_2$O), 3.41–3.35 (m, 2H, C*H*$_2$OBn), 3.13 (dd, *J* 14.0, 10.1 Hz, 1H), 3.07 (dd, *J* 11.0, 8.2 Hz, 1H, NHC*H*HCHCH$_2$OBn), 3.04–2.97 (m, 2H), 2.91 (dd, *J* 13.7, 7.5 Hz, 1H), 2.77 (dd, *J* 13.5, 7.4 Hz, 1H), 2.73 (dd, *J* 11.3, 5.8 Hz, 1H), 2.66 (dd, *J* 11.2, 5.7 Hz, 1H, NHCH*H*CHCH$_2$OBn), 2.38–2.23 (m, 1H, N*H*), 2.20–2.13 (m, 1H, C*H*CH$_2$NSO$_2$Ph), 1.95 (dq, *J* 12.8, 6.5 Hz, 1H, C*H*CH$_2$OBn), 1.87 (tt, *J* 13.9, 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 0.85 (d, *J* 6.6 Hz, 2H, CH$_3$), 0.80 (d, *J* 6.6 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.06, 138.96, 132.99, 129.58, 129.00, 128.20, 127.87, 73.82, 73.59, 57.60, 53.32, 52.16, 51.02, 44.37, 43.28, 27.71, 20.71; IR (film) *v*: 2960, 2926, 2869, 1448, 1336, 1158, 1092, 750, 693, 582 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{33}N_2O_4S$ [M+H+] 417.2212. Found 417.2221.

4.5.14. Synthesis of amine 1 (BZN) via organocatalytic Michael addition catalyzed by Hayashi–Jørgensen catalyst (cat. I) and subsequent reductive cyclization (Strategy I)

To a solution of nitroalkene **3** (72 mg, 0.37 mmol, 1.0 equiv) in 1 mL of $CHCl_3$, Hayashi–Jørgensen catalyst **cat. I** (12 mg, 0.037 mmol, 10 mol%) and benzoic acid (22 mg, 0.185 mmol, 0.5 equiv) were added, and the mixture was stirred at room temperature for 10 min, then a solution of aldehyde **2** (100 mg, 0,37 mmol, 1.0 equiv) in 1 mL of $CHCl_3$ was added. The resulting mixture was stirred for ~90 min, at the same temperature until complete conversion of the starting substrate (reaction progress was monitored by TLC and ^{1}H NMR). At the moment of complete conversion, the reaction was quenched with satd aq $CuSO_4$ (2 ml), and stirred for 15 min. After phase separation, the aqueous layer was washed with $CHCl_3$ (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure at 20 °C (without bath hitting) to give 161 mg of crude γ-nitroaldehydes **4** as a yellow oil, which was used for the next step without further purification.

To a solution of crude γ-nitroaldehyde **4** in 2 mL of MeOH, Zn powder (605 mg, 9.25 mmol, 25.0 equiv) was added, the mixture was cooled to 0 °C, and acetic acid (2.0 mL) was added. The reaction was stirred at 0 °C for 3 days. Then the reaction was quenched with 4 M aq NaOH to pH = 7, and diluted with CH_2Cl_2 (5 mL). After phase separation, the aqueous layer was washed with $CHCl_3$ (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (108:8:1 AcOEt/MeOH/30–33% NH_3 aq); to afford 102 mg (66%) of amine **1** (BZN).

4.5.15. Synthesis of amine 1 (BZN) via organocatalytic Michael addition catalyzed by POSS-supported Hayashi–Jørgensen catalyst (cat. II) and subsequent reductive cyclization (Strategy II)

To a solution of nitroalkene **3** (72 mg, 0.37 mmol, 1.0 equiv) in 2 mL of $CHCl_3$, POSS-supported Hayashi–Jorgensen catalyst **cat. II** (105 mg, 0.074 mmol, 20 mol%) was added, and the mixture was stirred at room temperature for 10 min, then a solution of aldehyde **2** (100 mg, 0,37 mmol, 1.0 equiv) in 2 mL of $CHCl_3$ was added. The resulting mixture was stirred for 3 days, at the same temperature until complete conversion of starting substrate (reaction progress was monitored by TLC and ^{1}H NMR). Then, solvent was removed on rotary evaporation (at 20 °C without bath hitting), and the crude

reaction mixture was treated with MTBE (10 mL) to precipitate the catalyst. After filtration, the precipitate was washed with MTBE (2 × 2 mL), and then dried in a high vacuum to afford 85 mg (81%) of the recovered catalyst (**cat. II**), which was used for the next catalytic cycle.

The combined MTBE filtrates were concentrated under reduced pressure at 20 °C (without bath hitting) to give crude γ-nitroaldehyde **4**, which was used for the next step without further purification.

To a solution of crude γ-nitroaldehyde **4** in 2 mL of MeOH, Zn powder (605 mg, 9.25 mmol, 25.0 equiv) was added, the mixture was cooled to 0 °C, and acetic acid (2.0 mL) was added. The reaction was stirred at 0 °C for 3 days. Then the reaction was quenched with 4 M aq NaOH to pH = 7, and diluted with CH_2Cl_2 (5 mL). After phase separation, the aqueous layer was washed with $CHCl_3$ (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (108:8:1 AcOEt/MeOH/30–33% NH_3 aq); to afford 96 mg (62%) of amine **1** (BZN).

4.5.16. The Synthesis of amine 1 (BZN) via organocatalytic Michael addition catalyzed by Wang resin-supported Hayashi–Jørgensen catalyst (cat. III) and subsequent reductive cyclization (Strategy III)

To a solution of nitroalkene **3** (72 mg, 0.37 mmol, 1.0 equiv) in 2 mL of $CHCl_3$, Wang resin-supported Hayashi–Jørgensen catalyst **cat. III** (74 mg, 0.074 mmol, 20 mol%) and a solution of aldehyde **2** (100 mg, 0,37 mmol, 1.0 equiv) in 2 mL of $CHCl_3$ were added. The resulting mixture was left for 15 h, at the room temperature until complete conversion of the starting substrate (reaction progress was monitored by TLC and ^1H NMR). Then, the catalyst **cat. III** was filtered; washed with $CHCl_3$ (3 × 10 mL), and then dried in a high vacuum to afford 74 mg (100%) of the recovered catalyst **cat**. **III**, which was used for the next catalytic cycle.

The combined $CHCl_3$ filtrates were concentrated under reduced pressure at 20 °C (without bath hitting) to give crude γ-nitroaldehyde **4**, which was used for the next step without further purification.

To a solution of crude γ-nitroaldehyde **4** 2 mL of MeOH, Zn powder (605 mg, 9.25 mmol, 25.0 equiv) was added, the mixture was cooled to 0 °C, and acetic acid (2.0 mL) was added. The reaction was stirred at 0 °C for 3 days. Then the reaction was quenched with 4 M aq NaOH to pH = 7, and diluted with CH_2Cl_2 (5 mL). After phase separation, the aqueous layer was washed with $CHCl_3$ (3 × 3 mL). The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (108:8:1 AcOEt/MeOH/30–33% NH_3 aq); to afford 100 mg (65%) of amine **1** (BZN).

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A. Supplementary data

Supplementary data (the copies of ^1H, ^{13}C NMR, NOE, HPLC spectra) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetasy.2017.10.016.

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