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Multicomponent reactions

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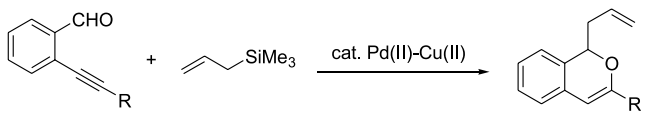
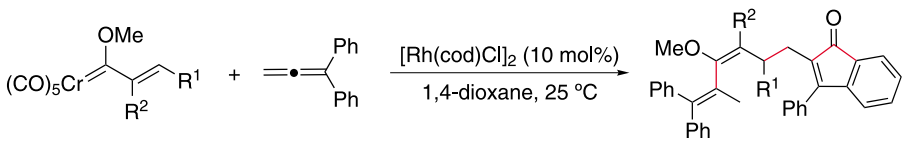
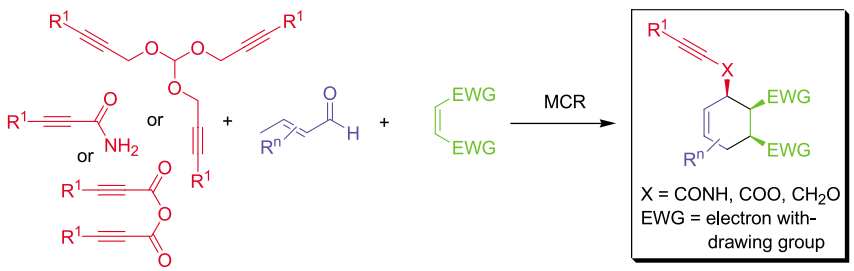
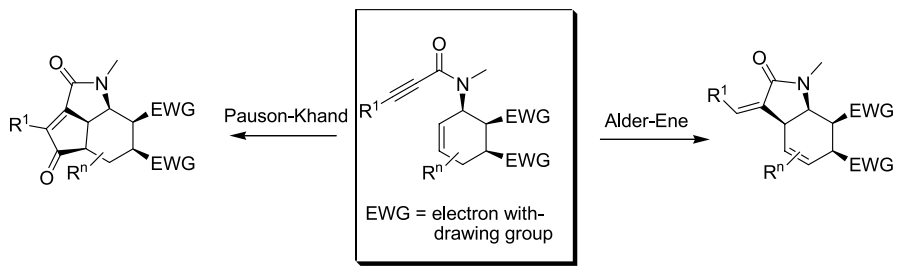


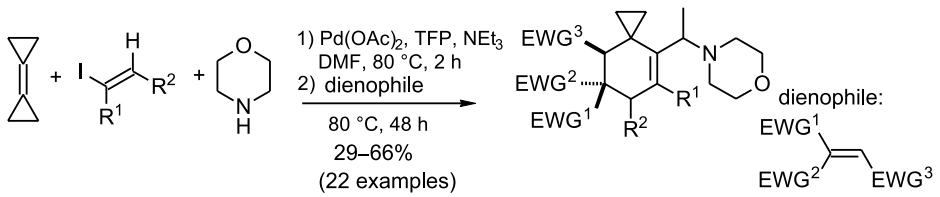


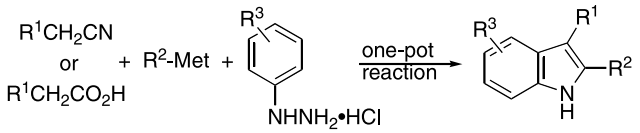


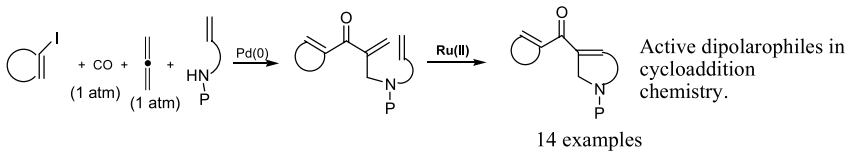
Enyne-reaction precursors were synthesized in good yield via multicomponent reactions of aldehydes, dienophiles and propargylic derivatives.

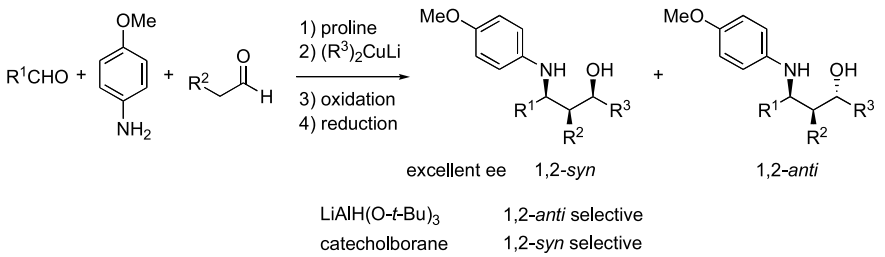


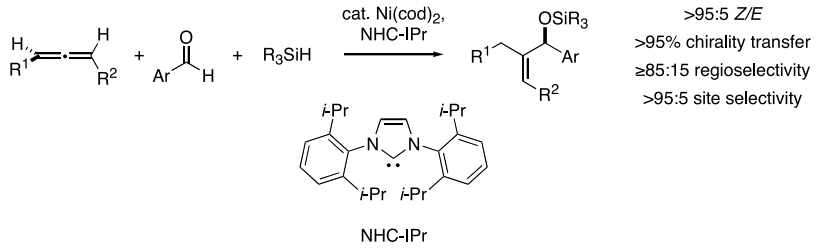
Novel functionalized enynes successfully underwent Pauson–Khand and Alder–Ene reactions.

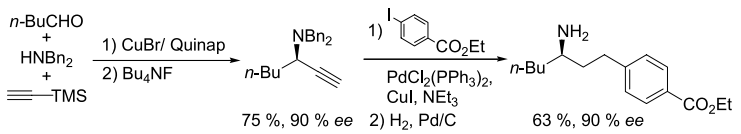


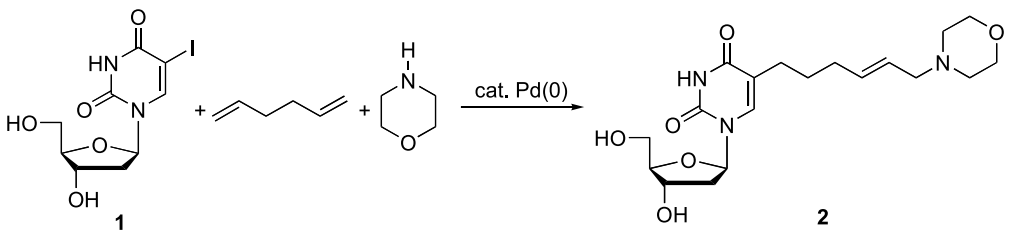


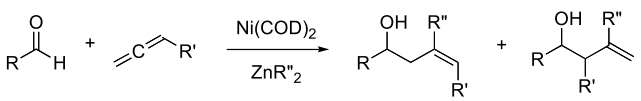




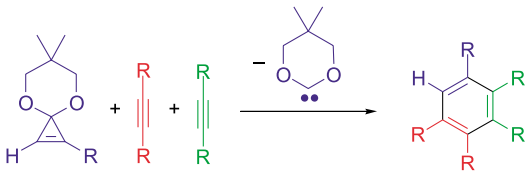


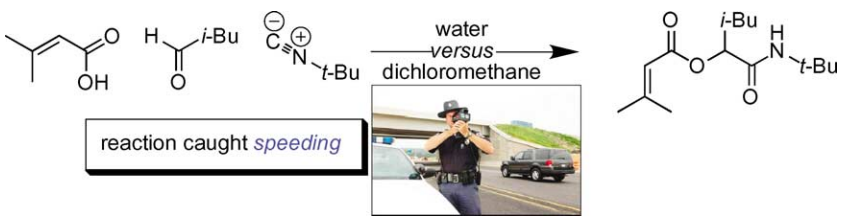


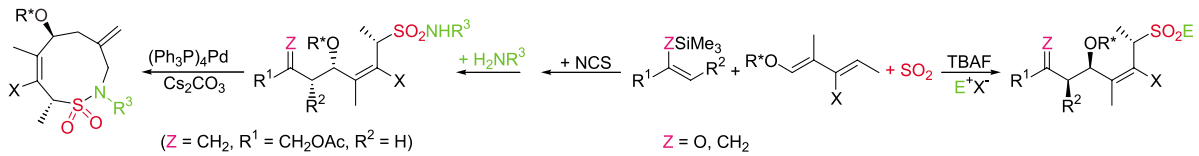


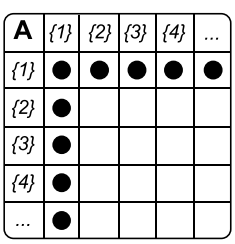


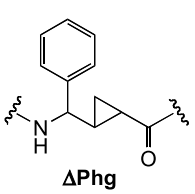
Fully intermolecular and partially intramolecular examples reported.

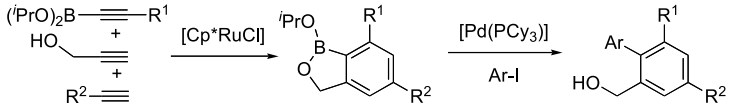


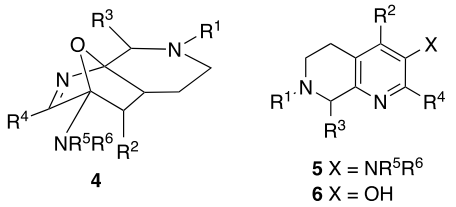












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5 X = NR^5R^6
6 X = OH

Multicomponent synthesis of heterocycles **4**, **5** and **6** are reported.

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COVER

The cover picture shows an enantioselective and regioselective nickel-catalyzed multicomponent coupling of chiral allenes, aldehydes and silanes.

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Preface

Multicomponent reactions

The complexity of organic target molecules is constantly increasing and novel strategies allowing the efficient formation of new carbon–carbon bonds between functionalized moieties are needed. The chemist's ability to make targets of utmost complexity, however, must not hide the fact that the practical construction techniques available to prepare elaborate products are still woefully inadequate. A seemingly trivial but rather serious limitation in practice is set by the mere number of steps accumulating in linear sequences and by the extensive protecting-group strategies used.

These drawbacks are serious and advocating the 'economy of steps' as a priority issue, the development of more and more efficient and new methodology has to be found. Despite the tremendous progress in this area, a much larger panel of reactions achieving a significant increase in structural complexity per chemical steps is necessary. This is particularly true for transformations, which involve more than one bond-making event and particularly if functional groups are present in the carbon skeleton. Indeed, the need for preparing complex polyfunctional molecules in the total synthesis of natural products and in pharmaceutical research requires the development of new reactions, selective organometallic reagents and catalysts for organic synthesis.

Therefore, multiple component (MC) reactions are particularly effective at building functionalized, drug-likes structures from different families of compounds in a single step and we believe that inventing and developing new ones is an important pursuit in academic chemistry.

The time is apt for synthetic chemists to fully enter the world of 'economy of steps' and the primary purpose in editing this special issue is to bring together, in a single volume, all the remarkable recent achievements in this field and to give a unique overview on the many possibilities that offer the multiple component condensation reactions in solving challenging problems in synthetic organic chemistry.

I wish to express my sincere and deep appreciation to all authors and coauthors who contributed insightful papers on their most recent research findings. I also would like to thank the reviewers for their critical comments and Professors Harry Wasserman and Richard Taylor for the invitation to edit this special issue and for their helpful suggestions.

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Three-component indole synthesis using *ortho*-dihaloarenes

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Abstract—A three-component synthesis of substituted indoles is accomplished starting from *ortho*-dihaloarenes through the use of a multicatalytic system consisting of an *N*-heterocyclic carbene palladium complex and CuI. The corresponding indole derivatives are obtained as single regioisomers in high yields of isolated product.

1. Introduction

An important goal of modern synthetic chemistry is the development of highly efficient and selective processes that minimize the formation of waste.[1] The design of multi-component reactions (MCRs), in which three or more starting materials react in a highly selective sequence of chemical transformations, constitutes a powerful tool to achieving this goal.[2] Catalytic additions represent ideal reactions within the sequence, preventing the formation of undesired byproducts.[1,3] Addition reactions of simple amines onto unsaturated carbon–carbon multiple bonds attracted considerable attention recently.[4] Intramolecular hydroamination reactions were employed for efficient syntheses of the indole backbone employing *ortho*-alkynylaniline derivatives **5**.[5–10] On the contrary, much less attention was paid to the use of *ortho*-alkynylhaloarenes **3**,[11,12] and a direct indole synthesis employing easily accessible *ortho*-dihaloarenes **1** was not reported. Transition metal-catalyzed C–N bond forming reactions using aryl halides proved to be a versatile method for the synthesis of a variety of amines.[13,14] Inter alia, complexes featuring *N*-heterocyclic carbenes[15] showed high catalytic activity in the coupling of aryl chlorides.[16] In addition, such complexes were used as catalysts for Sonogashira coupling reactions between aryl bromides and phenylacetylene.[17] Consequently, we wondered if a multicatalytic[18] regioselective three-component indole synthesis could be devised using easily available *ortho*-dihaloarenes **1** (Scheme 1).

Herein, we wish to report a full account on an unprecedented three-component indole synthesis starting from *ortho*-dihaloarenes **1**.[19]

Keywords: Indoles; Multi-component reaction; Multi-catalytic reaction.
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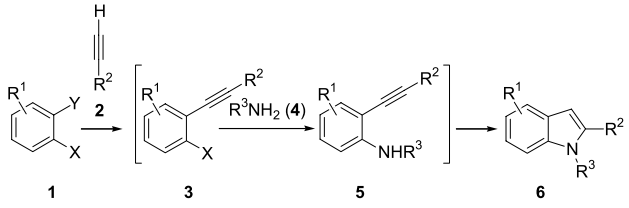
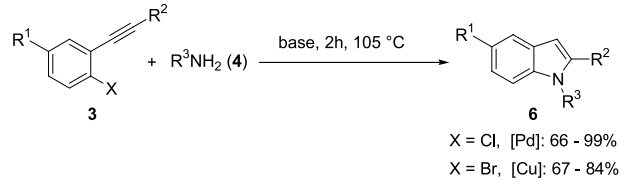
2. Results and discussion

On the outset of our studies, we explored a one-pot sequence consisting of a transition metal-catalyzed amination reaction of *ortho*-alkynylhaloarenes **3** and an intramolecular hydroamination (Scheme 2).[12] While aryl bromides were converted using a copper catalyst, aryl chlorides required the use of a palladium complex. Both protocols allowed for quantitative conversion of starting material **3** within 2 h in good to excellent yields of isolated product.

In contrast to the previously described method,[11] the protocol was not only applicable to sterically hindered amines, but also to simple, less sterically demanding alkyl-substituted amines. Furthermore, it was not limited to simple alkyl-substituted alkynes, but could also be used for the conversion of aryl-substituted derivatives with excellent



Scheme 1. Indole synthesis using *ortho*-dihaloarenes.



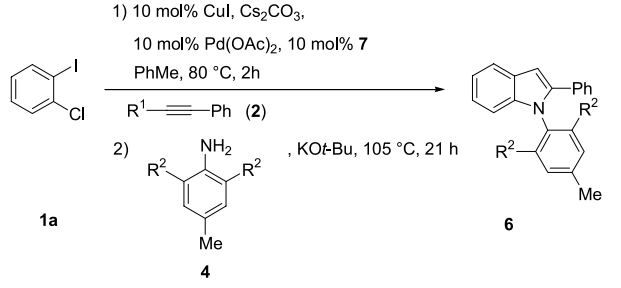
Scheme 2. Indole synthesis using *ortho*-alkynylhaloarenes **3** and amines **4**.

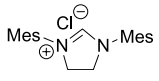
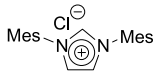
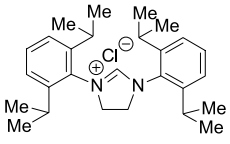
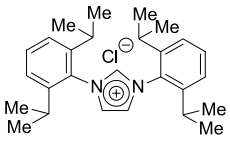
yields. Accordingly, we focused on the use of aryl-substituted alkynes throughout our studies on the development of a multicatalytic three-component indole synthesis.

2.1. Development and optimization of the three-component reaction

The catalytic efficiency of palladium complexes derived from in situ generated *N*-heterocyclic carbenes (NHC) was evaluated in the three-component reaction, employing chloroiodobenzene **1a**, phenylacetylene (**2a**) and *para*-toluidine (**4a**) (Table 1). Mesityl-substituted carbene ligand precursors **7a** and **7b** failed to give any desired product due to a significantly reduced activity in the Sonogashira coupling of alkyne **2a** (entries 1 and 2). Contrarily, sterically congested preligands **7c** (entry 3) and **7d** (entry 4) gave rise to the corresponding indole **6a**. The catalytic activity of the complex derived from imidazolium salt **7d** was generally superior to the one observed for the corresponding imidazolinium salt **7c** (entries 3 and 5 vs entries 4 and 6, respectively). The conversion of silyl-substituted alkyne **2b** in the Sonogashira coupling[20] was also viable, but less efficient. This resulted in a longer reaction time and a significantly reduced yield of indole **6a** (entry 7). For the amination–hydroamination sequence KO*t*-Bu was used as base. The milder base Cs_2CO_3[21] could also be used, thereby expanding the functional group tolerance (entry 8). However, the cyclization reaction of the generated *ortho*-alkynylanilines **3** was found incomplete with Cs_2CO_3 when using alkyl-substituted amines (vide infra). Therefore, we employed throughout the subsequent studies KO*t*-Bu.

Table 1. Influence of the carbene precursor on the one-pot indole synthesis



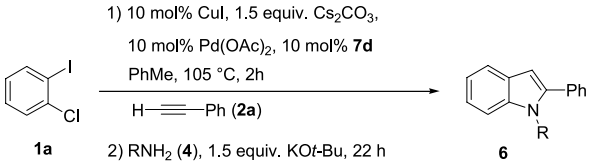
Entry	Ligand **7**	R^1	R^2	Isolated yield[a]
1	 **7a**	H **2a**	H **4a**	—
2	 **7b**	H **2a**	H **4a**	—
3	 **7c**	H **2a**	H **4a**	22% **6a**
4	 **7d**	H **2a**	H **4a**	65% **6a**
5	**7c**	H **2a**	Me **4b**	18% **6b**
6	**7d**	H **2a**	Me **4b**	58% **6b**
7	**7d**	TMS **2b**	H **4a**	42% **6a**[b,c]
8	**7d**	H **2a**	H **4a**	68% **6a**[b]

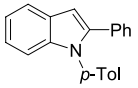
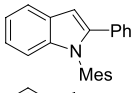
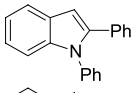
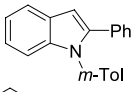
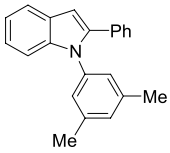
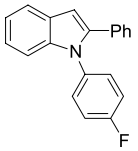
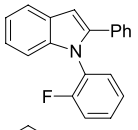
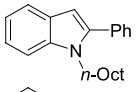
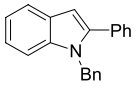
[a] Isolated yield of analytically pure product.
[b] Using Cs_2CO_3 instead of KO*t*-Bu for the amination.
[c] Sonogashira coupling: 14 h, 105 °C.

2.2. Scope of the three-component indole synthesis

With an optimized catalyst in hand, we studied the scope of the three-component indole synthesis employing

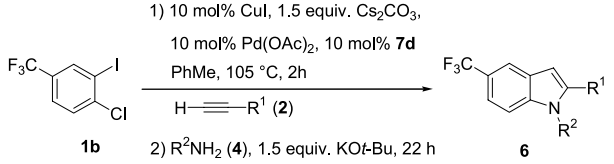
Table 2. Three-component indole synthesis starting from chloroiodoarene **1a**

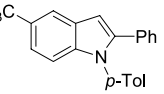
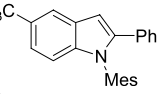
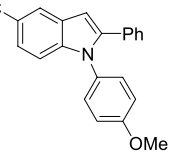
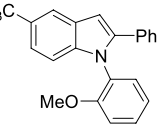
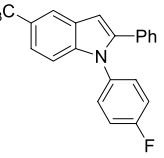
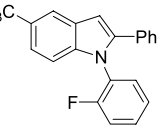


Entry	R	Product	Isolated yield (%)[a]
1	4-MeC_6H_4	 **6a**	65
2	2,4,6-$Me_3C_6H_2$	 **6b**	58
3	Ph	 **6c**	52
4	3-MeC_6H_4	 **6d**	66
5	3,5-$Me_2C_6H_3$	 **6e**	67
6	4-FC_6H_4	 **6f**	54
7	2-FC_6H_4	 **6g**	61
8	*n*-Oct	 **6h**	58[b]
9	$PhCH_2$	 **6i**	50[b]

[a] Isolated yield of analytically pure product.
[b] KO*t*-Bu (2.5 equiv).

Table 3. Three-component synthesis of substituted indole derivatives **6**



Entry	R	Product		Isolated yield (%)[a]
1	4-MeC_6H_4		**6j**	63
2	2,4,6-$Me_3C_6H_2$		**6k**	68[b]
3	4-$MeOC_6H_4$		**6l**	65
4	2-$MeOC_6H_4$		**6m**	76
5	4-FC_6H_4		**6n**	79
6	2-FC_6H_4		**6o**	74

[a] Isolated yield of analytically pure product.
[b] KO*t*-Bu (2.5 equiv).

chloroiodobenzene **1a**, phenylacetylene (**2a**) and a variety of different amines **4** (Table 2).

Electron-rich (entries 1–5) and electron-poor (entries 6 and 7) aniline derivatives were converted with a comparable efficacy. Importantly, less sterically hindered alkyl-substituted amines could be employed as well (entry 8). This allows for the installation of a benzyl-group on nitrogen of the indole moiety (entry 9). The conversion of chloroiodoarene **1b**, bearing an electron-withdrawing substituent, proceeded also well (Table 3). Accordingly, the corresponding indoles **6** were obtained with good yields of isolated product. It is worthy to note that the indole derivatives were generated as single regioisomers.

3. Conclusion

In summary, we reported the development of an efficient three-component indole synthesis, which makes use of easily accessible *ortho*-dihaloarenes, terminal alkynes and differently substituted amines. A single catalytic system consisting of an in situ generated palladium carbene complex and CuI gives rise to a highly regioselective transformation and leads to the indole derivatives in good yields of isolated product.

4. Experimental

4.1. General

All three-component reactions were carried out on a 1 mmol scale under N_2 using pre-dried glassware. Chemicals were obtained from commercial sources, and were used without further purification. Toluene was freshly distilled from sodium under nitrogen. Yields refer to isolated compounds, estimated to be >95% pure as determined by ^{1}H NMR and GC. Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: ^{1}H and ^{13}C were recorded on a Bruker AC 300 or AMX 600, ^{19}F was recorded on a Varian VXR 400 in the solvent indicated; chemical shifts (δ) are given in ppm, coupling constants (J) in Hz.

4.1.1. Representative procedure for three-component indole synthesis: 2-phenyl-1-*p*-tolyl-1*H*-indole (6a).[22] A solution of Cs_2CO_3 (489 mg, 1.50 mmol), HIPrCl (**7d**) (43 mg, 0.10 mmol) and $Pd(OAc)_2$ (22 mg, 0.10 mmol) in toluene (3 mL) was stirred at ambient temperature for 30 min. Chloroiodobenzene **1a** (239 mg, 1.00 mmol), CuI (19 mg, 0.10 mmol) and phenylacetylene (**2a**) (153 mg, 1.50 mmol) were added. The reaction mixture was stirred at 105 °C for 2 h and was thereafter allowed to cool to room temperature. KO*t*-Bu (168 mg, 1.50 mmol) and *p*-toluidine (**4a**) (129 mg, 1.20 mmol) were added and the reaction was heated at 105 °C for 21 h. Et_2O (60 mL), aq NH_3 (1 N, 15 mL) and brine (50 mL) were added to the cold suspension. The separated aq phase was washed with Et_2O (2×60 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (silica gel, *n*-pentane/Et_2O 500:1) yielded 2-phenyl-1-*p*-tolyl-1*H*-indole (**6a**) as a yellow oil (185 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, J=6.2, 2.9 Hz, 1H), 7.22–7.00 (m, 12H), 6.70 (d, J=0.7 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 139.1, 137.0, 135.9, 132.6, 129.9, 128.9, 128.2, 128.1, 127.8, 127.2, 122.2, 120.5, 120.4, 110.7, 103.4, 21.1. IR (KBr): 3029, 1511, 1456, 1440, 1351, 1320, 1209, 1109, 793, 761, 747, 697 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 283 (100) [M$^+$], 282 (12), 267 (10), 165 (6). HR-MS (EI) *m*/*z* calcd for $C_{21}H_{17}N$ 283.1361, found 283.1375.

4.1.2. 1-(2,4,6-Trimethylphenyl)-2-phenyl-1*H*-indole (6b). Following the general procedure, indole **6b** (180 mg, 58%) was obtained as a yellow oil after purification by column chromatography on silica gel (*n*-pentane/Et_2O 300:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (m, 1H), 7.20–7.00 (m, 7H), 6.87 (s, 2H), 6.76 (s, 1H), 6.71 (m, 1H), 2.23 (s, 3H), 1.72 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 138.0, 138.0, 137.9, 136.9, 133.9, 132.8, 129.2, 128.3, 127.5, 127.2, 122.1, 120.4, 120.2, 110.5, 102.0, 21.1, 17.7. IR (KBr): 3057, 3027, 2919, 1603, 1472, 1375, 1210, 1029, 855, 791, 738, 695 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 311 (100) [M$^+$], 296 (19), 234 (13), 140 (12). HR-MS (EI) *m*/*z* calcd for $C_{23}H_{21}N$ 311.1674, found 311.1698.

4.1.3. 1,2-Diphenyl-1*H*-indole (6c).[23] Following the general procedure, indole **6c** (139 mg, 52%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 500:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (ddd, J=6.0, 3.1, 0.7 Hz, 1H), 7.48–7.25 (m, 11H), 7.23 (d, J=3.1 Hz, 1H), 7.21 (d, J=3.1 Hz, 1H), 6.85 (d, J=0.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 139.0, 138.5, 132.5, 129.2, 128.9, 128.3, 128.1, 128.0, 127.3, 127.2, 122.3, 120.7, 120.5, 110.6, 103.7. IR (KBr): 3054, 1596, 1499, 1456, 1381, 1352, 1324, 747, 762, 736, 698 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 269 (100) [M^+], 165 (14), 134 (7). HR-MS (EI) *m*/*z* calcd for $C_{20}H_{15}N$ 269.1204, found 269.1166.

4.1.4. 2-Phenyl-1-*m*-tolyl-1*H*-indole (6d). Following the general procedure, indole **6d** (188 mg, 66%) was obtained as a yellow oil after purification by column chromatography on silica gel (*n*-pentane/Et_2O 500:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.75–7.71 (m, 1H), 7.36–7.15 (m, 11H), 7.09–7.05 (m, 1H), 6.85 (d, J=0.8 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 139.2, 139.1, 138.4, 132.6, 129.0, 128.8, 128.5, 128.2, 128.1, 128.0, 127.2, 125.2, 122.2, 120.6, 120.5, 110.7, 103.5, 21.3. IR (KBr): 3057, 2920, 1603, 1590, 1490, 1457, 1442, 1351, 1322, 784, 761, 747, 700 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 283 (100) [M^+], 267 (16), 165 (11), 134 (7). HR-MS (EI) *m*/*z* calcd for $C_{21}H_{17}N$ 283.1361, found 283.1337.

4.1.5. 1-(3,5-Dimethylphenyl)-2-phenyl-1*H*-indole (6e).[24] Following the general procedure, indole **6e** (197 mg, 67%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 500:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.75–7.71 (m, 1H), 7.38–7.20 (m, 8H), 7.03 (m, 1H), 6.93 (m, 2H), 6.85 (d, J=0.8 Hz, 1H), 2.34 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 139.1, 138.9, 138.3, 132.7, 128.9, 128.8, 128.2, 128.1, 127.2, 125.7, 122.1, 120.5, 120.4, 110.8, 103.3, 21.2. IR (KBr): 3044, 2918, 1610, 1594, 1487, 1459, 1354, 1328, 1310, 854, 763, 749, 702 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 297 (100) [M^+], 281 (10), 267 (6), 165 (6), 134 (5). HR-MS (EI) *m*/*z* calcd for $C_{22}H_{19}N$ 297.1517, found 297.1500.

4.1.6. 1-(4-Fluorophenyl)-2-phenyl-1*H*-indole (6f). Following the general procedure, indole **6f** (155 mg, 54%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 400:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.72 (m, 1H), 7.33–7.21 (m, 10H), 7.19–7.21 (m, 2H), 6.85 (d, J=0.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4 (d, J=247.4 Hz), 140.8, 139.1, 134.5 (d, J=2.9 Hz), 132.3, 129.6 (d, J=8.5 Hz), 128.9, 128.2, 128.2, 127.4, 122.4, 120.8, 120.6, 116.2 (d, J=22.6 Hz), 110.4, 103.7. ^{19}F NMR (375 MHz, $CDCl_3$): −113.0 (tt, J=8.4, 5.0 Hz). IR (KBr): 3070, 1600, 1510, 1459, 1221, 1210, 850, 767, 749, 699 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 287 (100) [M^+], 183 (5), 165 (5). HR-MS (EI) *m*/*z* calcd for $C_{20}H_{14}NF$ 287.1110, found 287.1102.

4.1.7. 1-(2-Fluorophenyl)-2-phenyl-1*H*-indole (6g). Following the general procedure, indole **6g** (174 mg, 61%) was obtained as a yellow oil after purification by column chromatography on silica gel (*n*-pentane/Et_2O 300:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.75–7.72 (m, 1H), 7.44–7.15 (m, 12H), 6.87 (d, J=0.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1 (d, J=251.7 Hz), 141.3, 139.0, 132.3, 130.5, 129.5 (d, J=7.6 Hz), 128.5, 128.4, 128.2, 127.5, 126.5 (d, J=12.6 Hz), 124.6 (d, J=4.1 Hz), 122.5, 120.9, 120.6, 116.8 (d, J=19.7 Hz), 110.5, 103.8. ^{19}F NMR (375 MHz, $CDCl_3$): −118.9 (m). IR (KBr): 3060, 1604, 1504, 1455, 1380, 1326, 1268, 1229, 816, 797, 759, 696 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 287 (100) [M^+], 267 (11), 165 (9). HR-MS (EI) *m*/*z* calcd for $C_{20}H_{14}NF$ 287.1110, found 287.1076.

4.1.8. 1-(*n*-Octyl)-2-phenyl-1*H*-indole (6h). Following the general procedure, indole **6h** (178 mg, 58%) was obtained as a yellow oil after purification by column chromatography on silica gel (*n*-pentane/Et_2O 400:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J=7.9 Hz, 1H), 7.43–7.20 (m, 6H), 7.14 (dt, J=7.6, 1.3 Hz, 1H), 7.04 (dt, J=7.4, 1.0 Hz, 1H), 6.43 (d, J=0.7 Hz, 1H), 4.05 (t, J=7.6 Hz, 2H), 1.60 (t, J=7.4 Hz, 2H), 1.20–1.05 (m, 10H), 0.77 (t, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 137.3, 133.3, 129.4, 128.4, 128.2, 127.9, 121.4, 120.5, 119.7, 110.0, 102.0, 43.9, 31.7, 29.9, 29.1, 29.0, 26.7, 22.6, 14.1. IR (KBr): 3030, 2927, 2854, 1605, 1460, 1348, 1161, 1013, 786, 748, 699 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 305 (70) [M^+], 207 (18), 206 (100), 204 (12). HR-MS (EI) *m*/*z* calcd for $C_{22}H_{27}N$ 305.2143, found 305.2129.

4.1.9. 1-Benzyl-2-phenyl-1*H*-indole (6i).[25] Following the general procedure, indole **6i** (140 mg, 50%) was obtained as yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 400:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, J=5.9, 0.8 Hz, 1H), 7.36–7.00 (m, 11H), 6.92 (dd, J=8.2, 1.8 Hz, 2H), 6.56 (s, 1H), 5.26 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8, 138.2, 138.0, 132.7, 129.2, 128.7, 128.5, 128.3, 128.0, 127.1, 125.9, 121.9, 120.5, 120.1, 110.5, 102.3, 47.7. IR (KBr): 3026, 1494, 1462, 1344, 1306, 1175, 1158, 1026, 772, 749, 697 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 283 (100) [M^+], 193 (10), 165 (11), 91 (77). HR-MS (EI) *m*/*z* calcd for $C_{21}H_{17}N$ 283.1361, found 283.1376.

4.1.10. 5-Trifluoromethyl-2-phenyl-1-*p*-tolyl-1*H*-indole (6j). Following the general procedure, indole **6j** (222 mg, 63%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 200:1). ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.43 (dd, J=8.7, 1.2 Hz, 1H), 7.34 (d, J=8.7 Hz, 1H), 7.32–7.29 (m, 5H), 7.27 (d, J=8.2 Hz, 2H), 7.16 (d, J=8.2 Hz, 2H), 6.89 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 140.3, 137.7, 135.2, 131.9, 130.1, 129.0, 128.2, 127.7, 127.7, 127.5, 125.3 (q, J=271.7 Hz), 122.9 (q, J=31.7 Hz), 118.8 (q, J=2.9 Hz), 118.1 (q, J=3.5 Hz), 110.9, 103.8, 21.2. ^{19}F NMR (375 MHz, $CDCl_3$): −59.3 (s). IR (KBr): 3032, 1516, 1343, 1326, 1271, 1168, 1162, 1131, 1114, 1056, 898, 812, 765, 750, 700 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 351 (100) [M^+], 335 (7). HR-MS (EI) *m*/*z* calcd for $C_{22}H_{16}NF_3$ 351.1235, found 351.1257.

4.1.11. 5-Trifluoromethyl-1-(2,4,6-trimethylphenyl)-2-phenyl-1*H*-indole (6k). Following the general procedure, indole **6k** (256 mg, 68%) was obtained as a yellow oil after purification by column chromatography on silica gel

(*n*-pentane/Et_2O 200:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (dd, $J=0.8$, 0.8 Hz, 1H), 7.35 (dd, $J=8.6$, 1.3 Hz, 1H), 7.28–7.16 (m, 6H), 6.96–6.87 (m, 3H), 2.35 (s, 3H), 1.81 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 139.2, 138.6, 136.8, 133.2, 132.1, 129.4, 128.4, 127.8, 127.6, 127.5, 127.2 (q, $J=271.4$ Hz), 122.7 (q, $J=31.4$ Hz), 118.8 (q, $J=3.5$ Hz), 118.2 (q, $J=4.4$ Hz), 110.7, 102.7, 21.1, 17.6. ^{19}F NMR (375 MHz, $CDCl_3$): -59.2 (s). IR (KBr): 3029, 2973, 2921, 1706, 1611, 1489, 1451, 1366, 1340, 1322, 1268, 1158, 1116, 1054, 810, 762, 752, 694 cm^{-1}. MS (EI) *m/z* (relative intensity) 379 (100) [M^+], 364 (22), 349 (5), 302 (10), 286 (6). HR-MS (EI) *m/z* calcd for $C_{24}H_{20}NF_3$ 379.1548, found 379.1537.

4.1.12. 5-Trifluoromethyl-1-(4-methoxyphenyl)-2-phenyl-1*H*-indole (6l). Following the general procedure, indole **6l** (240 mg, 65%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 300:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (dd, $J=0.8$, 0.8 Hz, 1H), 7.40 (dd, $J=8.7$, 1.8 Hz, 1H), 7.30–7.27 (m, 6H), 7.17 (dm, $J=9.0$ Hz, 2H), 6.95 (dm, $J=9.0$ Hz, 2H), 6.86 (d, $J=0.7$ Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 142.7, 140.5, 131.9, 130.6, 129.1, 129.0, 128.3, 127.8, 127.4, 125.3 (q, $J=271.7$ Hz), 123.3 (q, $J=31.7$ Hz), 118.8 (q, $J=3.5$ Hz), 118.1 (q, $J=4.4$ Hz), 114.7, 110.9, 103.5, 55.5. ^{19}F NMR (375 MHz, $CDCl_3$): -59.3 (s). IR (KBr): 3057, 2966, 1516, 1341, 1326, 1272, 1256, 1170, 1116, 1054, 1029, 813, 767, 751, 701 cm^{-1}. MS (EI) *m/z* (relative intensity) 367 (100) [M^+], 352 (12), 322 (6). HR-MS (EI) *m/z* calcd for $C_{22}H_{16}NOF_3$ 367.1184, found 367.1199.

4.1.13. 5-Trifluoromethyl-1-(2-methoxyphenyl)-2-phenyl-1*H*-indole (6m). Following the general procedure, indole **6m** (277 mg, 76%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 200:1). ^1H NMR (600 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.40–7.36 (m, 2H), 7.28–7.22 (m, 6H), 7.11 (d, $J=8.6$ Hz, 1H), 7.02 (ddd, $J=7.6$, 7.6, 1.2 Hz, 1H), 6.97 (d, $J=7.6$ Hz, 1H), 6.85 (s, 1H), 3.51 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.4, 143.4, 140.4, 132.4, 129.9, 129.8, 128.3, 128.1, 127.7, 127.7, 126.7, 125.4 (q, $J=271.1$ Hz), 122.7 (q, $J=31.7$ Hz), 121.0, 118.6 (q, $J=2.9$ Hz), 118.1 (q, $J=3.5$ Hz), 112.4, 111.0, 103.0, 55.4. ^{19}F NMR (375 MHz, $CDCl_3$): -59.2 (s). IR (KBr): 3067, 1506, 1339, 1323, 1282, 1269, 1167, 1112, 1053, 1025, 766, 754, 698 cm^{-1}. MS (EI) *m/z* (relative intensity) 367 (100) [M^+], 336 (9), 290 (5). HR-MS (EI) *m/z* calcd for $C_{22}H_{16}NOF_3$ 367.1184, found 367.1135.

4.1.14. 5-Trifluoromethyl-1-(4-fluorophenyl)-2-phenyl-1*H*-indole (6n). Following the general procedure, indole **6n** (281 mg, 79%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 200:1). ^1H NMR (600 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.41 (dd, $J=8.7$, 1.1 Hz, 1H), 7.28–7.20 (m, 8H), 7.14–7.11 (m, 2H), 6.85 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.8 (d, $J=248.3$ Hz), 142.6, 140.3, 133.9, 131.6, 129.6 (d, $J=8.2$ Hz), 129.0, 128.4, 128.0, 127.6, 125.2 (q, $J=271.7$ Hz), 123.2 (q, $J=31.7$ Hz), 119.1 (q, $J=2.9$ Hz), 118.3 (q, $J=3.5$ Hz), 116.5 (d, $J=21.9$ Hz), 110.7, 104.1. ^{19}F NMR (375 MHz, $CDCl_3$): -59.4 (s), -112.0 (tt, $J=8.4$, 4.6 Hz). IR (KBr): 3081, 1513, 1341, 1325, 1268, 1227, 1168, 1131, 1111, 1056, 862, 821, 808, 764, 746, 699 cm^{-1}. MS (EI) *m/z* (relative intensity) 355 (100) [M^+], 285 (16), 183 (8), 165 (8). HR-MS (EI) *m/z* calcd for $C_{21}H_{13}NF_4$ 355.0984, found 355.1004.

4.1.15. 5-Trifluoromethyl-1-(2-fluorophenyl)-2-phenyl-1*H*-indole (6o). Following the general procedure, indole **6o** (264 mg, 74%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 200:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (dd, $J=0.8$, 0.8 Hz, 1H), 7.44–7.36 (m, 2H), 7.30–7.15 (m, 9H), 6.88 (d, $J=0.8$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0 (d, $J=252.1$ Hz), 143.1, 140.2, 131.6, 130.1 (d, $J=7.6$ Hz), 128.5, 128.4, 128.1, 127.9, 127.0, 125.7 (d, $J=12.6$ Hz), 125.2 (q, $J=271.4$ Hz), 124.8 (d, $J=3.8$ Hz), 123.3 (q, $J=31.7$ Hz), 119.2 (q, $J=3.5$ Hz), 118.3 (q, $J=4.1$ Hz), 117.0 (d, $J=20.0$ Hz), 110.8, 104.1. ^{19}F NMR (375 MHz, $CDCl_3$): -59.4 (s), -119.0 (m). IR (KBr): 1507, 1343, 1326, 1232, 1166, 1133, 1113, 1055, 812, 762, 697 cm^{-1}. MS (EI) *m/z* (relative intensity) 355 (100) [M^+], 336 (10), 285 (8), 165 (4). HR-MS (EI) *m/z* calcd for $C_{21}H_{13}NF_4$ 355.0984, found 355.1002.

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Metal catalyzed multicomponent syntheses of secondary propargylamides and oxazoles from silylimines, acid chlorides, and alkynes

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Abstract—Copper(I) and zinc(II) catalyzed routes to construct secondary propargylamides in one-pot procedures from aldehydes, $LiN(TMS)_2$, acid chlorides, and alkynes are described. This reaction has been subsequently used to provide a one-pot synthesis of oxazoles from four simple building blocks.

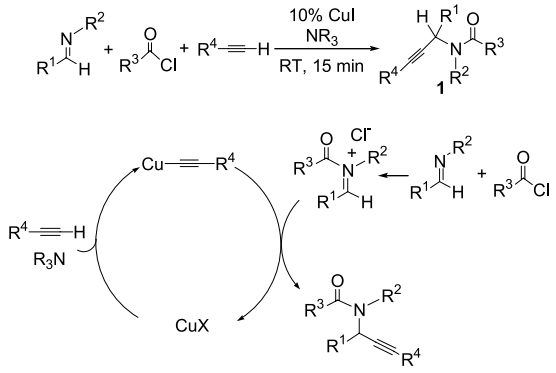
1. Introduction

Multicomponent coupling reactions (MCRs) represent efficient methods of rapidly increasing molecular complexity in a modular fashion.[1] From early examples, such as the Strecker,[2] Hantsch,[3] and Mannich[4] reactions, to more recent reports,[5] this approach has been used to prepare a wide range of important chemical structures. In principle, transition metal catalysis can provide a useful tool in the design of new MCRs, through the ability to both induce and control reactivity. Overall, this can allow the use of more readily available, easily diversified, and less complex building blocks, coupled together all at once via a metal-based mechanism.[6]

One class of molecules towards which metal catalyzed multicomponent coupling has recently been applied are propargylamides. We[7] and others[8,9] have shown that these compounds, and their amine derivatives, can be assembled from available building blocks, such as imines, aldehydes, amines, acid chlorides, alkynes, using a range of metal catalysts. Of the many propargylamides used in synthesis, secondary amides have found particular utility. These core structures are present in a variety of biologically active molecules (e.g., oxotremorine[10] and a range of fungicides and herbicides).[11] In addition, they are useful synthons in the formation of heterocycles[12–14] and biomimetic polymers.[15] Despite this utility, the current metal catalyzed multicomponent routes to propargylamides all generate tertiary amides, and do not provide direct access to the secondary propargylamide core.[16] We describe herein, our studies towards the development of a route to construct secondary propargylamides, via the copper or zinc catalyzed coupling of imines, acid chlorides, and terminal alkynes. This process has been subsequently employed to provide a novel route to construct tri-substituted oxazoles from four readily available building blocks in a single pot reaction.

2. Results and discussion

We have previously reported that tertiary propargylamides (**1**) can be prepared through the copper catalyzed three-component coupling of imines, acid chlorides, and alkynes (Scheme 1).[7]



Scheme 1. Three-component synthesis of tertiary propargylamides.

Keywords: Alkynes; Oxazoles; Multicomponent.
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This reaction is considered to proceed through the attack of a copper-acetylide on an in situ generated *N*-acyl iminium salt. In order to extend this approach to secondary propargylamides, N–H substituted imines would be required as substrates, which are typically unstable.[17] However, trimethylsilyl-substituted imines (**2**) have been used as N–H imine equivalents for nucleophilic addition chemistry,[18] suggesting their potential utility in this system. Not surprisingly, however, our initial attempt to employ these imines in the copper catalyzed multicomponent coupling with benzoyl chloride and phenylacetylene led instead to the formation of *N*-acyl imines **3**,[19] eliminating TMSCl in the process (Fig. 1).

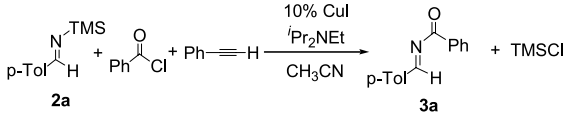


Figure 1. Reaction of trimethylsilyl-substituted imine **2a** with acid chloride and alkyne.

While in principle **3a** could react with an in situ generated copper-acetylide to form a propargylamide, even upon prolonged heating at 105 °C, no reaction was observed. The lack of alkyne addition to the *N*-acyl imine is likely the result of its lower electrophilicity relative to *N*-acyl iminium salts (e.g., in Scheme 1). Considering that Lewis acids have been shown to catalyze addition reactions to aldehydes and imines,[20] Lewis acid co-catalysts were examined in concert with copper salts. As was hoped, the reaction of **3a** and phenylacetylene in the presence of 10% CuI and 20% $BF_3 \cdot Et_2O$ leads to the formation of the desired propargylamide **4a** in 83% yield. This reaction can also be performed in a multicomponent fashion, allowing the genertion of **4a** in similar yield directly from *N*-trimethylsilyl imine **2a**, acid chloride, and alkyne (Fig. 2). Alternatively, the construction of the TMS-substituted imine can be performed in the same reaction pot, eliminating the need to isolate these sensitive substrates (Fig. 3, Table 1, **4a**).[†] The latter provides a modular method to construct secondary propargylamides directly from aldehydes, silylamide, acid chlorides, and alkynes.

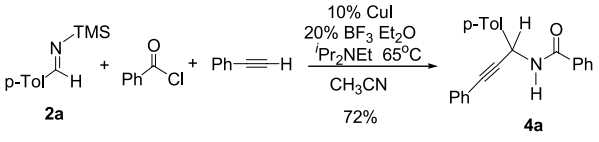


Figure 2. CuI/BF_3 catalyzed synthesis of **4a**.

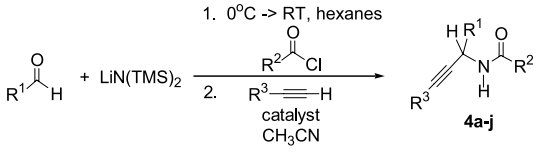


Figure 3. A one-pot synthesis of propargylamides from aldehydes, acid chlorides, silylamide, and alkynes.

Table 1. Copper(I) and zinc(II) catalyzed multicomponent syntheses of secondary propargylamides (Fig. 3)[a]

Compound	R^1	R^2	R^3	Catalyst[b]	Yield (%)
4a	*p*-Tol	Ph	Ph	CuI/BF_3	80
4b	^{t}Bu	Ph	^{n}Bu	CuI/BF_3	88
4c	*p*-Tol	Vinyl	Ph	CuI/BF_3	57
4d	*p*-An	^{i}Pr	Ph	CuI/BF_3	92
4e	^{t}Bu	*p*-An	^{n}Bu	CuI/BF_3	87
4f	*p*-An	^{t}Bu	Ph	$Zn(OTf)_2$	73
4g	^{t}Bu	*p*-I–$_6$H$_4$	Ph	$Zn(OTf)_2$	67
4h	*p*-Tol	Ph	CH_2OTMS	$Zn(OTf)_2$	62[c]
4i	Ph	^{i}Bu	Ph	$Zn(OTf)_2$	91
4j	Ph	Ph	Ph	$Zn(OTf)_2$	89

[a] Aldehyde (0.63 mmol), 0.63 mmol LHMDS, and 0.83 mmol acid chloride in hexanes, followed by 0.83 mmol alkyne 0.63 mmol $EtiPr_2N$ and catalyst in CH_3CN (7 ml).
[b] With 10% CuI with 20% BF_3 diethyletherate at 65 °C for 14 h, or 10% $Zn(OTf)_2$ at ambient temperature for 10 h.
[c] Product isolated as the deprotected hydroxy-propargylamide.

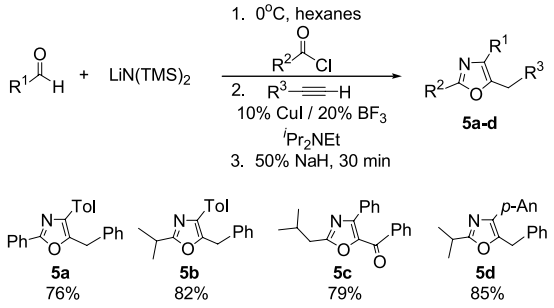
In addition to the use of Lewis acids to increase the electrophilicity of **3**, an alternative approach to this reaction involves increasing the nucleophilicity of the metal-acetylide. In particular, zinc(II) salts have been shown by Carreira to form zinc-acetylides in a similar manner to copper acetylides, and have a higher propensity for addition to such substrates as aldehydes,[21a] imines,[21b,c] and enones.[21d] Indeed, 10% $Zn(OTf)_2$ can be employed as a catalyst for this same multicomponent reaction, in this case under more mild conditions than that with copper, leading to the formation of secondary propargylamide products after only 10 h at ambient temperature (Table 1, **4f–j**).

As shown in Table 1, these reactions can be readily diversified, allowing the formation of secondary amides with a range of aldehyde, acid chloride, and alkyne substrates. This includes aryl and non-enolizable alkyl aldehydes,[22] as well as aryl, alkyl, α,β-unsaturated, and functionalized acid chlorides. Aryl, alkyl, and functionalized alkynes can also be successfully incorporated into the propargylamide product. In general, both catalyst systems provide the products in similarly high yields.

Considering the utility of secondary propargylamides as synthetic building blocks, their generation by this multicomponent reaction provides the opportunity to consider the synthesis of other products in a similar modular fashion. As an illustration of this feature, we have probed the coupling of this reaction with the synthesis of oxazoles.[23] It has been reported that secondary propargylamides undergo cyclization to form oxazoles in the presence of base,[12] palladium,[13] or silica gel catalysts.[14] Thus, performing the catalytic synthesis of **4a** followed by the addition of catalytic NaH to the same reaction pot leads to the overall construction of oxazole **5a** in 76% yield (Scheme 2). This cycloisomerization can be coupled with several of the propargylamide syntheses (**5a–d**),[‡] providing a one pot method to assemble oxazoles from four separate units.

[†] The hexane solvent and other volatile byproducts were removed in vacuo prior to the addition of the alkyne, catalyst, and base in acetonitrile.

[‡] In the case of oxazole **5c**, the 5-benzylic position spontaneously oxidizes in air giving a 5-aroyloxazole.



Scheme 2. Four-component synthesis of oxazoles.

3. Conclusions

In conclusion, we have developed a metal catalyzed multicomponent synthesis of secondary propargylamides from trimethylsilyl-substituted imines, alkynes, and acid chlorides. These processes rely upon the in situ generation of *N*-acylimines and metal-acetylides, which in the presence of either BF_3 (with copper-acetylides), or with the use of nucleophilic zinc(II)-acetylides, couple in a catalytic fashion. By combining this process with the cycloisomerization of the secondary propargylamide product, a modular method to assemble oxazoles in a single pot can be generated. The application of this chemistry to other secondary propargylamide targets is currently underway.

4. Experimental

4.1. General

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a vacuum atmospheres 553-2 dry box or by using standard Schlenk or vacuum line techniques. All reagents were purchased from Aldrich® and used as received. Acetonitrile was distilled from CaH_2 under nitrogen. Deuterated acetonitrile was dried as its protonated analogue, but was transferred under vacuum from the drying agent, and stored over 4 Å molecular sieves. ^1H and ^{13}C NMR spectra were recorded on JEOL 270, Varian Mercury 300 MHz, and Mercury 400 MHz spectrometers. Mass spectra were obtained from the McGill University mass spectral facilities.

4.2. Representative procedure for preparation of 4a–e

To 1,1,1,3,3,3-hexamethyldisilazane (0.14 mL, 0.66 mmol) in a 25 mL reaction bomb equipped with a stir bar in a 0 °C ice bath, was added a 2.5 M solution of BuLi in hexanes (0.25 mL, 0.66 mmol) over 10 min, under nitrogen. Tolualdehyde (77 mg, 0.63 mmol) was then added over 1 h. The reaction was allowed to warm to ambient temperature, acryloyl chloride (75 mg, 0.83 mmol) in acetonitrile (3 mL) was added, and the mixture stirred for 30 min. The solvents and $(TMS)_2O$ were removed in vacuo, the residue dissolved in acetonitrile (2 mL), and phenylacetylene (65 mg, 0.63 mmol) in acetonitrile (1 mL), copper(I) iodide (12 mg, 0.063 mmol) in acetonitrile (2 mL), boron trifluoride diethyl etherate (18 mg, 0.126 mmol), and diisopropylethylamine (110 μL, 0.63 mmol) in acetonitrile (2 mL) were added. The mixture was stirred at 65 °C for 14 h, the solvent was removed in vacuo, and the crude product was purified with column chromatography using ethyl acetate/hexanes as eluent.

4.2.1. *N*-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-benzamide 4a. Isolated yield: 80%. ^1H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.80 (d, 2H, $J=7.8$ Hz), 7.58–7.37 (m, 7H), 7.30 (d, 3H, $J=8.7$ Hz), 7.23–7.17 (d, 2H, $J=11.7$ Hz), 6.84 (d, 1H, $J=8.4$ Hz), 6.45 (d, 1H, $J=8.4$ Hz), 2.40 (s, 3H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 166.3, 138.2, 136.4, 134.1, 132.1, 132.0, 129.7, 128.8, 128.7, 128.5, 127.4, 127.3, 122.8, 87.5, 85.1, 45.8, 21.6. ν_{max} (KBr): 3236 (N–H), 1631 (C=O). HRMS for $C_{23}H_{19}NO$, calculated: 325.1467, found: 325.1458.

4.2.2. *N*-(1-*tert*-butyl-hept-2-ynyl)-benzamide 4b. Isolated yield: 88%. ^1H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.80–7.72 (m, 2H), 7.49–7.36 (m, 3H), 6.20 (d, 1H, $J=8.7$ Hz), 4.80 (dd, 1H, $J=1.5$, 8.7 Hz), 2.18 (t, 2H, $J=6.6$ Hz), 1.55–1.37 (m, 4H), 1.06 (s, 9H), 0.92 (t, 3H, $J=6.6$ Hz). ^{13}C NMR (75.5 MHz, 60 °C, $CDCl_3$): δ 166.7, 134.8, 131.7, 128.8, 127.2, 84.5, 78.3, 51.4, 36.4, 31.2, 26.4, 22.3, 18.7, 14.0. ν_{max} (KBr): 3267 (N–H), 1634 (C=O). HRMS for $C_{18}H_{25}NO$, calculated: 271.1936, found: 271.1932.

4.2.3. *N*-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-acrylamide 4c. Isolated yield: 57%. ^1H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.48–7.43 (m, 4H), 7.39–7.28 (m, 3H), 7.18 (d, 2H, $J=7.8$ Hz), 6.43–6.29 (m, 2H), 6.21–6.07 (m, 2H), 5.69 (dd, 1H, $J=1.5$, 8.7 Hz), 2.39 (s, 3H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 164.1, 138.0, 136.0, 131.8, 130.3, 129.4, 128.5, 128.3, 127.4, 127.1, 122.5, 87.0, 84.8, 44.9, 21.1. ν_{max} (KBr): 3274 (N–H), 1656 (C=O). HRMS for $C_{19}H_{17}NO$, calculated: 275.1310, found: 275.1304.

4.2.4. *N*-[1-(4-methoxy-phenyl)-3-phenyl-prop-2-ynyl]-isobutyramide 4d. Isolated yield: 92%. ^1H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.53–7.41 (m, 4H), 7.36–7.29 (m, 3H), 6.90 (d, 2H, $J=8.4$ Hz), 6.22 (d, 1H, $J=8.4$ Hz), 6.07 (d, 1H, $J=8.4$ Hz), 3.82 (s, 3H), 2.49–2.35 (m, 1H), 1.24–1.17 (m, 6H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 175.6, 159.5, 132.0, 131.7, 128.7, 128.5, 128.5, 122.8, 114.3, 87.7, 84.8, 55.6, 44.7, 35.9, 19.9, 19.7. ν_{max} (KBr): 3304 (N–H), 1640 (C=O). HRMS for $C_{20}H_{21}NO_2$, calculated: 307.1572, found: 307.1581.

4.2.5. *N*-(1-*tert*-butyl-hept-2-ynyl)-4-methoxy-benzamide 4e. Isolated yield: 87%. ^1H NMR (270 MHz, 25 °C, $CDCl_3$): δ 7.70 (d, 2H, $J=8.7$ Hz), 6.86 (d, 2H, $J=8.7$ Hz), 6.19 (d, 1H, $J=9.6$ Hz), 4.78 (d, 1H, $J=9.6$ Hz), 3.82 (s, 3H), 2.18 (t, 3H, $J=6.6$ Hz), 1.56–1.30 (m, 4H), 1.05 (s, 9H), 0.92 (t, 3H, $J=6.6$ Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 170.9, 158.7, 137.5, 136.7, 136.6, 131.5, 129.4, 128.4, 128.3, 127.9, 127.7, 125.5, 113.4, 63.4, 54.5, 39.4, 19.4, 12.8. ν_{max} (KBr): 3318 (N–H), 1629 (C=O). HRMS for $C_{19}H_{27}NO_2$, calculated: 301.2042, found: 301.2031.

4.3. Procedure for the preparation of 4f–j

An analogous procedure to the formation of **4a–e** was followed, except instead of adding CuI and boron trifluoride, zinc(II) triflate (24 mg, 0.063 mmol) was added

as catalyst, and the mixture was stirred at ambient temperature for 10 h. The solvent was removed in vacuo, and the crude product purified by column chromatography using ethyl acetate/hexanes as eluent.

4.3.1. *N*-[1-(4-methoxy-phenyl)-3-phenyl-prop-2-ynyl]-2,2-dimethyl-propionamide 4f. Isolated yield: 73%. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.47 (d, 4H, J=6.9 Hz), 7.36–7.31 (m, 3H), 6.89 (d, 2H, J=8.7 Hz), 6.22 (s, 2H), 3.80 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 177.2, 159.5, 132.0, 131.7, 128.7, 128.5, 128.4, 122.8, 114.2, 87.9, 84.8, 55.6, 44.9, 39.1, 27.8. ν_{max} (KBr): 3409 (N–H), 1648 (C=O). HRMS for $C_{21}H_{23}NO_2$, calculated: 321.1729, found: 321.1739.

4.3.2. *N*-(1-*tert*-butyl-3-phenyl-prop-2-ynyl)-4-iodo-benzamide 4g. Isolated yield: 67%. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.80 (d, 2H, J=8.4 Hz), 7.51 (d, 2H, J=8.4 Hz), 7.45–7.38 (m, 2H), 7.33–7.25 (m, 3H), 6.23 (d, 1H, J=9.6 Hz), 5.06 (dd, 1H, J=3.6, 6.0 Hz), 1.17 (s, 9H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 165.9, 137.8, 133.8, 131.7, 128.6, 128.4, 128.3, 122.6, 98.6, 87.2, 84.0, 51.4, 36.3, 26.1. ν_{max} (KBr): 3296 (N–H), 1645 (C=O). HRMS for $C_{20}H_{20}NOI$, calculated: 417.0590, found: 417.0580.

4.3.3. *N*-(4-hydroxy-1-*p*-tolyl-but-2-ynyl)-benzamide 4h. Isolated yield: 62%. ^{1}H NMR (270 MHz, 20 °C, $CDCl_3$): δ 7.71 (d, 2H, J=6.3 Hz), 7.50–7.29 (m, 5H), 7.11 (d, 2H, J=6.3 Hz), 6.62 (d, 1H, J=9.4 Hz), 6.51 (d, 1H, J=9.4 Hz), 4.33 (dd, 2H, J=3.2, 13.4 Hz), 2.37–2.22 (m, 4H). ^{13}C NMR (68.0 MHz, 20 °C, $CDCl_3$): δ 167.2, 138.5, 135.8, 133.6, 132.0, 129.3, 128.6, 127.1, 125.9, 80.0, 79.7, 74.4, 56.2, 21.1. ν_{max} (KBr): 3272 (N–H), 1648 (C=O). HRMS for, calculated: 279.1259, found: 279.1265.

4.3.4. *N*-(1,3-diphenyl-prop-2-ynyl)-3-methyl-butyramide 4i. Isolated yield: 91%. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.57 (d, 2H, J=6.3 Hz), 7.50–7.39 (m, 2H), 7.38–7.23 (m, 6H), 6.51 (d, 1H, J=8.4 Hz), 6.29 (d, 1H, J=8.4 Hz), 2.30–2.08 (m, 3H), 1.00 (m, 6H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 171.6, 139.4, 132.0, 128.9, 128.7, 128.5, 128.2, 127.3, 122.8, 87.6, 84.9, 46.1, 45.3, 26.7, 22.9. ν_{max} (KBr): 3308 (N–H), 1641 (C=O). HRMS for $C_{20}H_{21}NO$, calculated: 291.1623, found: 291.1621.

4.3.5. *N*-(1,3-diphenyl-prop-2-ynyl)-benzamide 4j. Isolated yield: 89%. ^{1}H NMR (300 MHz, 80 °C, CD_3CN): δ 7.83 (d, 2H, J=8.4 Hz), 7.66 (d, 2H, J=8.4 Hz), 7.52–7.30 (m, 11H), 6.76 (d, 1H, J=8.4 Hz), 6.50 (d, 1H, J=8.4 Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 166.3, 139.4, 134.2, 132.0, 131.9, 129.0, 128.8, 128.7, 128.5, 128.3, 127.4, 127.3, 122.8, 87.4, 85.4, 46.1. ν_{max} (KBr): 3290 (N–H), 1633 (C=O). HRMS for $C_{22}H_{17}NO$, calculated: 311.1310, found: 311.1302.

4.4. Representative procedure for the preparation of oxazoles 5a–c

Upon completion of either the copper or zinc catalyzed synthesis of the propargylamides, before removal of solvent, NaH (7.2 mg, 0.31 mmol) in 2 mL of acetonitrile was added and the reaction mixture was stirred for 30 min. The mixture was then quenched with 5 mL of methanol, the solvent removed in vacuo, and the product purified by column chromatography using ethyl acetate/hexanes as eluent.

4.4.1. 5-Benzyl-2-phenyl-4-*p*-tolyl-oxazole 5a. Isolated yield: 76%. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 8.11 (d, 2H, J=6.6 Hz), 7.68 (d, 2H, J=8.4 Hz), 7.52–7.21 (m, 10H), 4.36 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 160.2, 145.4, 137.7, 137.6, 137.5, 130.3, 129.6, 129.4, 129.0, 128.9, 128.5, 127.9, 127.1, 127.0, 126.5, 32.4, 21.7. ν_{max} (KBr): 2964, 1604, 1555, 1495, 1262, 1100. HRMS calculated for $C_{23}H_{19}NO$, calculated: 325.1467, found: 325.1457.

4.4.2. 5-Benzyl-2-isopropyl-4-*p*-tolyl-oxazole 5b. Isolated yield: 82%. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.57 (d, 2H, J=8.4 Hz), 7.36–7.17 (m, 7H), 4.21 (s, 2H), 3.20–3.04 (m, 1H), 2.39 (s, 3H), 1.40 (d, 6H, J=6.9 Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 167.6, 144.4, 137.8, 137.3, 135.6, 129.7, 129.5, 128.9, 128.4, 127.0, 126.8, 32.2, 28.9, 21.7, 21.0. ν_{max} (KBr): 2972, 1659, 1611, 1413, 1286, 1178. HRMS for $C_{20}H_{21}NO$, calculated: 291.1623, found: 291.1627.

4.4.3. (2-Isobutyl-4-phenyl-oxazol-5-yl)-phenyl-methanone 5c. Isolated yield: 79%. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 8.00–7.92 (m, 2H), 7.85 (d, 2H, J=8.4 Hz), 7.56–7.48 (m, 1H), 7.44–7.34 (m, 5H), 2.80 (d, 2H, J=7.2 Hz), 2.38–2.23 (m, 1H), 1.08 (d, 6H, J=4.2 Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 183.4, 165.9, 147.7, 143.7, 137.6, 133.0, 130.9, 129.8, 129.7, 129.4, 128.5, 128.4, 37.6, 28.0, 22.8. ν_{max} (KBr): 2959, 1651, 1557, 1486, 1447, 1232, 1145. HRMS calculated for $C_{20}H_{19}NO_2$, calculated: 305.1416, found: 305.1408.

4.4.4. 5-Benzyl-2-isopropyl-4-(4-methoxy-phenyl)-oxazole 5d. Isolated yield: 85%. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.56 (d, 2H, J=8.4 Hz), 7.36–7.18 (m, 5H), 6.91 (d, 2H, J=8.4 Hz), 4.20 (s, 2H), 3.81 (s, 3H), 3.18–3.03 (m, 1H), 1.40 (d, 6H, J=6.9 Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 167.5, 159.1, 143.9, 137.9, 135.4, 128.9, 128.4, 126.8, 125.2, 114.3, 55.6, 32.1, 28.9, 21.0. ν_{max} (KBr): 2971, 1605, 1583, 1512, 1495, 1454, 1303, 1251, 1174. HRMS calculated for$C_{20}H_{21}NO_2$, calculated: 307.1572, found: 307.1570.

Supplementary material

^{1}H and ^{13}C NMR spectra of compounds **4a–j** and **5a–d**. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2005.09.096.

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Domino allylation and cyclization of *ortho*-alkynylbenzaldehydes with allyltrimethylsilane catalyzed by Pd(II)–Cu(II) bimetallic systems

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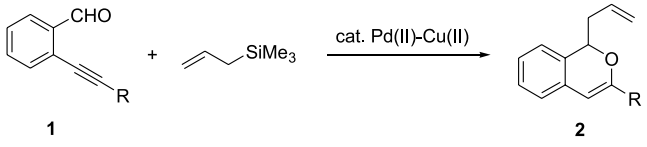
Abstract—The reaction of *ortho*-alkynylated benzaldehydes **1** with allyltrimethylsilane under the $Pd(OAc)_2$–$CuCl_2$ catalyst system gave the isochromene derivatives **2** together with the chlorinated products **3**. When the reaction was conducted in the presence of half equiv of H_2O, the formation of **3** was suppressed and **2** was obtained in good to high yields. When the reaction of **1a** was carried out with trimethylsilylcyanide instead of allylsilane, the cyano group-substituted isochromene **9** was obtained in 94% yield.

1. Introduction

Bimetallic catalysts attract significant attention of synthetic chemists for developing new transformations.[1] Recently, we found that the combination of Pd(0) and Cu(I) produced a quite suitable catalyst system for the synthesis of several nitrogen-containing heterocyclic compounds.[2] Moreover, we reported a novel synthetic method for oxygen-containing heterocyclic compounds; the acetylenic arylaldehydes **1** reacted with alcohols in the presence of Pd(II) catalyst to give 1-alkoxy-isochromene derivatives.[3] This is a quite useful method for the synthesis of the alkoxy-substituted cyclic alkenyl ethers; for example, BCH-2051, as potent antitumor agent, was synthesized efficiently via this methodology.[3b] However, when the reactions of **1** were carried out with nucleophilic alkyl organometallics, such as allyl Grignard reagent, the desired alkyl-substituted isochromenes were not obtained; only alcohols can be used as a pronucleophile under the previous conditions. Recently, Barluenga and his co-workers reported the synthetic method of isochromene derivatives from the *ortho*-alkynyl arylaldehydes by using bis(pyridine) iodonium tetrafluoroborate (IPy_2BF_4) as a metal-free electrophile.[4a] They showed that not only heteroatom nucleophiles, such as alcohols, but also carbon pronucleophiles, such as allyltrimethylsilane, silyl enol ethers, phenol, and *N*,*N*-dimethylaniline, can be used as nucleophiles. 1-Alkyl (or aryl) substituted isochromene derivatives were synthesized by this method. Larock also reported the similar transformations by using other electrophiles, such as NBS, I_2, ICl, *p*-$O_2NC_6H_4SCl$, and PhSeBr.[4b] However, both reactions needed a stoichiometric amount of electrophiles as promoters and those reactions did not proceed catalytically. Herein, we wish to report that the domino type reaction of **1** with allyltrimethylsilane proceeds using the Pd(II)–Cu(II) bimetallic catalyst system to give the isochromene derivatives **2**, having an allyl group at 1-position, in good to high yields (Eq. 1).



1 2 (1)

2. Result and discussion

2.1. Domino allylation and cyclization

We examined the reaction of **1** with allyltrimethylsilane using palladium–copper bimetallic catalysts under various conditions and the results are summarized in Table 1. When **1a** (R=Ph) was treated with allyltrimethylsilane in the presence of 5 mol% of $Pd(OAc)_2$, 20 mol% of Ph_3P, and 1.2 equiv of $CuCl_2$ in toluene at room temperature for 14 h, the domino reaction proceeded to afford **2a** in 29% yield together with the chlorinated product **3a** in 21% yield (entry 1).

Keywords: Domino reaction; Bimetallic catalyst; Allyltrimethylsilane; Cyclization; Isochromene skeleton; *ortho*-Alkynylbenzaldehyde; Palladium; Copper.
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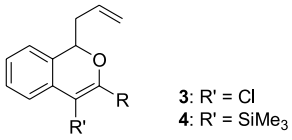
Since the silyl-substituted product **4** was not formed, we thought that trace amounts of water, which might exist in the reaction medium, would play an important role for the formation of **2a**. Therefore, we added H_2O to the reaction mixture for producing **2** selectively. First, we carried out the reaction in the presence of 1 equiv of H_2O. However, **2a** and **3a** were obtained in low yields (entry 2). On the other hand, **2a** was obtained in 37% yield as a sole product when the amount of H_2O was decreased to half equivalent (entry 3). It was found that $PdCl_2$ also catalyzed the domino allylation but the reaction was sluggish (entry 4). When the reaction was carried out in the absence of palladium catalyst, no products were obtained at all. This blank test clearly indicates that the present reaction is not promoted by $CuCl_2$; also it should be noted that the reaction did not proceed with palladium catalyst only. Furthermore, both $CuCl_2$ and PPh_3 were found to be essential because no products were formed in the reactions without each of them. Moreover, no reaction occurred in the presence of benzoquinone instead of $CuCl_2$. This result showed that $CuCl_2$ did not work as an oxidative agent. Interestingly, when the reaction was carried out using (p-$MeOC_6H_4)_3P$ instead of Ph_3P, the chemical yield of **2a** increased dramatically and the reaction time became much shorter, although a small amount of **3a** was produced as a by-product (entry 5). Optimization experiments revealed that the use of 0.5 equiv of $CuCl_2$ gave **2a** in 81% yield without formation of **3a** (entry 6). Other ligands shown in entries 7–9 were less effective. The chemical yield was increased up to 84% when 2 equiv of allyltrimethylsilane were used (entry 10). The domino reaction also proceeded well with other substrates. The reaction of **1b**, bearing p-$CF_3C_6H_5$ group at the terminus of alkyne, proceeded smoothly to give **2b** in 64% yield (entry 11), while the reaction of **1c** (R=p-$MeOC_6H_4$) gave a mixture of **2c** and **3c** in 56 and 16% yields, respectively (entry 12). Not only aromatic groups but also alkenyl and alkyl groups were usable as substituents at the terminus (entries 13 and 14). On the other hand, the reaction of benzaldehyde itself with allyltrimethylsilane under the same reaction conditions, indicated in entry 6 of Table 1, afforded no allylation product and the starting material (benzaldehyde) was recovered. This result showed that the alkynyl group of **1** was essential for the domino allylation of aldehyde with allyltrimethylsilane.

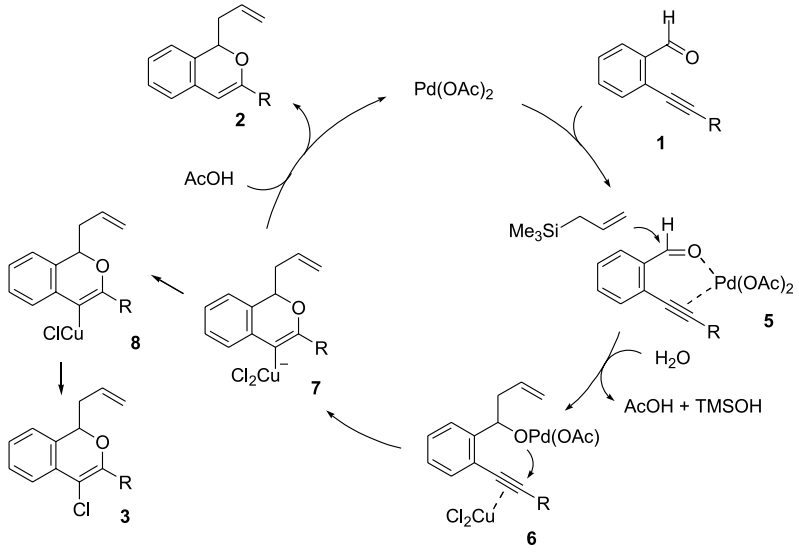


A proposed mechanism for the present domino reaction is shown in Scheme 1. As we mentioned above, the allylation of benzaldehyde with allyltrimethylsilane under the present reaction conditions did not proceed. This result suggested that the σ–π chelate complex **5** would be formed by the coordination of the carbonyl oxygen and the triple bond of **1** to $Pd(OAc)_2$, which would enhance the electrophilicity of the carbonyl group. In comparison with the σ-coordination of the C=O of benzaldehyde to $Pd(OAc)_2$, the bidentate σ–π chelation facilitates the nucleophilic attack to the C=O of **1**.[5] The subsequent nucleophilic attack of allylsilane to the electron-deficient carbonyl group forms the intermediate **6**. The coordination of the triple bond of **6** to $CuCl_2$ promotes the cyclization reaction to produce the copper ate complex **7**. Acetic acid, which is generated in the step from **5** to **6**, reacts with **7** to give the product **2** and regenerate the Pd catalyst. Indeed, when the reaction of **1a** with allylsilane was carried out in the presence of AcOH instead of H_2O, the reaction completed within 3 h and **2a** was obtained in 80% yield. On the other hand, when the reaction was conducted without addition of any proton sources, namely, under the conditions of entry 1, the chlorinated products **3** are formed by the reductive elimination of Cu(0) through the intermediate **8**. According to the proposed mechanism, 1 equiv of H_2O is needed for the completion of the reaction. However, the present reaction proceeded well with half an equiv of H_2O as mentioned

Table 1. Domino allylation and cyclization of **1** with allyltrimethylsilane[a]

Entry	1	R	$CuCl_2$	R_3P	Time	2	Yield (%)[b]	3	Yield (%)[b]
1[c]	**1a**	Ph	1.2	PPh_3	14 h	**2a**	29	**3a**	21
2[d]	**1a**	Ph	1.2	PPh_3	2 days	**2a**	21	**3a**	7
3	**1a**	Ph	1.2	PPh_3	2 days	**2a**	37		
4[e]	**1a**	Ph	1.2	PPh_3	3 days	**2a**	34		
5	**1a**	Ph	1.2	(p-$MeOC_6H_4)_3P$	7 h	**2a**	72	**3a**	6
6	**1a**	Ph	0.5	(p-$MeOC_6H_4)_3P$	19 h	**2a**	81		
7	**1a**	Ph	0.5	(m-$MeOC_6H_4)_3P$	12	**2a**	62		
8	**1a**	Ph	0.5	[2,4,6-tri(MeO) $C_6H_4]_3P$	3 days	**2a**	43		
9	**1a**	Ph	0.5	(p-$CF_3C_6H_4)_3P$	18 h	**2a**	46	**3a**	10
10[f]	**1a**	Ph	0.5	(p-$MeOC_6H_4)_3P$	12 h	**2a**	84		
11	**1b**	p-$CF_3C_6H_4$	0.5	(p-$MeOC_6H_4)_3P$	20 h	**2b**	64		
12	**1c**	p-$MeOC_6H_4$	0.5	(p-$MeOC_6H_4)_3P$	20 h	**2c**	56	**3c**	16
13	**1d**	Cyclohexenyl	0.5	(p-$MeOC_6H_4)_3P$	1 days	**2d**	74		
14	**1e**	Pr	0.5	(p-$MeOC_6H_4)_3P$	4 h	**2e**	53		

[a] Reactions of **1** with 1.2 equiv of allyltrimethylsilane were carried out in the presence of 5 mol% of $Pd(OAc)_2$, 20 mol% of ligand, and half equiv of H_2O in toluene at room temperature unless otherwise noted.
[b] Determined by ^1H NMR spectra of the reaction products using p-xylene as an internal standard.
[c] Reaction was performed without addition of H_2O.
[d] Reaction was carried out in the presence of 1 equiv of H_2O.
[e] $PdCl_2$ was used instead of $Pd(OAc)_2$.
[f] Reaction was conducted in the presence of 2 equiv of allyltrimethylsilane.

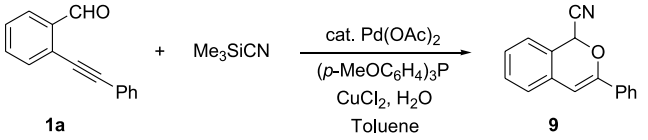


Scheme 1.

above. Probably, TMSOH, generated in the step from **5** to **6**, would be converted to siloxane under the present reaction conditions and this conversion would supply the required half an equiv of H_2O.

2.2. Domino cyanation and cyclization

It was found that the present domino type reaction proceeded not only with allyltrimethylsilane but also with trimethylsilylcyanide. Indeed, when **1a** was treated with trimethylsilylcyanide in the presence of Pd(II)–Cu(II) catalyst, the cyclic alkenyl ether **9** was obtained in 94% yield as a sole product (Eq. 2).



(2)

3. Conclusion

A novel and efficient synthetic method for isochromene skeleton has been developed though the precise reaction mechanism is still unclear. It is well known that allyltrimethylsilane and trimethylsilylcyanide are easy to handle practically in organic synthesis since they are stable, less reactive, and less toxic. However, due to their low reactivities, strong Lewis acids or Lewis bases are needed for allylation and cyanation of carbonyl group with those reagents.[6–8] On the contrary, the present reaction proceeded well under nearly neutral conditions. The present domino type reaction is useful for the one-pot synthesis of the 1,3-disubstituted cyclic alkenyl ether moiety of isochromene derivatives, since only a limited number of methodologies are known for the synthesis of those compounds.[3,4] Further studies to elucidate the mechanism of this reaction and to extend the scope of synthetic utility are in progress in our laboratory.

4. Experimental

4.1. General

Melting points were measured on a MRK 8026 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-AL 400 (400 MHz) spectrometers. Chemical shift of ^1H NMR were expressed in parts per million downfield from tetramethylsilane with reference to internal residual $CHCl_3$ ($\delta=7.26$) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard ($\delta=77.0$) in $CDCl_3$. IR spectra were measured on a Shimadzu FTIR-8200A Spectrometer. Low-resolution mass spectrometry data were acquired using a HP5973 instrument. High-resolution mass spectra (HRMS) were recorded on BRUKER DALTONICS APEX III spectrometer. Analytical thin-layer chromatography (TLC) were performed on a glass plates (Merck Kieselgel 60 F_{254}, layer thickness 0.2 mm). Visualization was accompanied by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. Column chromatography was performed on silica gel (Merck Kieselgel 70–230 mesh). All manipulations were carried out under argon atmosphere using standard Schlenk techniques.

4.1.1. Synthesis of 1-allyl-3-phenyl-1*H*-isochromene (2a). To a suspension of $Pd(OAc)_2$ (5.6 mg, 5 mol%), (p-$MeOC_6H_4)_3P$ (35 mg, 20 mol%), and $CuCl_2$ (34 mg, 0.25 mmol) in toluene (2 mL) was added H_2O (4.5 μL, 0.25 mmol) at room temperature with vigorous stirring. The starting material **1a** (103 mg, 0.5 mmol) and allyltrimethylsilane (0.16 mL, 1.0 mmol) were added to the resulting mixture successively and the mixture was stirred for 12 h. A saturated aqueous solution of NH_4Cl was added, and the mixture was extracted with ether three times. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to leave the crude product, which was purified by silica gel column chromatography using hexane–ether (15/1) as an eluent to give **2a** (104 mg, 0.42 mmol) in 84% yield.

Yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75–7.01 (m, 9H), 6.41 (s, 1H), 5.96 (m, 1H), 5.34 (dd, $J=5$, 8.5 Hz, 1H), 5.10–5.15 (m, 2H), 2.55–2.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.4, 134.5, 134.0, 130.9, 128.7, 128.2, 127.9, 126.3, 125.1, 123.9, 117.7, 100.3, 77.7, 38.4. IR (neat) 3068, 1627, 1603, 1493, 1279, 1063, 915, 762 cm^{-1}. MS (EI) *m/z* 207 (100), 248 (M^+, 6.8). HRMS calcd for $C_{18}H_{16}O$ 248.121, found 248.121.

4.1.2. Synthesis of 1-allyl-3-(4-trifluoromethyl-phenyl)-1*H*-isochromene (2b). Yellow solid, mp 42.0–43.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, $J=8.1$ Hz, 2H), 7.64 (d, $J=8.5$ Hz, 2H), 7.25 (m, 2H), 7.15 (dd, $J=7.4$, 1.1 Hz, 1H), 7.08 (d, $J=7.1$ Hz, 1H), 6.52 (s, 1H), 5.98 (ddt, $J=17.1$, 10.2, 6.8 Hz, 1H), 5.39 (dd, $J=8.5$, 4.9 Hz, 1H), 5.18–5.11 (m, 2H), 2.87–2.83 (m, 1H), 2.60–2.53 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.8, 137.9, 133.7, 131.1, 130.4, 130.2, 128.1, 127.0, 125.2, 125.2, 125.1, 124.3, 124.0, 122.7, 117.9, 102.1, 77.8, 38.7. IR (neat) 3074.3, 2925.8, 1699.2, 1614.3, 1515.9, 1488.9, 1452.3, 1323.1, 1184.2, 1112.9, 1070.4, 975.9, 912.3, 835.1, 759.9, 694.3, 646.1 cm^{-1}. MS (EI) *m/z* 275 (100), 316 (M^+, 7.2). Anal. Calcd for $C_{19}H_{15}F_3O$: C, 72.14; H, 4.78; F, 18.02. Found C, 71.96; H, 5.01; F, 18.28.

4.1.3. Synthesis of 1-allyl-3-(4-methoxy-phenyl)-1*H*-isochromene (2c). White solid, mp 55.0–57.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70–7.68 (m, 2H), 7.25–7.21 (m, 1H), 7.16–7.12 (m, 1H), 7.09–7.03 (m, 2H), 6.95–6.89 (m, 2H), 6.31 (s, 1H), 6.04–5.94 (m, 1H), 5.32 (dd, $J=8.5$, 4.9 Hz, 1H), 5.17–5.10 (m, 2H), 2.89–2.81 (m, 1H), 2.58–2.51 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.8, 137.9, 133.7, 131.1, 130.4, 130.2, 128.1, 127.0, 125.2, 125.2, 125.1, 124.3, 124.0, 122.7, 117.9, 102.1, 77.8, 38.7. IR (neat) 2997.2, 2837.1, 1604.7, 1508.2, 1487.0, 1417.6, 1321.1, 1251.7, 1182.3, 1066.6, 977.8, 837.0, 810.0, 783.0, 763.8 cm^{-1}. MS (EI) *m/z* 237 (100), 278 (M^+, 10.3). HRMS (APCI) calcd for $C_{19}H_{18}O_2$ ($[M+H]^+$) 279.139, found 279.138.

4.1.4. Synthesis of 1-allyl-3-cyclohex-1-enyl-1*H*-isochromene (2d). Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (ddd, $J=7.6$, 7.6, 1.2 Hz, 1H), 7.15 (ddd, $J=7.3$, 7.3, 1.2 Hz, 1H), 7.06–7.04 (m, 2H), 6.52–6.51 (m, 1H), 6.04–5.92 (m, 1H), 5.92 (m, 1H), 5.20–5.13 (m, 3H), 2.84–2.76 (m, 1H), 2.59–2.52 (m, 1H), 2.34–2.22 (m, 4H), 1.80–1.64 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 134.2, 131.2, 130.6, 127.7, 126.9, 125.8, 123.8, 123.7, 117.3, 99.3, 99.3, 77.2, 38.1, 25.7, 24.4, 22.7, 22.2. IR (neat) 3072.4, 2929.7, 2858.3, 2829.4, 1637.5, 1612.4, 1568.0, 1487.0, 1450.4, 1436.9, 1390.6, 1315.4, 1240.1, 1068.5, 1045.3, 995.2, 794.6, 748.3 m^{-1}. MS (EI) *m/z* 211 (100), 252 (M^+, 9.6). HRMS (EI) calcd for $C_{18}H_{20}O$ (M^+) 252.151, found 252.151.

4.1.5. Synthesis of 1-allyl-3-propyl-1*H*-isochromene (2e). Pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (ddd, $J=7.4$, 7.4, 1.4 Hz, 1H), 7.09 (ddd, $J=7.4$, 7.4, 1.4 Hz, 1H), 6.94 (ddd, $J=14.1$, 7.6, 1.0 Hz, 2H), 5.92–5.87 (m, 1H), 5.59 (s, 1H), 5.15–5.08 (dd, $J=8.1$, 5.1 Hz, 1H), 5.13–5.08 (m, 2H), 2.79–2.71 (m, 1H), 2.51–2.43 (m, 1H), 2.22–2.10 (m, 2H), 1.67–1.52 (m, 2H), 0.97 (q, $J=6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.9, 134.2, 130.9, 129.9, 127.7, 125.4, 124.0, 122.7, 117.4, 77.48, 38.8, 36.0, 20.2, 13.8. IR (neat) 2960.5, 2933.5, 2871.8, 1651.0, 1488.9, 1454.2, 1382.9, 1155.3, 914.2, 746.4 cm^{-1}. MS (EI) *m/z* 173 (100), 214 (M^+, 12). HRMS (EI) calcd for $C_{18}H_{16}O$ (M^+) 214.136, found 214.135.

4.1.6. Synthesis of 3-phenyl-1*H*-isochromene-1-carbonitrile (9). White needle, mp 122–123.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77–7.75 (m, 2H), 7.47–7.39 (m, 5H), 7.32–7.21 (m, 3H), 6.64 (s, 1H), 6.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ 151.3, 132.7, 130.3, 130.2, 129.5, 128.4, 127.5, 125.2, 124.7, 124.2, 122.9, 116.4, 102.0, 102.0, 66.3, 31.6, 22.7, 14.1. IR (neat) 2358.8, 2341.4, 1622.0, 1568.0, 1539.1, 1487.0, 1456.2, 1352.0, 1271.0, 1064.6, 912.3, 819.7, 769.5, 756.0, 688.5, 651.9, 497.6 cm^{-1}. MS (EI) *m/z* 233 (M^+, 100). Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found C, 82.37; H, 5.00; N, 5.92.

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Tetrahedron

Rhodium(I) catalyzed four-component reaction of Fischer alkenyl carbene complexes and 1,1-diphenylallene

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Abstract—Alkyl substituted chromium Fischer carbene complexes react with 1,1-diphenylallene in the presence of rhodium(I) catalysts (10 mol%) to yield highly substituted dienyl indenone derivatives. In this process a catalytic chromium(0)–rhodium(I) exchange occurs, four new C–C bonds are created, and four-components (two allenes, the carbene ligand and one CO ligand) are joined in a chemo- and regioselective manner.

1. Introduction

Multicomponent reactions (MCRs) have become an important tool for the efficient synthesis of a wide variety of organic molecules.[1] These strategies offer significant advantages over more traditional approaches allowing the construction of complex molecular architectures from easily available and simple precursors in a single synthetic operation without the need for isolation of intermediates. On the other hand, Fischer carbene complexes are recognized as versatile organometallic intermediates in organic synthesis.[2] Fischer carbene complexes are also excellent partners in MCRs mainly due to the ability of this type of compounds to generate in their reactions with unsaturated substrates highly reactive intermediates capable of further transformations. Moreover, Fischer carbene complexes can act as a source of two or more components in MCRs (most frequently the carbene and CO ligands).[3]

Whereas alkynes are the most commonly employed counterparts in the MCRs of Fischer carbene complexes, the use of allenes in this type of process is almost unknown. Thus, an isolated example was published in 1987 by Aumann et al. wherein a thermal [2+2+1] cyclization of group 6 phenyl(ethoxy)carbene complexes with 2 equiv of phenylallene is reported to yield substituted cyclopentanes, via isolable trimethylenemethane intermediates (Fig. 1).[4,5]

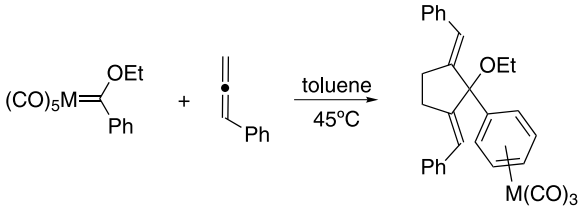

Figure 1.

Recently we focused our attention on the reactivity of Fischer alkenyl carbene complexes toward allenes (Scheme 1). While the thermal reaction of chromium carbene complexes **1** with allenes **2** results in the formation of the metathesis dienes **3**, annulated products resulting from [3+2] and [3+2+2] cyclization reactions were observed if the reaction is run in the presence of rhodium(I) catalysts. Interestingly, cyclopentene **4** and cycloheptene **5** derivatives are selectively formed when [Rh(naphthalene)-(cod)]$^+$ and [Rh(cod)Cl]$_2$ catalysts, respectively, are used.[6,7] This means that more than two-components can participate by an appropriate selection of the catalyst. Continuing our studies on this field we report herein the reaction of carbene complexes **1** with 1,1-diphenylpropadiene that constitutes a new example of a four-component process of Fischer carbene complexes.

2. Results and discussion

In the course of our studies on the cyclization of alkenyl Fischer carbene complexes and allenes, it was found that the reaction with diphenylallene follows a reaction course

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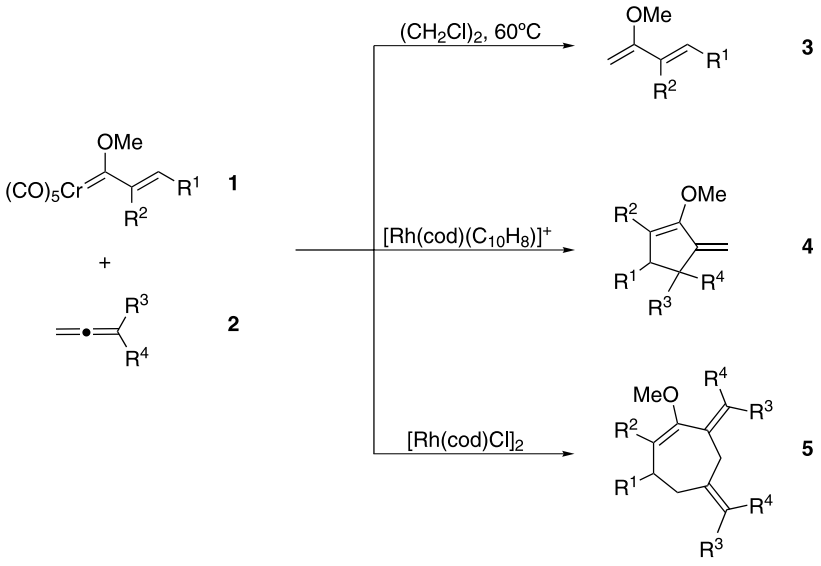


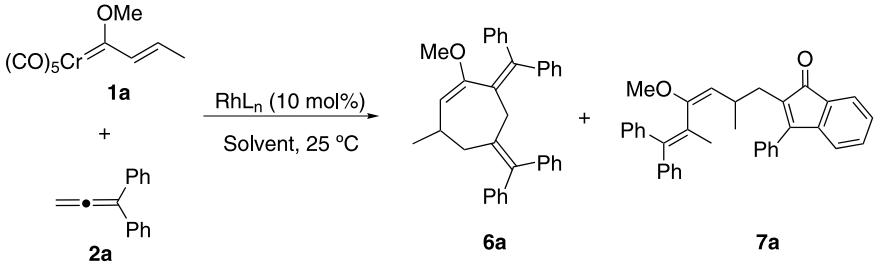
Scheme 1.

different than that encountered for aliphatic or 1-phenyl substituted allenes. For instance, the treatment of complex **1a** with diphenylallene **2a** (3 equiv) and 10 mol% of the cationic complex [Rh(naphthalene)(cod)][SbF_6] (CH_2Cl_2, 25 °C, 72 h) in dichloromethane did not lead to the expected [3+2] cycloadduct. Instead, a small amount of the [3+2+2] cycloadduct **6a** (5%) along with the substituted indenone **7a** (21%) was obtained (Scheme 2, entry 1, Table 1). The structural assignment of **7a** was made on the basis of their spectroscopic data.[8]

There are some interesting features concerning the formation of compound **7a**: (i) Compound **7a** is a four-component product arising from the coupling of two allene units, an alkenyl(methoxy)carbene ligand and a CO ligand; (ii) the process involves the formation of four C–C bonds in a specific way; (iii) the reaction proved to be totally regio- and stereoselective and (iv) an *ortho* C–H bond activation of a phenyl group takes place.

The significant complexity increase generated by this new reaction prompted us to investigate this process in more detail (Table 1). First, the formation of cycloadduct **6** can be completely inhibited by using the neutral catalyst [Rh(cod)Cl]$_2$ (compare entries 1 and 2). Among the different solvents that were then tested, we found dioxane to be the most efficient in terms of reaction time and yield (entry 8).[9]

The optimal reaction conditions (neutral rhodium catalyst, room temperature, dioxane) were then applied to other

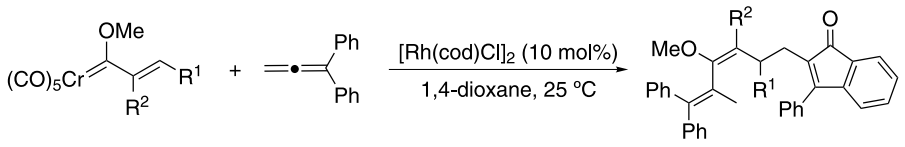


Scheme 2.

Table 1. Rhodium(I) catalyzed reaction of pentacarbonyl[(methoxy)(3-buten-1-ylidene)]chromium(0) **1a** and 1,1-diphenylallene **2a**[a]

Entry	Rhodium complex	Solvent	*t* (h)	**6a** Yield %	**7a** Yield %[b]
1	[Rh(naphthalene)(cod)][SbF_6]	CH_2Cl_2	72	5	21
2	[Rh(cod)Cl]$_2$	CH_2Cl_2	72	—	26
3	[Rh(cod)Cl]$_2$	Toluene	168	—	—[c]
4	[Rh(cod)Cl]$_2$	Hexane	168	—	—[c]
5	[Rh(cod)Cl]$_2$	Diethyl ether	72	—	21
6	[Rh(cod)Cl]$_2$	THF	36	—	38
7	[Rh(cod)Cl]$_2$	Acetonitrile	48	—	29
8	[Rh(cod)Cl]$_2$	Dioxane	16	—	60

[a] All reactions were carried out with 3 equiv of **2a** at room temperature.
[b] Yield of isolated products.
[c] The starting carbene complex **1a** (80–90%) was recovered unaltered.



1a-e **2a** **7a-e**

Scheme 3.

alkenyl carbene complexes **1b–e** (Scheme 3, Table 2). Thus, when β-alkyl substituted carbene complexes **1b–d** were reacted with 1,1-diphenylallene the four-component products **7b–d** were exclusively formed in moderate yields (entries 2–4). Interestingly, α-alkyl substituted alkenyl carbene complexes also work well as it is exemplified in the reaction of the (α-methyl)vinylcarbene **1e** that yields the corresponding indenone **7e** (entry 5).

Table 2. Rhodium(I) catalyzed multicomponent reaction of alkenyl Fischer carbene complexes **1a–e** and 1,1-diphenylallene **2a**[a]

Entry	R^1	R^2	*t* (h)	**7** (%)[b]
1	Me	H	16	**7a** (60)
2	Benzyl	H	16	**7b** (48)
3	*n*-Butyl	H	16	**7c** (51)
4	*i*-Butyl	H	16	**7d** (56)
5	H	Me	40	**7e** (40)

[a] All reactions were carried out with 3 equiv of **2a** at room temperature in 1,4-dioxane.
[b] Yield of isolated products.

The structure of compounds **7a–e** was corroborated by a single-crystal X-ray analysis performed on **7d** (Fig. 2).[10] It shows that the dienyl moiety of compound **7d** adopts a non-planar conformation in the solid state as a consequence of the atropoisomerism about the sp^2–sp^2 single bond of the butadiene unit (C_2–C_3) (C_1–C_2–C_3–C_4 dihedral angle $= -79°$).[11]

A mechanistic proposal for the formation of compounds **7** is depicted in Scheme 4. The process would be initiated by chromium–rhodium exchange yielding the rhodium(I) carbene complex **I**[12,13] followed by [4+2] cycloaddition through the less substituted C=C bond of the allene to generate the intermediates **II**, as previously proposed.[7] Insertion of a second molecule of allene would give rise to the metallacyclooctene species **III**[14], which would suffer a *ortho*-metallation process to generate the Rh(V) alkyl-hydride intermediate **IV**.[15] The metallacycle **V**, resulting from reductive elimination of **IV**, would undergo insertion of CO and reductive elimination to furnish the observed adduct and the active rhodium catalyst species.

The present four-component process appears to be limited to the use of 1,1-diarylallene. Thus, when carbene complex **1a** was mixed with 1-phenylallene **2b** (3 equiv) in the presence of 10 mol% of $[Rh(cod)Cl]_2$, under the optimized reaction conditions, the four-component adduct was not formed, but the reaction proceeds through the [3+2+2] cyclization pathway leading to the 1,3-dibenzylidenecycloheptane derivative **8** with moderate yield and total diastereoselectivity (Scheme 5).[16] This in agreement with the reaction course proposed and implies that the two insertion processes are regio- and diastereoselective leading to the metallacycle intermediate **VI**, wherein the stereochemical relationship of rhodium and phenyl prevents the *ortho*-metallation process.

In summary, we have devised a new rhodium-catalyzed multicomponent reaction in which an alkenyl(methoxy)-carbene ligand, two diphenylallene units and a CO ligand are selectivity assembled. This process, which leads to the simultaneous creation of four carbon–carbon bonds in a single synthetic operation, represents another example of the particular ability of Fischer carbene complexes to disclose new avenues in synthetic organometallic chemistry.

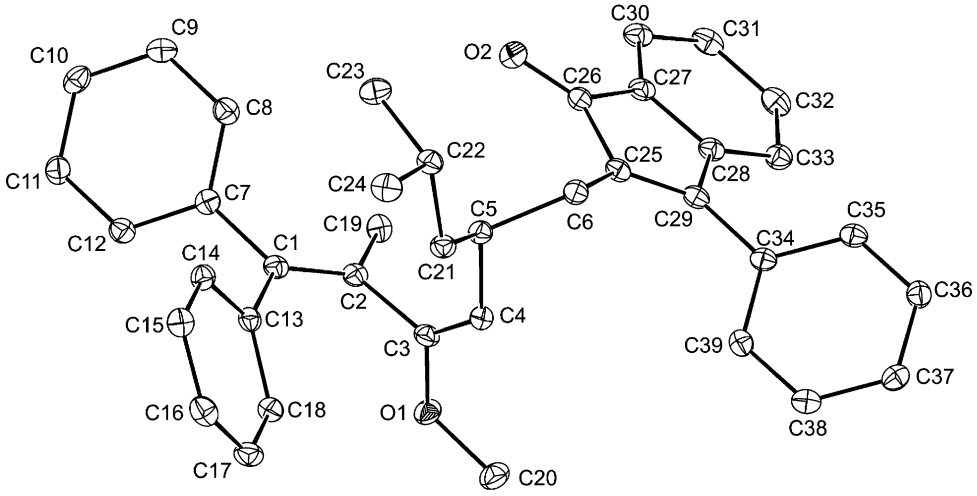
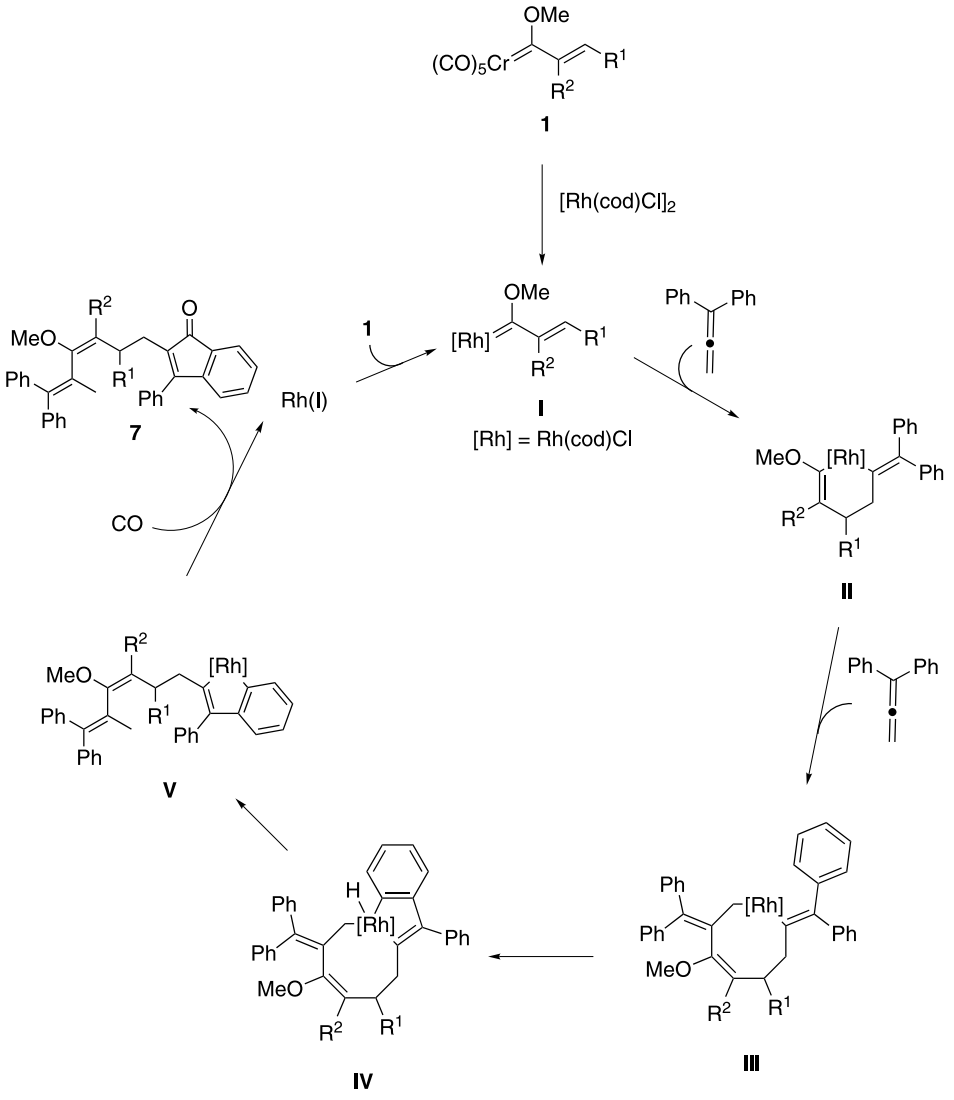
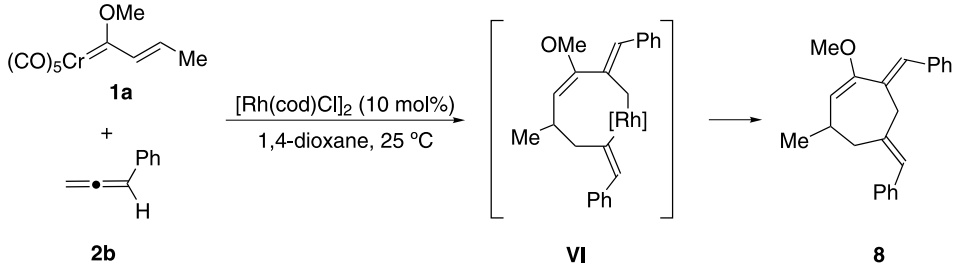


Figure 2. X-ray structure of compound **7d** (ellipsoids at 30% probability level).



Scheme 4.



Scheme 5.

3. Experimental

All reactions were carried out under N_2 using standard Schlenck techniques. THF, diethyl ether, toluene, dioxane, and hexane were destilled from sodium–benzophenone and CH_2Cl_2 and acetonitrile were destilled from CaH_2. TLC was performed on aluminum-backed plates coated with silica gel 60 with F254 indicator. Flash column chromatography was carried out on silica gel 60 (230–240 mesh). ^1H NMR (200, 300, 400 MHz) and ^{13}C NMR (50.5, 70.5, 100 MHz) spectra were measured in $CDCl_3$ at room temperature on a Bruker AC-200, AC-300 and AMX-400 instruments, respectively, with tetramethylsilane ($\delta=0.0$, ^1H NMR), $CDCl_3$ ($\delta=77.0$, ^{13}C NMR) as internal standard. Carbon multiplicities were assigned by DEPT techniques. IR spectra were carried out in a Mattson 3000 FTIR instrument using CCl_4. Elemental analyses were carried out on Perkin–Elmer 2400 and Carlo Erba 1108 microanalyzers.

Fischer carbene complexes **1a–e** were prepared from the corresponding vinyllithium compounds following

the general procedure described by Fischer.[17] 1,1-Diphenylallene **2a** and phenylallene **2b** were prepared according to literature procedures.[18] All other reagents, catalysts or solvents used in this work were of the best commercial grade available and used without further purification.

3.1. General procedure for the rhodium(I) catalyzed reaction of Fischer carbene complexes 1a–e and 1,1-diphenylallene 2a

To a solution of alkenyl Fischer carbene complex **1a–e** (0.5 mmol) and $[Rh(cod)Cl]_2$ (24 mg, 0.05 mmol) in 1,4-dioxane (10 mL) 1,1-diphenylallene **2a** (288 mg, 1.5 mmol) was added. The mixture was stirred at room temperature until disappearance of the starting carbene complex (16–40 h, checked by TLC). The solvent was then removed under reduced pressure and the resulting residue was dissolved in a CH_2Cl_2–Et_2O (1/10) mixture and filtered through a short pad of Celite. The solvents were removed in vacuo and the residue was subjected to flash chromatography (SiO_2, 5:1 hexanes/ethyl acetate) to yield dienyl indenone derivatives **7a–e** as yellow solids. Crystals of compound **7d** suitable for X-ray analysis were obtained by slow evaporation of the solvent at room temperature of a hexanes/ethyl acetate solution of the compound.

3.1.1. 2-[(*E*)-4-Methoxy-2,5-dimethyl-6,6-diphenylhexa-3,5-dienyl]-3-phenyl-1*H*-inden-1-one (7a). One hundred and forty nine milligrams (60%); [Found: C, 87.00; H, 6.42. $C_{36}H_{32}O_2$ requires C, 87.06; H, 6.49]; IR (cm^{-1}): 1708, 1558; ^1H NMR: 0.20 (br s, 3H), 1.54 (s, 3H), 2.17 (m, 1H), 2.23 (m, 1H), 2.45 (m, 1H), 3.33 (s, 3H), 3.68 (d, J= 10.4 Hz, 1H), 6.89 (m, 1H), 7.11 (m, 5H), 7.15 (m, 1H), 7.28 (m, 3H), 7.34 (m, 3H), 7.46 (m, 3H), 7.53 (m, 3H); ^{13}C NMR: 20.2 (CH_3), 21.4 (CH_3), 31.8 (CH_2), 32.8 (CH), 53.9 (CH_3), 103.6 (CH), 120.5 (CH), 122.3 (CH), 126.5 (CH), 126.6 (CH), 127.3 (CH), 128.0 (CH), 128.2 (CH), 128.7 (CH), 128.9 (CH), 129.6 (CH), 129.9 (CH), 130.9 (C), 133.2 (CH), 134.4 (C), 141.6 (C), 142.2 (C), 142.5 (C), 146.0 (C), 155.5 (C), 155.6 (C), 198.5 (C).

3.1.2. 2-[(*E*)-2-Benzyl-4-methoxy-5-methyl-6,6-diphenylhexa-3,5-dienyl]-3-phenyl-1*H*-inden-1-one (7b). One hundred and thirty seven milligrams (48%); [Found: C, 88.169; H, 6.41. $C_{42}H_{36}O_2$ requires C, 88.08; H, 6.34]; ^1H NMR: 1.47 (s, 3H), 1.65–1.70 (m, 1H), 1.88–1.95 (m, 2H), 2.19–2.24 (m, 1H), 2.76–2.80 (m, 1H), 3.44 (s, 3H), 3.85 (d, J=10.5 Hz, 1H), 6.92–6.96 (m, 2H), 7.00–7.20 (m, 10H), 7.21–7.28 (m, 3H), 7.31–7.41 (m, 5H), 7.45–7.52 (m, 4H); ^{13}C NMR: 20.2 (CH_3), 28.3 (CH_2), 38.5 (CH), 41.5 (CH_2), 53.9 (CH_3), 101.8 (CH), 120.4 (CH), 122.3 (CH), 125.5 (CH), 126.2 (C), 126.6 (CH), 126.7 (CH), 127.4 (CH), 127.6 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.5 (C), 128.6 (CH), 128.9 (CH), 129.3 (CH), 129.6 (CH), 129.9 (CH), 130.0 (C), 130.1 (C), 130.9 (C), 132.9 (C), 133.1 (CH), 140.1 (C), 141.6 (C), 142.2 (C), 147.5 (C), 156.2 (C), 198.3 (C).

3.1.3. 2-[(*E*)-2-Butyl-4-methoxy-5-methyl-6,6-diphenylhexa-3,5-dienyl]-3-phenyl-1*H*-inden-1-one (7c). One hundred and thirty seven milligrams (51%); [Found: C, 86.86; H, 7.07. $C_{39}H_{38}O_2$ requires C, 86.95; H, 7.11]; IR (cm^{-1}): 1708, 1586; ^1H NMR: 0.78 (t, J=7.1 Hz, 3H), 0.90–1.05 (m, 4H), 1.32–1.48 (m, 2H), 1.66 (s, 3H), 2.00 (m, 1H), 2.40 (m, 2H), 3.44 (s, 3H), 3.84 (d, J=10.1 Hz, 1H), 6.97 (d, J=6.9 Hz, 1H), 7.10–7.32 (m, 12H), 7.40 (m, 3H), 7.47 (m, 3H); ^{13}C NMR: 14.2 (CH_3), 20.5 (CH_3), 23.1 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 35.6 (CH_2), 37.8 (CH), 53.9 (CH_3), 103.0 (CH), 120.4 (CH), 122.3 (CH), 126.6 (CH), 127.3 (CH), 128.0 (CH), 128.2 (CH), 128.7 (CH), 128.9 (CH), 129.6 (CH), 130.0 (CH), 131.1 (C), 132.5 (C), 133.2 (CH), 134.7 (C), 141.7 (C), 142.5 (C), 146.2 (C), 155.5 (C), 155.8 (C), 198.4 (C).

3.1.4. 2-[(*E*)-4-Methoxy-5-methyl-2-(2-methylpropyl)-6,6-diphenylhexa-3,5-dienyl]-3-phenyl-1*H*-inden-1-one (7d). One hundred and fifty one milligrams (56%); [Found: C, 86.91; H, 7.10. $C_{39}H_{38}O_2$ requires C, 86.95; H, 7.11]; IR (cm^{-1}): 1703, 1549; ^1H NMR: 0.65 (d, J=6.4 Hz, 3H), 0.74 (d, J=6.5 Hz, 3H), 0.90–1.05 (m, 4H), 0.82–0.93 (m, 2H), 1.45 (m, 1H), 1.62 (s, 3H), 1.81–1.88 (m, 1H), 2.35 (m, 1H), 2.49 (m 1H), 3.40 (s, 3H), 3.80 (d, J=10.2 Hz, 1H), 6.96 (d, J=7.1 Hz, 1H), 7.05–7.18 (m, 7H), 7.21–7.38 (m, 5H), 7.48 (m, 3H), 7.53 (m, 3H); ^{13}C NMR: 20.7 (CH_3), 21.1 (CH_3), 23.7 (CH_3), 24.8 (CH), 28.0 (CH_2), 35.3 (CH), 44.5 (CH_2), 53.8 (CH_3), 103.5 (CH), 120.3 (CH), 122.3 (CH), 126.5 (CH), 126.6 (CH), 127.2 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.6 (CH), 128.9 (CH), 129.8 (C), 129.9 (CH), 130.9 (C), 133.1 (CH), 134.7 (C), 141.6 (C), 142.0 (C), 142.4 (C), 145.9 (C), 155.5 (C), 155.6 (C), 198.4 (C).

3.1.5. 2-[(*E*)-4-Methoxy-3,5-dimethyl-6,6-diphenylhexa-3,5-dienyl]-3-phenyl-1*H*-inden-1-one (7e). Ninety nine milligrams (40%); [Found: C, 86.97; H, 6.45. $C_{36}H_{32}O_2$ requires C, 87.06; H, 6.49]; IR (cm^{-1}): 1712, 1500; ^1H NMR: 1.42 (s, 3H), 1.72 (s, 3H), 1.92–1.99 (m, 2H), 2.30 (t, J=10.2 Hz, 2H), 3.64 (s, 3H), 7.00 (d, J=7.1 Hz, 1H), 7.13 (br s, 5H), 7.15–7.28 (m, 3H), 7.30–7.40 (m, 4H), 7.42–7.50 (m, 6H); ^{13}C NMR: 13.8 (CH_3), 20.9 (CH_3), 21.9 (CH_2), 32.9 (CH_2), 56.1 (CH_3), 113.7 (C), 120.5 (CH), 122.3 (CH), 126.3 (CH), 126.6 (CH), 127.3 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.7 (C), 128.9 (CH), 129.1 (CH), 129.7 (CH), 130.0 (C), 131.0 (C), 132.7 (C), 133.1 (CH), 135.1 (C), 142.3 (C), 134.3 (C), 145.8 (C), 149.1 (C), 155.1 (C), 198.0 (C).

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8. Structure of compound **7a** was established by 1D and 2D NMR data, including the examination of long-range ^{1}H–^{13}C connectivities obtained from HMBC 2D NMR experiments and NOESY experiment.
9. Other neutral rhodium(I) complexes like $[Rh(CO)_2Cl]_2$ or $[Rh(nbd)Cl]_2$ were also effective for the coupling of Fischer carbene complex **1a** and allene **2a** but they did not improve the chemical yield.
10. Crystallographic data (excluding structure factors) for the compound **7d** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 270298. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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14. Reductive elimination on metallacyclooctene intermediates **III** could explain the formation of compound **6a** (see Scheme 2).
15. Rh(V) and Ir(V) intermediates related to **IV** have been proposed in *ortho* metallation reactions. See: Gómez, M.; Robinson, D. J.; Matlis, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 825. For reviews on C–H activation processes, see: (a) Shilov, A. E.; Shulpin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403.
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A facile and efficient synthesis of enyne-reaction precursors by multicomponent reactions

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Abstract—Using improved reaction protocols for three-component coupling reactions of aldehydes, dienophiles, and amides (AAD-reaction) or anhydrides (ANAD-reaction) or orthoesters (ALAD-reaction), a variety of functionalized hexahydroisoindolo derivatives were synthesized and fully characterized. Condensation of ubiquitous available aldehydes with unsaturated amides or anhydrides or orthoesters and subsequent Diels–Alder reactions with electron deficient dienophiles furnishes *endo*-selective enyne-reaction precursors in good to excellent yield.

1. Introduction

With regard to the development of sustainable chemical methods, new reactions should proceed with cheap and easily available substrates, at best in a common apparatus giving a quantitative yield at a fast rate and 100% atom economy. Clearly, for multi-step synthetic procedures the number of reaction and purification steps are among the most important criteria for the efficiency and practicability of the process and should be as low as possible. Concerning to these aspects, multicomponent[1] and domino reactions[2] offer significant advantages (Fig. 1).

As a special benefit to the classical step by step formation of individual bonds in the target molecule, MCRs (or domino reactions) take advantage of the simultaneous formation of several bonds in only one operational step. Moreover, this approach allows also for the avoidance of intermediate separation, changing the reaction conditions, or adding any further reagents. Since isolated products include structural features of all employed reactants, MCRs often enable the enhancement of structural diversity in an unprecedented way. In addition, opportunities arise for an easier synthesis of compound libraries. Therefore, in the last decade research both in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products.[3]

In the past we were especially interested in the development of transition metal-catalyzed three- and four-component coupling reactions. For instance, our investigations include hydroaminomethylation of olefins,[4] and amidocarbonylation of aldehydes.[5]

With respect to the latter work,[6] we discovered the first multicomponent reaction of amides, aldehydes, and dienophiles (AAD-reaction). More recently, instead of amides also carboxylic acid anhydrides (ANAD-reaction) or alcohols as well as orthoesters (ALAD-reaction) have been used. Covering this broad range of substrates, we have actually synthesized more than 200 carbo- and heterocyclic compounds with high efficiency (Scheme 1).[7]

Based on a simple condensation reaction, the underlying mechanism takes advantage of the in situ formation of substituted 1,3-butadienes as key intermediates, which are subsequently converted with electron-deficient dienophiles in a Diels–Alder reaction to the corresponding products.

Several other groups have demonstrated the versatility of

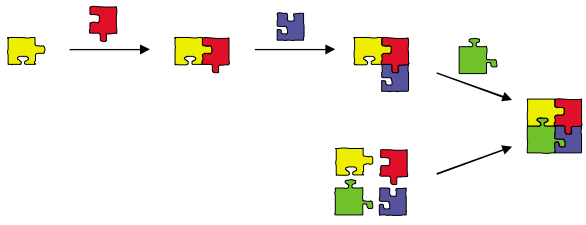

Figure 1. Schematic representation of multi-step versus multicomponent assembly.

Keywords: Enynes; Aldehydes; Diels–Alder reaction; Multicomponent coupling reaction.
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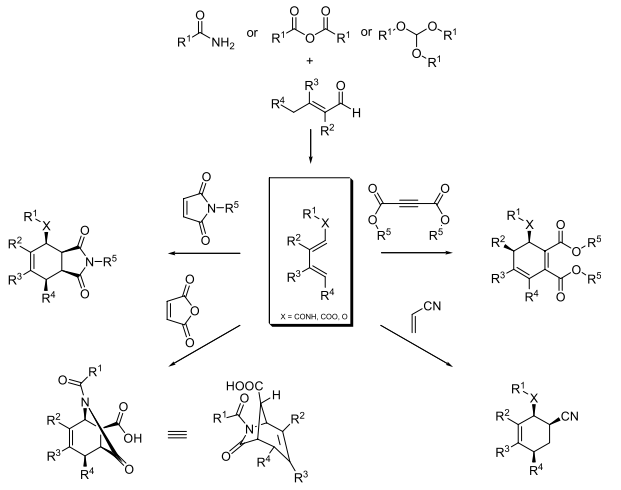
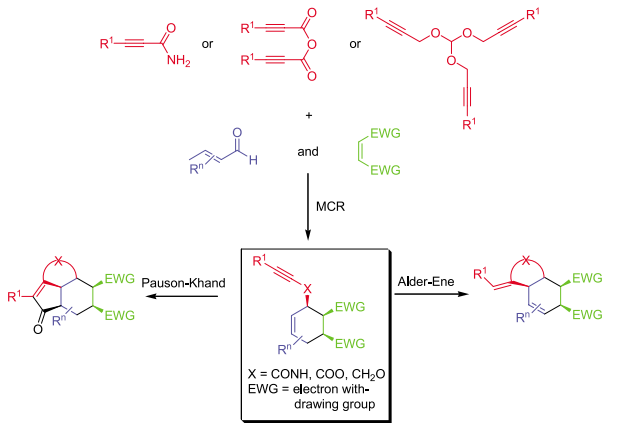


Scheme 1. Schematic representation of the AAD-, ANAD-, ALAD-reaction protocol.

isolated functionalized 1,3-butadienes for Diels–Alder chemistry.[8] Prominent examples include the preparation of pumiliotoxin,[9] gephyrotoxin,[10] dendrobine,[11] and tabersonine.[12]

So far the synthetic utility of our domino sequence has been shown in the preparation of substituted anilines,[13] luminoles,[14] and phenanthridone[15] derivatives. The latter reaction is a nice example for the powerful combination of MCRs with subsequent catalytic reactions. In order to expand this concept further on we envisioned the application of acetylenic derivatives in AAD reactions with subsequent catalytic enyne-functionalizations (Scheme 2; see also following paper).

To the best of our knowledge there are no multicomponent reactions of aldehydes, dienophiles, and acetylenic derivatives known. Here, we wish to report on the successful application of our multicomponent coupling protocol for the straightforward synthesis of various hexahydroisoindole derivatives, which are functionalized by an additional alkyne group. These compounds represent valuable enyne-reaction precursors and constitute prominent substrates for additional ring closing reactions via Alder–Ene[16]- as well as Pauson–Khand[17]-reactions.



Scheme 2. Sequential AAD- and enyne reactions.

2. Results and discussion

Based on examinations of the three-component coupling reaction of amides, aldehydes, and dienophiles (AAD-reaction), we started synthesizing enyne-reaction precursors, using our recently improved 2nd generation MCR protocol.[18] Comprising toluene as suitable solvent, reactions were carried out in the presence of a catalytic amount of *p*-TSA and acetic acid anhydride as a water scavenging agent. To achieve full conversion, reactions were allowed to react for 24–120 h at 110 °C.

Initially, we studied the influence of differently substituted α,β-unsaturated aldehydes in the presence of 3-phenylpropynoic acid amide[19] and *N*-methylmaleimide. As a result of that, a variety of alkyl-substituted products were obtained in good yields ranging from 71 to 81% (Table 1, entries **1a**–**6a**). It is remarkable that the employed alkynoic acid amide reacts selectively in the desired fashion and not as a competing dienophile.

In the next set of experiments, we examined the influence of functionalized propiolamide derivatives on the conversion with crotonaldehyde, and *N*-methylmaleimide. Using propiolamide, terolic acid amide, and pent-2-ynenoic acid amide, the desired products were obtained in yields of 69, 60, and 80%, respectively (Table 1, entries **7a**–**9a**). In order to study also the influence of other dienophiles, acrylonitrile, dimethyl but-2-ynedioate, and 1,4-phenylene dimaleimide, were employed and gave yields of 58, 36, and 80%, respectively (Table 1, entries **10a**–**12a**).

In addition to amides, acetylenic carboxylic acid anhydrides (ANAD-reaction) and acetylenic orthoesters (ALAD-reaction) can serve as substrates and lead to an increase of structural diversity.[20] Following the previous ANAD-reaction protocol, initial experiments concentrated on the employment of phenyl propiolic acid anhydride, crotonaldehyde and *N*-methylmaleimide as starting materials. To our surprise the target product is not obtained at all, presumably due to the poor reactivity of the chosen anhydride. Changing the reaction conditions (140 °C, 24–48 h) led to no improvement. However, reaction of phenyl propiolic acid with oxalyl dichloride to the corresponding acid chloride, and subsequent addition of crotonaldehyde and potassium butoxide at −78 °C in THF, gave the buta-1,3-dienyl 3-phenylpropiolate as an intermediate (not isolated). After addition of *N*-methylmaleimide to the reaction mixture the desired product is isolated in 30% yield (Table 1, entry **13a**). Next, tris(prop-2-ynyloxy)-methane[21] was used for the synthesis of propargylic ether-substituted cyclohexenes. Depending on the choice of the aldehyde, the products were isolated in the range of 67–84% yield (Table 1, entries **14a**–**17a**).

To pursue ring closing reactions on nitrogen tethered enyne-precursors, it is often necessary to protect the heteroatom in an additional step for successful conversions.[22] Therefore, we studied also the protection of the synthesized enyne-AAD-products, using standard protocols with alkylating reagents.[23]

However, several approaches using strong bases like

Table 1. Synthesis of enyne-precursors via AAD-, ANAD-, ALAD-MCR

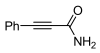
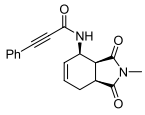
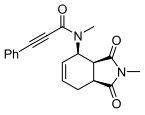
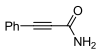
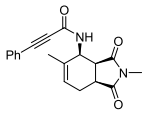
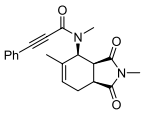
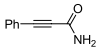
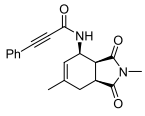
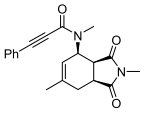
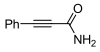
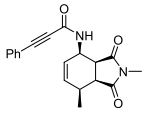
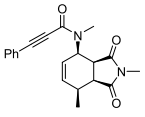
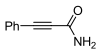
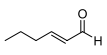
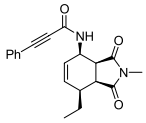
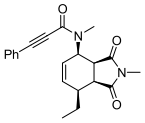
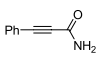
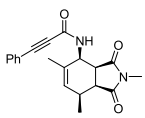
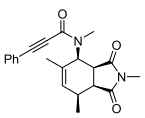
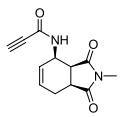
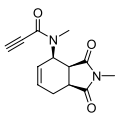
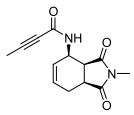
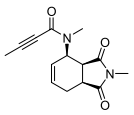
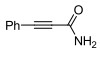
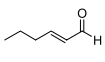
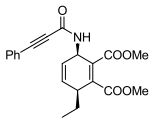
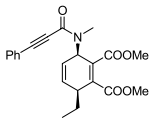
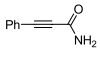
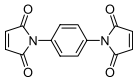
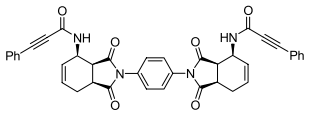
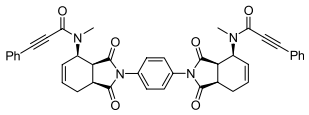
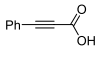
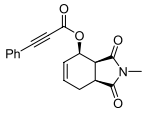
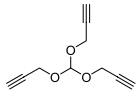
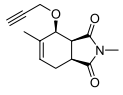
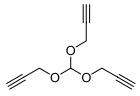
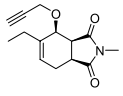
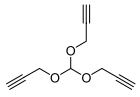
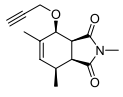
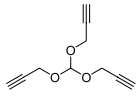
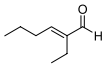
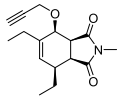
Entry	Amide	Aldehyde	Dienophile	AAD-product	Yield [%]	AAD-PG	Yield [%]
1				 **1a**	71[a]	 **1b**	80[b]
2				 **2a**	81[a]	 **2b**	61[b]
3				 **3a**	74[a]	 **3b**	73[b]
4				 **4a**	74[a]	 **4b**	55[b]
5				 **5a**	75[a]	 **5b**	64[b]
6				 **6a**	77[a]	 **6b**	70[b]
7				 **7a**	69[a]		0[b]
8				 **8a**	60[a]	 **8b**	63[b]
9				**9a**	80[a]	**9b**	60[b]
10				**10a**	58[a,c]	**10b**	75[b]

Table 1 (*continued*)

Entry	Amide	Aldehyde	Dienophile	AAD-product	Yield [%]	AAD-PG	Yield [%]
11				 **11a**	36[a,d]	 **11b**	72[b]
12				 **12a**	80[a,d]	 **12b**	47[b]
13				 **13a**	30[e]		
14				 **14a**	73[f]		
15				 **15a**	67[f]		
16				 **16a**	84[f]		
17				 **17a**	80[f]		

[a] Reaction conditions: Amide (5 mmol), aldehyde (5 mmol), dienophile (7.5 mmol), toluene (20 mL), Ac_2O (5 mmol), *p*-TSA (2 mol%), 24 h, 110 °C.
[b] Reaction conditions: AAD-product (3 mmol), Ag_2O (9 mmol), MeI (18 mmol), THF (15 mL), 48 h, 65 °C.
[c] Reaction conditions: Instead of toluene, NMP (20 mL) was used as solvent. acrylonitrile (60 mmol).
[d] Reaction conditions: Instead of toluene, 1,4-dioxane (20 mL) was used as solvent.
[e] Reaction conditions: Phenyl propiolic acid (10 mmol), oxalyl dichloride (10 mmol), THF (5 mL), 1 h, room temperature; then addition of the reaction mixture to: potassium butoxide (10 mmol), crotonaldehyde (10 mmol), THF (30 mL), −78 °C, 1 h; then addition of 15 mmol *N*-methylmaleimide to the crude mixture, 24 h, 60 °C.
[f] Reaction conditions: Tris(prop-2-ynyloxy)methane (5 mmol), aldehyde (5 mmol), dienophile (7.5 mmol), toluene (20 mL), *p*-TSA (2 mol%), 24 h, 110 °C.

sodium hydride, potassium butoxide, lithium diisopropylamide and methyl iodide as methylating agent remained unsuccessful. In all of these cases, we observed side reactions leading to complete decomposition of the starting materials. Obviously, this might be explained by the reactivity of the acidic protons adjacent to the carbonyl groups. To circumvent these problems, we decided to apply the silver (I)-oxide/methyl iodide protocol[24] for the protection reactions. With the exception of one case (Table 1, entry **7a**), we obtained the corresponding *N*-methyl derivatives in satisfying yields from 47% through 80% (Table 1, entries **1b–12b**).

For all products one- and two-dimensional NMR experiments unambiguously established the stereo-chemical structure. In all cases we observe the selective *endo* addition of the dienophile during the Diels–Alder step. Thus, analyses of the ^1H–^1H coupling constants of the amide, ester and ether moiety as well as of their alkyl substituents on the cyclohexene ring revealed the exclusive formation of the all-*syn* products. This results in bowl- or crown-shaped cyclohexenes with all substituents on one side of the ring.

In summary, we have demonstrated here for the first time that alkynoic amides, orthoesters, and anhydrides can be

successfully used in multicomponent reactions with aldehydes and dienophiles. The resulting 17 enyne derivatives represent useful synthetic intermediates, which allow for numereous catalytic refinement reactions (see also following manuscript).

3. Experimental

3.1. General

All reactions were run in ACE pressure tubes from Aldrich. Unless otherwise noted, all reagents were used as received from commercial suppliers. Silica gel column chromatography was performed with 230–400 mesh ASTM silica gel from Merck. Melting points were recorded on a Galen III (Cambridge Instruments) and are uncorrected. IR spectra as solids were recorded as nujol mulls using KBr plates or KBr pellets on a Nicolet Magna 550, liquids were analyzed as capillary films. MS were obtained on an AMD 402/3 from AMD Intectra (EI, 70 eV). NMR data were recorded on a Bruker ARX 400 with QNP probe head. (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at 25 °C. GC analyses were performed on an HP 6890 equipped with a HP-5 capillary column (5% phenylmethylsiloxane, $L=30$, $d=250$ μm, $d_{film}=0.25$ μm) and an FID detector.

3.2. Procedure A

Amide (5 mmol), dienophile (7.5 mmol; in case of acrylonitrile, 60 mmol were employed) and *p*-toluenesulfonic acid monohydrate (2 mol%) were combined in a threaded tube, and toluene (20 mL; in case of compound **10a**, NMP was used as solvent; in case of compounds **11a** and **12a**, 1,4-dioxane was used as solvent), aldehyde (5 mmol), and acetic acid anhydride (5 mmol) were added. Then, the reaction was stirred at 110 °C for a certain time. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding products. For reaction times, see paragraph pertinent to the corresponding product.

3.3. Procedure B

Tris(prop-2-ynyloxy)methane (5 mmol), *N*-methyl-maleimide (7.5 mmol) and *p*-toluenesulfonic acid monohydrate (2 mol%) were combined in a threaded tube, and toluene (20 mL), aldehyde (5 mmol), and acetic acid anhydride (5 mmol) were added. Then, the reaction was stirred at 110 °C for a certain time. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding products. For reaction times, see paragraph pertinent to the corresponding product.

3.4. Procedure C

Phenyl propiolic acid (10 mmol), oxalyl dichloride (10 mmol) and one drop of DMF were solved in 5 mL THF. After complete conversion, the crude mixture was added under inert gas to a stirred solution of potassium butoxide (10 mmol), crotonaldehyde (10 mmol), and 30 mL THF at −78 °C. The reaction was allowed to stir for 1 h and then warmed up to room temperature. Next, *N*-methyl-maleimide (5 mmol) was added and the solution was stirred again for 24 h at 60 °C. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding product.

3.5. Procedure D

AAD-product (3 mmol), Ag_2O (9 mmol), methyl iodide (18 mmol) and THF (15 mL) were combined in a threaded tube. Then, the reaction was stirred at 65 °C for 48 h. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding products.

3.6. Procedure E

Alkynoic acid ester (30 mmol) was dissolved in 4 equiv 25% NH_3/H_2O (120 mmol) and stirred at room temperature for 24 h (in case of methyl propiolate, reaction mixture was stirred for 1 h at −78 °C). Then, all volatile compounds were removed under reduced pressure at room temperature. While solvent removal, the corresponding amide precipitated easily. A further purification was not necessary.

3.7. Procedure F

Trimethoxmethane (50 mmol), *p*-toluenesulfonic acid monohydrate (2 mol%) were dissolved in prop-2-yn-1-ol (500 mmol) and stirred on a Dean–Stark apparatus at 80 °C for 40 h. Then, the corresponding Tris(prop-2-ynyloxy)-methane was distilled under reduced pressure. A further purification was not necessary.

3.7.1. *N*-(2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl)-3-phenylpropiolamide (1a). Procedure A. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=2:1): 0.32. Yield: 71%. Colorless solid. Mp: 175–177 °C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta=9.20$ (d, $J=7.53$ Hz, 1H, N*H*), 7.77–7.56 (m, 5H, *H*-Ar), 6.04 and 5.96 (both m, both 1H, C*H*=C*H*), 4.65 (m, 1H, NHC*H*CH), 3.63 (m, 1H, CHC*H*CON), 3.35 (m, 1H, CH_2CHCON), 2.91 (s, 3H, CONCH_3), 2.62 and 2.32 (both m, both 1H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): $\delta=179.5$ and 176.8 (2 CH*C*ON), 152.0 (C≡C*C*ON), 132.1 (2 *o*-*C*H-Ar), 130.3 (*p*-*C*H-Ar), 130.4 and 129.4 (*C*H=*C*H), 129.0 (2 *m*-*C*H-Ar), 119.7 (*i*-*C*-Ar), 83.9 (Ph*C*≡CCO), 83.4 (PhC≡*C*CO), 45.9 (NH*C*HCH), 41.7 (CH*C*HCON), 38.5 (CH_2*C*HCON), 24.5 (CONCH_3), 23.3 (*C*H_2). MS (EI, 70 eV): *m*/*z* (%)=308 (6) [M^+], 179 (100) [M^+−Ac], 129 (68), 94 (19), no other peaks >10%. IR (KBr): $1/\lambda=3383$ (s), 3061 (w), 2950 (w), 2847 (w), 2217 (m),1772 (m), 1696 (s), 1651 (s), 1507 (s), 1444 (s), 1386 (m), 1333 (m), 1291 (m), 1209 (w), 1006 (m), 932 (w), 867 (w), 758 (m), 694 (m), 569 (m) cm^{-1}. HR-MS (EI): calcd for $C_{18}H_{16}N_2O_3$: 308.11609; found 308.11630 [M]$^+$.

3.7.2. *N*-(2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl)-*N*-methyl-3-phenylpropiolamide (1b). Procedure D. 48 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.52. Yield: 80%. Colorless solid. Mp: 147–148 °C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta=7.68$–7.34 (m, 5H, *H*-Ar),

6.07 and 5.95 (both m, both 1H, C*H*=C*H*), 4.57 (m, 1H, N(CH$_3$)C*H*CH), 3.39 (m, 3H, C≡CCONC*H*$_3$), 3.21 (m, 1H, CHC*H*CON), 3.07 (m, 1H, CH$_2$C*H*CON), 2.76 (s, 3H, CONCH$_3$), 2.40 (m, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=180.4 and 177.5 (2 CH*C*ON), 146.9 (C≡CCON), 132.3 (*p*-*C*H-Ar), 129.0 and 128.6 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 119.4 (*i*-*C*-Ar), 130.7 and 129.7 (*C*H=*C*H), 92.2 (Ph*C*≡CCO), 77.1 (PhC≡*C*CO), 53.6 (N(CH$_3$)*C*HCH), 52.9 (C≡CCON*C*H$_3$), 45.1 (CH*C*HCON), 36.5 (CH$_2$*C*HCON), 24.0 (CON*C*H$_3$), 21.4 (*C*H$_2$). MS (EI, 70 eV): *m*/*z* (%)=322 (13) [M]$^+$, 307 (15), 160 (15), 129 (100) [Ac]$^+$, 77 (17), no other peaks >10%. IR (KBr): 1/λ=3456 (w), 3046 (w), 2937 (m), 2891 (m), 2223 (m), 1776 (s), 1701 (s) cm^{-1}. HR-MS (EI): calcd for $C_{19}H_{18}N_2O_3$: 322.13174; found 322.13181 [M]$^+$.

3.7.3. *N*-(2,3,3a,4,7,7a-Hexahydro-2,5-dimethyl-1,3-dioxo-1*H*-isoindol-4-yl)-3-phenylpropiolamide (2a). Procedure A. 24 h. R_f (SiO$_2$, *n*-heptane/EtOAc=1:1): 0.21. Yield: 81%. Colorless solid. Mp: 191–193 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.64 (d, *J*=9.31 Hz, 1H, CHN*H*), 7.77–7.46 (m, 5H, *H*-Ar), 5.68 (s, 1H, C*H*=C(CH$_3$)), 4.80 (t, 1H, *J*=7.33 Hz, CHC*H*NH), 3.42 (m, 1H, CHC*H*CON), 3.25 (m, 1H, CH$_2$C*H*CON), 2.88 (s, 3H, CONC*H*$_3$), 2.52 and 2.33 (both m, both 1H, C=CHC*H*$_2$CH), 1.74 (s, 3H, C*H*$_3$C=CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=179.6 and 178.0 (2 CH*C*ON), 152.3 (C≡C*C*ON), 136.5 (CH$_3$*C*=CH), 132.2 (*p*-*C*H-Ar), 130.3 and 128.9 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 119.6 (*i*-*C*-Ar), 121.7 (CH$_2$*C*H=C), 84.1 (Ph*C*≡CCO), 83.6 (PhC≡*C*CO), 47.1 (NH*C*HCH), 42.8 (CH*C*HCON), 38.4 (CH$_2$*C*HCON), 24.5 (CON*C*H$_3$), 22.9 (CH*C*H$_2$CH=CH$_3$), 19.5 (*C*H$_3$C=CH). MS (EI, 70 eV): *m*/*z* (%)=322 (3) [M]$^+$, 193 (100), 129 (48) [Ac]$^+$, 108 (20), no other peaks >10%. IR (KBr): 1/λ=3359 (s), 3065 (w), 2951 (w), 2896 (w), 2852 (w), 2216 (m), 1775 (s), 1693 (s) cm^{-1}. HR-MS (EI): calcd for $C_{19}H_{18}N_2O_3$: 322.13174; found. 322.13138 [M]$^+$.

3.7.4. *N*-(2,3,3a,4,7,7a-Hexahydro-2,5-dimethyl-1,3-dioxo-1*H*-isoindol-4-yl)-*N*-methyl-3-phenylpropiolamide (2b). Procedure D. 48 h. R_f (SiO$_2$, *n*-heptane/EtOAc=1:1): 0.41. Yield: 61%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.72–7.36 (m, 5H, *H*-Ar), 5.59 (s, 1H, C*H*=C(CH$_3$)), 4.51 (d, *J*=2.57 Hz, 1H, CHC*H*NCH$_3$), 3.37 (s, 3H, CHNC*H*$_3$), 3.21–3.06 (m, 2H, 2 C*H*CONCH$_3$), 2.75 (s, 3H, CONC*H*$_3$), 2.39 (m, 2H, C*H*$_2$), 1.79 (s, 3H, C*H*$_3$C=CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=180.6 and 177.5 (2 *C*ONCH$_3$), 146.1 (C≡C*C*ON), 136.4 (*p*-*C*H-Ar), 132.2 and 129.6 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 130.6 (CH$_3$*C*=CH), 123.0 (CH$_2$*C*H=CCH$_3$), 119.5 (*i*-*C*-Ar), 91.5 (Ph*C*≡CCO), 77.5 (C≡*C*CO), 58.8 (CH*C*HNCH$_3$), 52.9 (C≡CCON*C*H$_3$), 45.8 (CH*C*HCO), 36.2 (CH$_2$*C*HCO), 23.9 (CON*C*H$_3$), 21.9 (*C*H$_3$C=CH), 21.7 (CH$_2$). MS (EI, 70 eV): *m*/*z* (%)=336 (20) [M]$^+$, 321 (66), 236 (17), 160 (81), 129 (100) [Ac]$^+$, 115 (14), 92 (56), 77 (19), no other peaks >10%. IR (KBr): 1/λ=3441 (w), 2972 (w), 2942 (m), 2907 (w), 2858 (w), 2227 (s), 1769 (s), 1703 (s), 1645 (s), 1489 (m), 1434 (s), 1385 (s), 1336 (w), 1299 (s), 1278 (s), 1204 (s), 1173 (m), 1016 (m), 961 (m), 902 (m), 760 (s), 691 (s), 619 (m), 532 (w), 407 (w) cm^{-1}. HR-MS (EI): calcd for $C_{20}H_{20}N_2O_3$: 336.14739; found. 336.14712 [M]$^+$.

3.7.5. *N*-(2,3,3a,4,7,7a-Hexahydro-2,6-dimethyl-1,3-dioxo-1*H*-isoindol-4-yl)-3-phenylpropiolamide (3a). Procedure A. 24 h. R_f (SiO$_2$, *n*-heptane/EtOAc=1:1): 0.22. Yield: 74%. Colorless solid. Mp: 103–105 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.96 (d, *J*=8.5 Hz, 1H, CON*H*CH), 7.57–7.40 (m, 5H, *H*-Ar), 5.46 (m, 1H, CHC*H*=C(CH$_3$)), 4.49 (m, 1H, NHC*H*CH), 3.42 (dd, *J*=1.18, 7.33 Hz, 1H, CHC*H*CON), 3.20 (m, 1H, CH$_2$-C*H*CON), 2.77 (s, 3H, CONC*H*$_3$), 2.37 (dd, *J*=2.37, 12.88 Hz, 1H, C*H*$_2$) and 2.27 (dd, *J*=6.93, 8.12 Hz, 1H, C*H*$_2$), 1.65 (s, 3H, CH$_3$–C=CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=179.3 and 176.8 (2 CH*C*ON), 152.0 (C≡C*C*ON), 136.9 (CH$_3$C=CH), 132.1 (*p*-*C*H-Ar), 130.2 and 128.9 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 119.8 (*i*-*C*-Ar), 121.9 (CH*C*H=C), 84.0 (Ph*C*≡CCO), 83.3 (PhC≡*C*CO), 46.2 (NH*C*HCH), 41.5 (CH*C*HCON), 38.8 (CH$_2$*C*HCON), 28.4 (*C*H$_2$), 24.5 (CON*C*H$_3$), 23.0 (*C*H$_3$C=CH). MS (EI, 70 eV): *m*/*z* (%)=322 (2) [M]$^+$, 193 (65), 129 (100) [Ac]$^+$, 108 (23), 75 (17), no other peaks >10%. IR (KBr): 1/λ=3373 (m), 3057 (w), 2946 (w), 2852 (w), 2215 (m), 1773 (m), 1697 (s) cm^{-1}. HR-MS (EI): calcd for $C_{19}H_{18}N_2O_3$: 322.13174; found. 322.13145 [M]$^+$.

3.7.6. *N*-(2,3,3a,4,7,7a-Hexahydro-2,5-dimethyl-1,3-dioxo-1*H*-isoindol-7-yl)-*N*-methyl-3-phenylpropiolamide (3b). Procedure D. 48 h. R_f (SiO$_2$, *n*-heptane/EtOAc=1:1): 0.62. Yield: 73%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.72–7.45 (m, 5H, *H*-Ar), 5.82 (m, 1H, CHC*H*=C(CH$_3$)), 4.58 (m, 1H, NHC*H*CH), 3.42 (s, 3H, CON(C*H*$_3$)CH), 3.31 (m, 1H, NCHC*H*CO), 3.06 (m, 1H, CH$_2$C*H*CO), 2.81 (s, 3H, CONC*H*$_3$), 2.42 and 2.33 (both m, both 1H, C*H*$_2$), 1.74 (s, 3H, C*H*$_3$C=CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=180.5 and 177.5 (2 CH*C*ON), 146.5 (C≡C*C*ON), 137.9 (CH$_3$C=CH), 132.4 and 129.0 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 130.6 (*p*-*C*H-Ar), 121.9 (CH*C*H=C), 119.4 (*i*-*C*-Ar), 92.2 (Ph*C*≡CCO), 77.2 (PhC≡*C*CO), 54.2 (N(CH$_3$)*C*HCH), 52.9 (N(*C*H$_3$)CH), 45.0 (CH*C*HCON), 36.9 (CH$_2$*C*HCON), 26.4 (*C*H$_2$), 23.9 (CON*C*H$_3$), 23.1 (*C*H$_3$C=CH). MS (EI, 70 eV): *m*/*z* (%)=336 (37) [M]$^+$, 321 (42), 236 (29), 225 (13), 210 (22), 160 (49), 129 (100), 115 (11), 77 (23), no other peaks >10%. IR (KBr): 1/λ=3374 (m), 3068 (w), 2953 (w), 2823 (w), 2209 (m), 1776 (m), 1695 (s) cm^{-1}. HR-MS (EI): calcd for $C_{20}H_{20}N_2O_3$: 336.14739; found. 336.14726 [M]$^+$.

3.7.7. *N*-(2,3,3a,4,7,7a-Hexahydro-2,7-dimethyl-1,3-dioxo-1*H*-isoindol-4-yl)-3-phenylpropiolamide (4a). Procedure A. 24 h. R_f (SiO$_2$, *n*-heptane/EtOAc=1:1): 0.22. Yield: 74%. Colorless solid. Mp: 155 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.06 (d, *J*=7.53 Hz, 1H, CON*H*CH), 7.62–7.41 (m, 5H, *H*-Ar), 5.79 and 5.68 (both m, both 1H, C*H*=C*H*), 4.45 (m, 1H, NHC*H*CH), 3.45 (m, 1H, CHC*H*CON), 3.10 (dd, *J*=1.58, 6.76 Hz, 1H, CH(CH$_3$)C*H*CON), 2.72 (s, 3H, CONCH$_3$), 2.46 (m, 1H, CH$_3$C*H*CH), 1.32 (d, *J*=7.33 Hz, 3H, C*H*$_3$CHCH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=177.2 and 176.5 (2 CH*C*ON), 152.0 (C≡C*C*ON), 134.5 (*p*-*CH*-Ar), 132.1 and 129.0 (2 *o*-*CH*-Ar and 2 *m*-*CH*-Ar), 119.7 (*i*-*C*-Ar), 130.3 and 128.8 (*C*H=*C*H), 83.9 (Ph*C*≡CCO), 83.3 (PhC≡*C*CO), 46.6 (NH*C*HCH), 42.6 (CH(CH$_3$)*C*HCON), 29.8 (CH$_3$*C*HCH), 24.3 (CON*C*H$_3$), 16.7 (*C*H$_3$CHCH). MS (EI, 70 eV): *m*/*z* (%)=322 (6) [M]$^+$, 193 (99), 129 (100) [Ac]$^+$, 108 (16), no other peaks >10%. IR (KBr): 1/λ=3384

(m), 3058 (w), 2974 (w), 2940 (w), 2841 (w), 2216 (m), 1768 (m), 1693 (s) cm^{-1}. HR-MS (EI): calcd for $C_{19}H_{18}N_2O_3$: 322.13174; found. 322.13140 $[M]^+$.

3.7.8. *N*-(2,3,3a,4,7,7a-Hexahydro-2,4-dimethyl-1,3-dioxo-1*H*-isoindol-7-yl)-*N*-methyl-3-phenylpropiolamide (4b). Procedure D. 48 h. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.7. Yield: 55%. Colorless solid. Mp: 91–92 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.67–7.42 (m, 5H, *H*-Ar), 5.92 (m, 2H, C*H*=C*H*), 4.56 (m, 1H, C*H*NCH_3), 3.57 (s, 3H, CON(CH_3)CH), 3.26 (m, 2H, NCHC*H*C*H*CH), 2.77 (s, 3H, CONCH_3), 1.30 (d, J = 7.33 Hz, 3H, CH_3CH). $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): δ = 178.1 and 176.4 (2 *C*ONCH_3), 146.9 (C≡C*C*ON), 135.4 (NCH*C*H=CH), 132.3 and 129.0 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 130.6 (*p*-*C*H-Ar), 128.7 (CH_3CH*C*H=CH), 119.4 (*i*-*C*-Ar), 92.2 (Ph*C*≡CCO), 77.1 (PhC≡*C*CO), 53.9 (N*C*H), 53.3 (CON(*C*H_3)CH), 45.4 (NCH*C*HCO), 42.0 (CH_3CH*C*HCO), 28.5 (CONCH_3), 24.0 (CH_3*C*HCH), 17.6 (CH_3CH). MS (EI, 70 eV): *m*/*z* (%) = 336 (17) $[M]^+$, 321 (26), 236 (11), 225 (19), 210 (30), 129 (100) $[Ac]^+$, 91 (11), 77 (10), no other peaks > 10%. IR (KBr): 1/λ = 3444 (w), 3037 (w), 2975 (w), 2940 (w), 2909 (w), 2221 (w), 1767 (s), 1700 (s), 1636 (s), 1491 (m), 1432 (s), 1382 (m), 1350 (w), 1287 (m), 1210 (m), 1070 (w), 999 (w), 801 (w), 761 (m), 688 (m), 530 (w) cm^{-1}. HR-MS (EI): calcd for $C_{16}H_{18}N_2O_4$: 336.14739; found. 336.14800 $[M]^+$.

3.7.9. *N*-(4-Ethyl-2,3,3a,4,7,7a-hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-7-yl)-3-phenylpropiolamide (5a). Procedure A. 24 h. R_f (SiO_2, *n*-heptane/EtOAc = 2/1): 0.31. Yield: 75%. Colorless solid. Mp: 134 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.11 (d, J = 7.13 Hz, 1H, N*H*), 7.71–7.47 (m, 5H, *H*-Ar), 5.87 (m, 1H, NHCHC*H*=CH), 5.79 (m, 1H, CH_2CHC*H*=CH), 4.50 (m, 1H, C*H*NHCO), 3.51 (t, J = 7.63 Hz, 1H, NHCHC*H*CO), 3.26 (t, J = 7.43 Hz, 1H, CH_2CHC*H*CO), 2.76 (s, 3H, CONCH_3), 2.23 (m, 1H, CH_2C*H*CH), 1.93–1.67 (dm, 2H, CH_2), 1.02 (t, J = 6.93 Hz, 3H, CH_3CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): δ = 177.2 and 176.6 (*C*ONCH_3), 152.0 (C≡C*C*ONH), 133.4 (*p*-*C*H-Ar), 132.2 and 129.1 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 130.3 (NHCH*C*H=CH), 128.9 (CH_2CH*C*H=CH), 119.7 (*i*-*C*-Ar), 83.9 (Ph*C*≡CCO), 83.4 (PhC≡*C*CO), 46.8 (CH*C*HNH), 42.5 (NHCHC*H*CO), 41.9 (CH_2CH*C*HCO), 37.3 (CH*C*HCH_2), 24.3 (CON*C*H_3), 23.7 (*C*H_2), 12.5 (CH_2*C*H_3). MS (EI, 70 eV): *m*/*z* (%) = 336 (7) $[M]^+$, 207 (100), 191 (12) $[M-Ac]^+$, 129 (96), 122 (12), 113 (53), 106 (21), 91 (21), 83 (11), 77 (20), 55 (11), 43 (58), 29 (19), no other peaks > 10%. IR (KBr): 1/λ = 3388 (m), 3056 (w), 2962 (m), 2935 (m), 2876 (w), 2830 (w), 2384 (w), 2217 (m), 1769 (m), 1694 (s), 1651 (s), 1503 (s), 1443 (m), 1387 (m), 1292 (m), 1213 (w), 1158 (w), 1100 (w), 1036 (w), 994 (m), 757 (m), 692 (w), 577 (m), 493 (w) cm^{-1}. HR-MS (EI): calcd for $C_{16}H_{18}N_2O_4$: 336.14739; found. 336.14798 $[M]^+$.

3.7.10. *N*-(4-Ethyl-2,3,3a,4,7,7a-hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-7-yl)-*N*-methyl-3-phenylpropiolamide (5b). Procedure D. 48 h. R_f (SiO_2, *n*-heptane/EtOAc = 1/2): 0.45. Yield: 64%. Colorless solid. Mp: 87–89 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.67–7.43 (m, 5H, *H*-Ar), 5.89 (m, 2H, C*H*=C*H*), 4.52 (m, 1H, C*H*NCH_3), 3.66 (s, 3H, CON(CH_3)CH), 3.31 (m, 2H, NCHC*H*C*H*CH), 2.76 (s, 3H, CONCH_3), 2.23 (m, 1H, CH_2C*H*CH), 1.92 and 1.80 (both m, both 1H, CH_2), 0.96 (t, J = 7.43 Hz, 3H, CH_3CH_2CH). $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): δ = 177.7 and 175.7 (2 *C*ONCH_3), 146.9 (C≡C*C*ON), 133.2 (NCH*C*H=CH), 132.3 and 129.0 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 131.0 (*p*-*C*H-Ar), 130.6 (CH_2CH*C*H=CH), 119.5 (*i*-*C*-Ar), 92.2 (Ph*C*≡CCO), 77.1 (PhC≡*C*CO), 54.7 (N*C*H), 53.4 (CON(*C*H_3)CH), 45.2 (NCH*C*HCO), 42.2 (CH_2CH*C*HCO), 36.3 (CH_2*C*HCHCO), 24.4 (CH_2), 24.2 (CON*C*H_3), 12.4 (*C*H_3CH_2CH). MS (EI, 70 eV): *m*/*z* (%) = 350 (13) $[M]^+$, 335 (21), 239 (17), 224 (27), 210 (14), 160 (11), 129 (100) $[Ac]^+$, 77 (11), no other peaks > 10%. IR (KBr): 1/λ = 3447 (w), 3047 (w), 2980 (m), 2959 (m), 2943 (m), 2874 (w), 2835 (w), 2221 (s), 1770 (s), 1700 (s), 1640 (s), 1622 (s), 1489 (m), 1458 (m), 1431 (s), 1378 (m), 1297 (s), 1212 (s), 1187 (s), 1101 (m), 979 (m), 880 (w), 769 (s), 695 (s), 598 (w), 430 (w) cm^{-1}. HR-MS (EI): calcd for $C_{21}H_{22}N_2O_3$: 350.16304; found. 350.16338 $[M]^+$.

3.7.11. *N*-(2,3,3a,4,7,7a-Hexahydro-2,5,7-trimethyl-1,3-dioxo-1*H*-isoindol-4-yl)-3-phenylpropiolamide (6a). Procedure A. 24 h. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.23. Yield: 77%. Colorless solid. Mp: 173–176 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.48 (d, J = 8.91 Hz, 1H, N*H*), 7.68–7.44 (m, 5H, *H*-Ar), 5.37 (m, 1H, CHC*H*=C(CH_3)), 4.65 (m, 1H, CHC*H*–NH), 3.34 (dd, J = 2.37, 6.14 Hz, 1H, CHC*H*CON), 3.11 (m, 1H, CH(CH_3)–C*H*CON), 2.78 (s, 3H, CONCH_3), 2.48 (m, 1H, CH_3C*H*CH), 1.65 (s, 3H, CH_3C=CH), 1.27 (d, J = 7.33 Hz, 3H, CHCH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): δ = 178.4 and 177.1 (CH*C*ONCH_3), 152.3 (C≡C*C*ONH), 136.3 (CH_3*C*=CH), 132.3 (*p*-*C*H-Ar), 130.5 and 129.0 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 127.5 (*C*H=C(CH_3)), 119.5 (*i*-*C*-Ar), 84.2 (Ph*C*≡CCO), 83.4 (PhC≡*C*CO), 48.2 (NH*C*HCH), 43.9 and 43.7 (2 CH*C*HCON), 29.6 (CON*C*H_3), 24.4 (CH*C*HCH_3), 18.3 (*C*H_3C=CH), 16.8 (CH*C*H_3). MS (EI, 70 eV): *m*/*z* (%) = 336 (2) $[M]^+$, 207 (100), 129 (65), 122 (17), no other peaks > 10%. IR (KBr): 1/λ = 3374 (m), 2978 (w), 2846 (w), 2214 (m), 1770 (m), 1691 (s) cm^{-1}. HR-MS (EI): calcd for $C_{20}H_{20}N_2O_3$: 336.14739; found. 336.15212 $[M]^+$.

3.7.12. *N*-(2,3,3a,4,7,7a-Hexahydro-2,4,6-trimethyl-1,3-dioxo-1*H*-isoindol-7-yl)-*N*-methyl-3-phenylpropiolamide (6b). Procedure D. 48 h. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.48. Yield: 70%. Colorless oil. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.66–7.48 (m, 5H, *H*-Ar), 5.38 (m, 1H, CHC*H*=C(CH_3)), 4.66 (m, 1H, CHC*H*N), 3.43 (s, 3H, CHNCH_3), 3.35 (m, 1H, CHC*H*CON), 3.12 (m, 1H, CH(CH_3)C*H*CON), 2.77 (s, 3H, CONCH_3), 2.47 (m, 1H, CH_3C*H*CH), 1.65 (s, 3H, CH_3C=CH), 1.28 (d, J = 7.33 Hz, 3H, CHCH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, DMSO-d_6): δ = 178.5 and 177.2 (2 CH*C*ONCH_3), 152.3 (C≡C*C*ON), 136.4 (CH_3*C*=CH), 132.4 (*p*-*C*H-Ar), 130.6 and 129.1 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 127.5 (*C*H=C(CH_3)), 119.6 (*i*-*C*-Ar), 84.3 (Ph*C*≡CCO), 83.2 (PhC≡*C*CO), 52.7 (CHNCH_3), 48.2 (N(CH_3)CHCH), 43.8 and 43.6 (2 CH*C*HCON), 29.5 (CON*C*H_3), 24.5 (CH*C*HCH_3), 18.4 (*C*H_3C=CH), 16.9 (CH*C*H_3). MS (EI, 70 eV): *m*/*z* (%) = 350 (4) $[M]^+$, 221 (34), 129 (100), 136 (23), 108 (12) no other peaks > 10%. IR (KBr): 1/λ = 3375 (m), 2976 (w), 2852 (w), 2221 (m), 1777 (m), 1697 (s), 1534 (m), 1467 (m), 1345 (w), 1215 (m), 1013 (w), 967 (w), 677 (w) cm^{-1}. HR-MS (EI): calcd for $C_{21}H_{22}N_2O_3$: 350.16304; found. 350.16304 $[M]^+$.

3.7.13. *N*-(2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl)propiolamide (7a). Procedure A. 24 h. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.08. Yield: 69%. Colorless solid. Mp: 163–165 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.95 (d, 1H, J = 7.53 Hz, N*H*), 5.86 (m, 1H, CHC*H*=CH), 5.76 (dm, 1H, CH_2CH=CH), 4.43 (m, 1H, C*H*NH), 4.16 (s, 1H, *H*C≡C), 3.41 (dd, 1H, J = 1.58, 7.33 Hz, CHC*H*CO), 3.16 (m, 1H, CH$_2$C*H*CO), 2.74 (s, 3H, CONCH_3), 2.46 and 2.15 (both m, both 1H, CH_2). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 179.5 and 176.8 (2 *C*ONCH$_3$), 151.4 (C≡C*C*ONH), 129.5 (CH*C*H=CH), 128.1 (CH$_2$*C*H=CH), 78.2 (H*C*≡CCO), 76.1 (C≡*C*CO), 45.8 (*C*HNH), 41.6 (CH*C*HCO), 38.4 (CH$_2$*C*HCO), 24.5 (CON*C*H$_3$), 23.2 (*C*H$_2$). MS (EI, 70 eV): *m*/*z* (%) = 232 (5) [M]$^+$, 214 (23), 179 (100), 163 (14), 146 (11), 121 (46), 112 (16), 105 (13), 94 (75), 78 (38), 66 (43), 58 (15), 54 (88), 39 (35), 28 (37), no other peaks >10%. IR (KBr): 1/λ = 3441 (w), 3235 (s), 3055 (m), 2959 (m), 2813 (w), 2110 (s), 1702 (s), 1633 (s), 1552 (s), 1437 (s), 1290 (s), 1109 (s), 1008 (s), 950 (m), 884 (m), 796 (m), 720 (s), 582 (m), 466 (m) cm^{-1}. HR-MS (EI): calcd for $C_{12}H_{12}N_2O_4$: 232.08479; found. 232.08452 [M]$^+$.

3.7.14. *N*-(2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl)but-2-ynamide (8a). Procedure A. 24 h. R_f (SiO_2, *n*-heptane/EtOAc = ½): 0.09. Yield: 60%. Colorless solid. Mp: 127–128 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.65 (d, 1H, J = 5.94 Hz, N*H*), 5.85 (m, 1H, CHC*H*=CH), 5.76 (m, 1H, CH=C*H*CH$_2$), 4.41 (m, 1H, C*H*NH), 3.39 (m, 1H, NHCHC*H*CO), 3.16 (m, 1H, CH$_2$C*H*CO), 2.73 (s, 3H, CONCH_3), 2.23–2.06 (m, 2H, CH_2), 1.96 (s, 3H, CH_3C≡C). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 179.5 and 176.9 (2 CH*C*ON), 152.2 (C≡CCON), 130.0 (CH*C*H=CH), 127.9 (CH$_2$*C*H=*C*H), 82.9 (CH$_3$*C*≡CCO), 75.4 (CH$_3$C≡*C*CO), 45.7 (*C*HNH), 41.6 (CH*C*HCO), 38.5 (CH$_2$*C*HCO), 24.5 (CON*C*H$_3$), 23.2 (*C*H$_2$), 3.0 (*C*H$_3$). MS (EI, 70 eV): *m*/*z* (%) = 246 (4) [M]$^+$, 179 (100) [M−Ac]$^+$, 163 (23), 146 (18), 121 (22), 67 (57), 39 (14), 28 (17), no other peaks >10%. IR (KBr): 1/λ = 3390 (s), 3377 (s), 2951 (w), 2919 (w), 2237 (m), 1766 (m), 1690 (s), 1648 (s), 1504 (s), 1436 (s), 1387 (s), 1332 (s), 1289 (s), 1125 (m), 1083 (m), 997 (m), 874 (w), 787 (w), 722 (m), 668 (m), 583 (m), 498 (w) cm^{-1}. HR-MS (EI): calcd for $C_{13}H_{14}N_2O_3$: 246.10044; found. 246.10023 [M]$^+$.

3.7.15. *N*-(2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl)-*N*-methylbut-2-ynamide (8b). Procedure D. 48 h. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.5. Yield: 63%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.84 (m, 1H, CHC*H*=CH), 5.75 (m, 1H, CH=C*H*CH$_2$), 4.42 (m, 1H, C*H*NCH$_3$), 3.39 (m, 1H, N(CH$_3$)CHC*H*CO), 3.17 (m, 1H, CH$_2$C*H*CO), 2.77 (s, 3H, CONCH_3), 2.21–2.09 (m, 2H, CH_2), 1.97 (s, 3H, CH_3C≡C). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 179.4 and 176.8 (2 CH*C*ON), 152.3 (C≡C*C*ON), 130.2 (CH*C*H=CH), 127.8 (CH$_2$-*C*H=*C*H), 82.8 (CH$_3$*C*≡CCO), 75.4 (C*H*$_3$C≡*C*CO), 53.3 (CHNCH_3), 45.8 (*C*HN), 41.7 (CH*C*HCO), 38.4 (CH$_2$-*C*HCO), 24.6 (CON*C*H$_3$), 23.3 (*C*H$_2$), 3.1 (*C*H$_3$). MS (EI, 70 eV): *m*/*z* (%) = 260 (19) [M]$^+$, 245 (85), 228 (25), 179 (20), 174 (12), 149 (77), 145 (11), 134 (13), 120 (13), 117 (22), 106 (15), 98 (100), 79 (53), 67 (60), 52 (15), 39 (40), 27 (11), no other peaks >10%. IR (KBr): 1/λ = 3451 (w), 3044 (w), 2981 (w), 2943 (m), 2898 (m), 2246 (m), 1773 (s), 1698 (s), 1641 (s), 1459 (m), 1431 (s), 1381 (m), 1272 (s), 1132 (m), 1065 (m), 1045 (m), 960 (m), 804 (m), 743 (m), 612 (m), 577 (w), 481 (w) cm^{-1}. HR-MS (EI): calcd for $C_{14}H_{16}N_2O_3$: 260.11609; found. 260.11583 [M]$^+$.

3.7.16. *N*-(2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl)pent-2-ynamide (9a). Procedure A. 24 h. R_f (SiO_2, *n*-heptane/EtOAc = ½): 0.25. Yield: 80%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.65 (d, 1H, J = 7.5 Hz, N*H*), 5.86 (ddd, 1H, J = 3.0, 6.6, 12.7 Hz, CHC*H*=CH), 5.76 (td, 1H, J = 3.0, 9.5 Hz, CH$_2$C*H*=CH), 4.42 (tdt, 1H, J = 2.7, 5.3, 7.9 Hz, C*H*NH), 3.40 (m, 1H, CHC*H*CO), 3.17 (m, 1H, H$_2$C*H*CO), 2.88 (s, 3H, CONCH_3), 2.46 (m, 2H, CH$_3$CH_2C≡C), 2.36 (m, 2H, CH=CHCH_2), 1.11 (t, 3H, J = 7.5 Hz, CH_3CH$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 179.8 and 177.3 (2 CH*C*ON), 152.6 (C≡C*C*ONH), 130.4 (CH=*C*HCH), 128.3 (CH$_2$*C*H=CH), 88.0 (CH$_2$*C*≡C), 75.9 (CH$_2$C≡*C*), 46.1 (*C*HNH), 42.0 (CH*C*HCO), 38.9 (CH$_2$*C*HCO), 24.8 (CON*C*H$_3$), 23.6 (*C*H$_2$C≡C), 13.1 (*C*H$_3$CH$_2$), 11.8 (CH=CHCH_2CH). MS (EI, 70 eV): *m*/*z* (%) = 260 (3) [M]$^+$, 179 (100), 163 (18), 146 (23), 121 (38), 94 (75), 81 (23), 66 (14), no other peaks >10%. IR (KBr): 1/λ = 3320 (m), 2983 (m), 2943 (m), 2235 (m), 1777 (m), 1705 (s), 1620 (s), 1526 (s), 1437 (m), 1376 (m), 1286 (m), 1120 (m), 1975 (m), 996 (m), 730 (w), 694 (w), 597 (w) cm^{-1}. HR-MS (EI): calcd for $C_{14}H_{16}N_2O_3$: 260.11609; found. 260.11562 [M]$^+$.

3.7.17. *N*-(2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl)-*N*-methylpent-2-ynamide (9b). Procedure D. 48 h. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.42. Yield: 60%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.08 (m, 1H, CHC*H*=CH), 6.01 (m, 1H, CH$_2$C*H*=CH), 3.40 (s, 3H, CHNCH_3), 3.29 (m, 1H, CHC*H*CO), 3.11 (q, 1H, J = 4.5 Hz, CH$_2$C*H*CO), 2.50 (m, 2H, CH$_3$CH_2C≡C), 2.47–2.37 (m, 2H, CHCH_2CH=CH), 1.20 (t, 3H, J = 7.83 Hz, CH_3CH$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 180.5 and 177.5 (2 CH*C*ON), 147.2 (C≡C*C*ON), 129.5 (CH*C*H=CH), 128.5 (CH$_2$*C*H=CH), 96.9 (CH$_2$*C*≡C), 68.9 (C≡*C*CO), 53.4 (*C*HNCH$_3$), 52.6 (CHN*C*H$_3$), 45.0 (CH*C*HCO), 36.4 (CH$_2$*C*HCO), 23.9 (CHCON*C*H$_3$), 21.4 (CH$_3$*C*H$_2$C≡C), 12.9 (*C*H$_3$CH$_2$), 11.8 (CH*C*H$_2$CH=CH). MS (EI, 70 eV): *m*/*z* (%) = 274 (23) [M]$^+$, 259 (40), 245 (75), 242 (22), 188 (14), 179 (18), 174 (26), 163 (33), 148 (75), 117 (26), 112 (100), 81 (98), 68 (47), 54 (70), 39 (18), 27 (21), no other peaks >10%. IR (KBr): 1/λ = 3461 (w), 3040 (w), 2980 (m), 2942 (m), 2242 (m), 1777 (m), 1705 (s), 1635 (s), 1435 (s), 1384 (s), 1317 (m), 1275 (s), 1197 (m), 1133 (m), 1073 (m), 1275 (s), 1133 (m), 1051 (m), 970 (m), 804 (m), 736 (m), 736 (m), 689 (m), 610 (w) cm^{-1}. HR-MS (EI): calcd for $C_{15}H_{18}N_2O_3$: 274.13174; found. 274.13159 [M]$^+$.

3.7.18. *N*-(6-Cyanocyclohex-2-enyl)-3-phenylpropiolamide (10a). Procedure A. 120 h. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.43. Yield: 58%. Colorless solid. Mp: 148 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.25 (d, J = 7.92 Hz, 1H, CHN*H*), 7.75–7.33 (m, 5H, *H*-Ar), 5.88 (m, 1H, CHC*H*=CH), 5.51 (dm, 1H, CH$_2$C*H*=CH), 4.61 (m, 1H, C*H*NH), 3.36 (m, 1H, C*H*CN), 2.11–1.96 (m, 2H, CH$_2$CH_2CH), 1.94–1.83 (m, 2H, CH$_2$CH_2CH=CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 152.2

(*C*ONH), 132.2 and 129.9 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 130.4 (*p*-*C*H-Ar), 129.0 (CH*C*H=CH), 124.5 (CH_2*C*H=CH), 120.3 (*C*N), 119.7 (*i*-*C*-Ar), 84.0 (Ph*C*≡CCO), 83.6 (PhC≡*C*CO), 44.7 (*C*HNH), 30.2 (*C*HCN), 22.3 (CH_2*C*H_2CHCN), 21.9 (CH_2*C*H_2CH=CH). MS (EI, 70 eV): *m*/*z* (%)=250 (27) $[M]^+$, 223 (14), 197 (19), 168 (14), 129 (100), 101 (16), 75 (25), 52 (13), no other peaks >10%. IR (KBr): 1/λ=3299 (m), 3032 (w), 2937 (w), 2848 (w), 2220 (m), 1633 (s), 1528 (s), 1490 (w), 1337 (w), 1276 (w), 1038 (w), 760 (m), 693 (m), 654 (w), 531 (w) cm^{-1}. HR-MS (EI): calcd for $C_{16}H_{14}N_2O$: 250.11061; found. 250.11013 $[M]^+$.

3.7.19. *N*-(6-Cyanocyclohex-2-enyl)-*N*-methyl-3-phenylpropiolamide (10b). Procedure D. 48 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.43. Yield: 75%. Colorless solid. Mp: 63–64 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.56–7.34 (m, 5H, *H*-Ar), 5.88 (m, 1H, CHC*H*=CH), 5.63 (tdd, 1H, *J*=2.0, 4.0, 10.0 Hz, CH_2C*H*=CH), 4.42 (m, 1H, CH=CHC*H*N), 3.84 (s, 3H, NCH_3), 2.99 (ddd, 1H, *J*=3.0, 4.6, 8.7 Hz, CH_2C*H*CN), 2.38–2.20 (m, 2H, CH_2CH_2CH), 2.13 and 1.98 (both m, both 1H, CH=CHCH_2). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=148.5 (*C*ON), 132.3 and 128.5 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 130.1 (CH*C*H=CH), 128.5 (*p*-*C*H-Ar), 126.4 (CH_2*C*H=CH), 120.6 (*i*-*C*-Ar), 120.2 (*C*N), 92.5 (Ph*C*≡CCO), 77.3 (PhC≡*C*CO), 55.1 (*C*HN), 53.9 (N*C*H_3), 32.6 (*C*HCN), 23.7 (CH_2*C*H_2CHCN), 22.3 (CH_2*C*H_2CH=CH). MS (EI, 70 eV): *m*/*z* (%)=264 (18) $[M]^+$, 237 (18), 211 (17), 129 (100), 98 (17), 84 (13), no other peaks >10%. IR (KBr): 1/λ=3436 (m), 3034 (w), 2944 (m), 2839 (m), 2225 (s), 1713 (w), 1630 (s), 1490 (m), 1434 (m), 1304 (s), 1212 (m), 1185 (m), 1001 (w), 871 (w), 759 (m), 691 (w) 595 (w) cm^{-1}. HR-MS (EI): calcd for $C_{17}H_{16}N_2O$: 264.12626; gef. 264.12608 $[M]^+$.

3.7.20. Dimethyl 3-(3-phenylpropiolamido)-6-ethylcyclohexa-1,4-diene-1,2-dicarboxylate (11a). Procedure A. 48 h. R_f (SiO_2, *n*-heptane/EtOAc=2/1): 0.27. Yield: 36%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.08 (d, *J*=8.3 Hz, 1H, N*H*), 7.57–7.40 (m, 5H, *H*-Ar), 5.89 (m, 1H, NHCHC*H*=CH), 5.70 (m, 1H, CH_2CHC*H*=CH), 5.26 (m, 1H, C*H*NH), 3.68 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.01 (m, 1H, CH_2C*H*CH=CH), 1.74–1.63 and 1.58–1.45 (both m, both 1H, CH_2), 0.86 (t, 3H, *J*=7.53 Hz, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=167.6 and 166.0 (2 *C*OOMe), 151.7 (*C*ONH), 141.4 (NHCHC=*C*COOMe), 132.1 and 129.0 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 130.3 (NHCH*C*H=CH), 130.0 (NHCH*C*COOMe), 129.4 (*p*-*C*H-Ar), 123.7 (CH_2CH*C*H=CH), 119.9 (*i*-*C*-Ar), 83.8 (Ph*C*≡CCO), 83.7 (PhC≡*C*CO), 52.2 (2 OCH_3), 43.2 (*C*HNH), 38.0 (CH_2*C*HCH=CH), 26.0 (CH_2), 10.5 (CH_3*C*H_2). MS (EI, 70 eV): *m*/*z* (%)=367 (5) $[M]^+$, 238 (100), 129 (65), 122 (23), no other peaks >10%. IR (KBr): 1/λ=3261 (m), 2953 (m), 2875 (w), 2216 (s), 1727 (s), 1630 (s), 1525 (m), 1434 (m), 1266 (s), 1211 (m), 1068 (m), 964 (m), 759 (s), 690 (m), 533 (w) cm^{-1}. HR-MS (EI): calcd for $C_{21}H_{21}NO_5$: 367.14197; found. 367.14178 $[M]^+$.

3.7.21. Dimethyl 3-(*N*-methyl-3-phenylpropiolamido)-6-ethylcyclohexa-1,4-diene-1,2-dicarboxylate (11b). Procedure D. 48 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.45. Yield: 72%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.61–7.38 (m, 5H, *H*-Ar), 5.9 (m, 1H, N(CH_3)-CHC*H*=CH), 5.69 (m, 1H, CH_2CHC*H*=CH), 5.25 (m, 1H, C*H*N), 3.67 (s, 3H, OCH_3), 3.62 (s,3H, OCH_3), 3.46 (s, 3H, CHNCH_3), 3.02 (m, 1H, CH_2C*H*CH=CH), 1.76–1.65 and 1.6–1.49 (both m, both 1H, CH_2), 0.88 (t, *J*=7.53 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=167.7 and 166.1 (2 *C*OOMe), 151.8 (*C*ON(CH_3)), 141.3 (N(CH_3)CHC=*C*COOMe), 132.2 and 129.1 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 130.4 (N(CH_3)CH*C*H=CH), 130.1 (N(CH_3)CH*C*COOMe), 129.5 (*p*-*C*H-Ar), 123.8 (CH_2CH*C*H=CH), 119.8 (*i*-*C*-Ar), 83.9 (Ph*C*≡CCO), 83.6 (PhC≡*C*CO), 54.8 (CHN*C*H_3), 52.3 (2 O*C*H_3), 43.1 (*C*HN), 38.0 (CH_2*C*HCH=CH), 26.1 (CH_2), 10.6 (CH_3*C*H_2). MS (EI, 70 eV): *m*/*z* (%)=381 (10) $[M]^+$, 322 (14), 264 (17), 129 (100), 107 (107), no other peaks >10%. IR (KBr): 1/λ=3263 (m), 2967 (m), 2892 (w), 2234 (s), 1735 (s), 1638 (s), 1529 (m), 1503 (m), 1441 (m), 1271 (s), 1222 (m), 1178 (m), 1067 (m), 1003 (m) 966 (m), 865 (m) 768 (s), 698 (m), 536 (w), 489 (w) cm^{-1}. HR-MS (EI): calcd for $C_{22}H_{23}NO_5$: 381.15762; found. 381.15749 $[M]^+$.

3.7.22. 1,4-Di-(*N*-(2,3,3a,4,7,7a-hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl)-3-phenylpropiolamide)-phenylene (12a). Procedure A. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.11. Yield: 80%. Colorless solid. Mp: 167 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.17 (d, 2H, *J*=7.73 Hz, 2 N*H*), 7.61 (m, 10H, 10 C*H*-Ar), 7.32 (s, 4H, 4 NCC*H*), 6.02 (m, 2H, 2 C*H*=CHCH$_2$), 5.94 (m, 2H, 2 CH=C*H*CH$_2$), 4.64 (m, 2H, 2 NHC*H*CH), 3.66 (dd, 2H, *J*=1.58, 7.33 Hz, 2 NHCHC*H*CO), 3.42 (m, 2H, 2 CH_2C*H*CO), 2.62 and 2.31 (both m, both 2H, 2 CH_2). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=178.6 and 175.6 (4 CH*C*ON), 152.1 (2 C≡C*C*ON), 132.1 and 132.0 (4 *o*-*C*H-Ar and 4 *m*-*C*H-Ar), 130.3 (2 NHCH*C*H=CH), 129.4 (2 *p*-*C*H-Ar), 129.0 (N*C*CH=CH), 128.4 (NC*C*H=CH), 127.4 (2 CH_2*C*H=CH), 119.7 (2 *i*-*C*-Ar), 83.9 (2 Ph*C*≡CCO), 83.4 (2 PhC≡*C*CO), 45.8 (2 NH*C*HCH), 42.1 (2 NHCH*C*HCO), 39.1 (2 CH_2*C*HCO), 23.3 (2 *C*H$_2$). MS (EI, 70 eV): *m*/*z* (%)=662 (1) $[M]^+$, 501 (43), 468 (31), 340 (22), 236 (42), 208 (22), 194 (19), 192 (12), 168 (17), 158 (23), 132 (17), 125 (25), 129 (100), 63 (11), 48 (19), 34 (14), no other peaks >10%. IR (KBr): 1/λ=3467 (w), 3039 (w), 2945 (w), 2221 (m), 1715 (s), 1646 (s), 1517 (s), 1378 (s), 1309 (s), 1215 (s), 1178 (s), 1017 (w), 893 (w), 822 (m), 757 (m), 688 (m), 532 (w) cm^{-1}. HR-MS (ESI): calcd for $C_{40}H_{30}N_4O_6$: 662.21653; found. 663.22660 $[M+H]^+$.

3.7.23. 1,4-Di-(*N*-(2,3,3a,4,7,7a-hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl)-*N*-methyl-3-phenylpropiolamide)-phenylene (12b). Procedure D. 48 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.23. Yield: 47%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.64–7.38 (m, 10H, 10 C*H*-Ar), 7.31 (s, 4H, 4 NCC*H*), 6.03 (m, 2H, 2 C*H*=CHCH$_2$), 5.96 (m, 2H, 2 CH=C*H*CH$_2$), 4.65 (m, 2H, 2 N(CH_3)C*H*CH), 3.67 (m, 2H, 2 N(CH_3)CHC*H*CO), 3.41 (m, 2H, 2 CH_2C*H*CO), 3.36 (m, 6H, 2 C≡CCONCH_3), 2.62 and 2.31 (both m, both 2H, 2 CH_2). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=178.7 and 175.7 (4 CH*C*ON), 152.2 (2 C≡C*C*ON), 132.2 and 132.0 (4 *o*-*C*H-Ar and 4 *m*-*C*H-Ar), 130.4 (2 NHCH*C*H=CH), 129.5 (2 *p*-*C*H-Ar), 129.0 (N*C*CH=CH), 128.5 (NC*C*H=CH), 127.4 (2 CH_2*C*H=CH), 119.7 (2 *i*-*C*-Ar), 83.8 (2 Ph*C*≡CCO),

83.3 (2 PhC≡*C*CO), 53.4 (2 CON(*C*H$_3$)CH), 45.9 (2 N*C*HCH), 42.2 (2 NCH*C*HCO), 39.1 (2 CH$_2$*C*HCO), 23.2 (2 *C*H$_2$). MS (EI, 70 eV): *m/z* (%)=690 (3) [M]$^+$, 529 (49), 496 (35), 368 (15), 296 (17), 264 (35), 236 (40), 232 (23), 222 (25), 220 (14), 211 (18), 206 (23), 204 (20), 196 (16), 186 (16), 160 (44), 153 (17), 136 (13), 129 (100), 117 (15), 105 (28), 91 (26), 77 (79), 69 (17), 52 (24), 32 (20), 28 (60), no other peaks >10%. IR (KBr): 1/λ=3467 (w), 3038 (w), 2943 (w), 2224 (m), 1712 (s), 1631 (s), 1514 (s), 1375 (s), 1303 (s), 1207 (s), 1175 (s), 1084 (m), 1007 (m), 895 (m), 819 (m), 757 (m), 689 (m), 531 (w) cm^{-1}. HR-MS (ESI): calcd for $C_{42}H_{34}N_4O_6$: 690.24783; found. 691.25603 [M+H]$^+$.

3.7.24. 2,3,3a,4,7,7a-Hexahydro-2-methyl-1,3-dioxo-1*H*-isoindol-4-yl 3-phenylpropiolate (13a). Procedure C. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.24. Yield: 30%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=7.75–7.49 (m, 5H, *H*-Ar), 6.16 and 6.06 (both m, both 1H, C*H*=C*H*), 5.60 (m, 1H, COOC*H*CH), 3.64 (dd, *J*=2.83, 6.93 Hz, 1H, CHC*H*CO), 3.33 (m, 1H, CH$_2$C*H*CO), 2.88 (s, 3H, CONC*H*$_3$), 2.48 (m, 2H, CHC*H*$_2$CH=). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=179.3 and 175.4 (2 *C*ONCH$_3$), 132.9 (*p*-*C*H-Ar), 129.1 and 126.6 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 118.2 (*i*-*C*-Ar), 131.4 and 131.3 (*C*H=*C*H), 86.3 (Ph–*C*≡C), 80.1 (C≡*C*–CO), 68.3 (OC*H*CH), 42.0 (CHC*H*CO), 36.8 (CH$_2$C*H*CO), 24.5 (CONC*H*$_3$), 22.0 (*C*H$_2$). MS (EI, 70 eV): *m/z* (%)=309 (14) [M]$^+$, 224 (31), 180 (79), 146 (15), 102 (94), 95 (34), 78 (100), 51 (32), 39 (27), 28 (19), no other peaks >10%. IR (KBr): 1/λ=3464 (m), 3057 (m), 2955 (m), 2224 (s), 1700 (s) cm^{-1}. HR-MS (EI): calcd for $C_{18}H_{15}NO_4$: 309.10011; found. 309.09981 [M]$^+$.

3.7.25. 3a,4,7,7a-Tetrahydro-2,5-dimethyl-4-(prop-2-ynyloxy)-2*H*-isoindole-1,3-dione (14a). Procedure B. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.43. Yield: 73%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=5.75 (m, 1H, CH$_2$C*H*=CMe), 4.30 (m, 1H, OC*H*CH), 3.99 (m, 2H, OC*H*$_2$C≡CH), 3.39 (m, 1H, OCH$_2$C≡C*H*), 3.09 (m, 1H, OCHC*H*CO), 3.02 (m, 1H, CH$_2$C*H*CO), 2.77 (s, 3H, CONC*H*$_3$), 2.33 and 2.17 (both m, both 1H, CHC*H*$_2$CH=CCH$_3$), 1.78 (s, 3H, C*H*$_3$C=CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=180.0 and 176.5 (2 *C*ONCH$_3$), 135.8 (CH$_3$*C*=CH), 125.0 (CH$_2$*C*H=C), 79.8 (HC≡*C*CH$_2$), 77.4 (H*C*≡CCH$_2$), 72.9 (O*C*HCH), 55.3 (HC≡C*C*H$_2$O), 44.8 (OCH*C*HO), 36.4 (CH$_2$*C*HCO), 24.2 (CONC*H*$_3$), 22.0 (CH*C*H$_2$CH=CCH$_3$), 21.7 (*C*H$_3$C=CH). MS (EI, 70 eV): *m/z* (%)=233 (6) [M]$^+$, 218 (11), 194 (32), 179 (28), 122 (100), 112 (16), 109 (38), 92 (94), 83 (37), 55 (37), 43 (15), 27 (24), no other peaks >10%. IR (KBr): 1/λ=2456 (m), 3267 (s), 2915 (m), 2859 (m), 2116 (w), 1776 (s), 1700 (s) cm^{-1}. HR-MS (EI): calcd for $C_{13}H_{15}NO_3$: 233.10519; found. 233.10606 [M]$^+$.

3.7.26. 5-Ethyl-3a,4,7,7a-tetrahydro-2-methyl-4-(prop-2-ynyloxy)-2*H*-isoindole-1,3-dione (15a). Procedure B. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=1/3): 0.44. Yield: 67%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=5.70 (m, 1H, CH$_2$C*H*=C), 4.33 (1H, d, *J*=2.37 Hz, OC*H*CH), 3.99 (1H, m, CHC*H*CO), 3.91 (1H, m, CH$_2$C*H*CON), 3.04 (m, 2H, OC*H*$_2$C≡CH), 2.76 (s, 3H, CONC*H*$_3$), 2.38 (m, 1H, *H*C≡CCH$_2$), 2.14 (m, 2H, C=CHC*H*$_2$CH), 0.93 (t, 3H, *J*=7.03 Hz, C*H*$_3$CH$_2$C=CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=180.0 and 176.5 (2 *C*ONCH$_3$), 141.3 (CH$_2$*C*=CH), 123.2 (CH$_2$*C*H=CEt), 79.8 (HC≡*C*CH$_2$), 77.4 (H*C*≡CCH$_2$), 72.4 (O*C*HCH), 55.2 (OC*H*$_2$C≡CH), 45.4 (OCH*C*HCO), 36.5 (CH$_2$*C*HCO), 27.7 (*C*H$_2$CHCH), 24.1 (CONC*H*$_3$), 22.0 (CH$_3$*C*H$_2$C=CH), 11.6 (*C*H$_3$CH$_2$C=CH). MS (EI, 70 eV): *m/z* (%)=247 (6) [M]$^+$, 218 (34), 208 (29), 191 (36), 136 (75), 123 (31), 112 (25), 107 (63), 95 (35), 91 (100), 79 (95), 69 (27), 58 (19), 53 (26), 39 (77), 29 (43), no other peaks >10%. IR (KBr): 1/λ=3459 (w), 3263 (s), 2963 (s), 2116 (w), 1776 (s), 1708 (s) cm^{-1}. HR-MS (EI): calcd for $C_{14}H_{17}NO_3$: 247.12084; found. 247.11924 [M]$^+$.

3.7.27. 3a,4,7,7a-Tetrahydro-2,5,7-trimethyl-4-(prop-2-ynyloxy)-2*H*-isoindole-1,3-dione (16a). Procedure B. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.5. Yield: 84% Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=5.54 (m, 1H, CHC*H*=CCH$_3$), 4.29 (m, 1H, OC*H*CH), 4.26 (m, 2H, OC*H*$_2$C≡CH), 3.45 (m, 1H, OCHC*H*CO), 3.41 (m, 1H, CH$_2$C*H*CO), 3.07 (m, 1H, *H*C≡C), 2.76 (s, 3H, CONC*H*$_3$), 2.50 (m, 1H, CH$_3$C*H*CH), 1.71 (s, 3H, C*H*$_3$C=CH), 1.21 (d, 3H, *J*=7.13 Hz, 3H, C*H*$_3$CHCH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=177.7 and 175.7 (2 *C*ONCH$_3$), 135.8 (CH$_3$*C*=CH), 129.0 (CHC*H*=CCH$_3$), 80.0 (H*C*≡C), 77.4 (HC≡*C*), 73.1 (O*C*HCH), 56.0 (O*C*H$_2$C≡CH), 43.6 (OCH*C*HCO), 42.2 (CH$_3$CH*C*HCO), 28.5 (CH$_3$*C*HCH), 24.2 (CONC*H*$_3$), 19.6 (*C*H$_3$C=CH), 17.2 (*C*H$_3$CHCH). MS (EI, 70 eV): *m/z* (%)=247 (7) [M]$^+$, 232 (11), 208 (13), 193 (19), 136 (100), 123 (32), 107 (45), 105 (14), 95 (37), 69 (36), 55 (19), 39 (55), no other peaks >10%. IR (KBr): 1/λ=3435 (m), 3264 (s), 3001 (m), 2963 (m), 2825 (m), 2125 (w), 1767 (s), 1689 (s) cm^{-1}. HR-MS (EI): calcd for $C_{14}H_{17}NO_3$: 247.12084; found. 247.11928 [M]$^+$.

3.7.28. 5,7-Diethyl-3a,4,7,7a-tetrahydro-2-methyl-4-(prop-2-ynyloxy)-2*H*-isoindole-1,3-dione (17a). Procedure B. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=1/3): 0.5. Yield: 80%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=5.39 (m, 1H, EtC=C*H*CH), 4.35 (d, 1H, *J*=2.37 Hz, OC*H*CH), 4.32 (m, 2H, OC*H*$_2$C≡CH), 3.45 (m, 1H, *H*C≡CCH$_2$), 3.13 (dd, 1H, *J*=6.34, 2.37 Hz, OCHC*H*CO), 2.82 (m, 1H, EtCHC*H*CO), 2.71 (s, 3H, CONC*H*$_3$), 2.12 (m, 1H, EtC*H*CH), 2.02 (m, 2H, CH$_3$C*H*$_2$C=CH), 1.86 and 1.59 (both m, both 1H, CH$_3$C*H*$_2$CH), 0.94 (t, 3H, *J*=7.33 Hz, C*H*$_3$CH$_2$C=CH), 0.85 (t, 3H, *J*=7.33 Hz, 3H, C*H*$_3$CH$_2$CH). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=177.4 and 175.4 (2 CONCH$_3$), 142.5 (Et*C*=CH), 124.8 (CH*C*H=CEt), 80.1 (H*C*≡CCH$_2$), 77.5 (HC≡*C*CH$_2$), 73.7 (O*C*HCH), 56.0 (O*C*H$_2$), 42.6 (O*C*HCHCO), 41.8 (EtCH*C*HCO), 36.1 (Et*C*HCH), 24.6 and 24.2 (2 *C*H$_2$), 24.1 (CONC*H*$_3$), 12.9 and 12.5 (2 *C*H$_3$). MS (EI, 70 eV): *m/z* (%)=275 (7) [M]$^+$, 246 (62), 236 (22), 219 (85), 192 (16), 163 (43), 151 (32), 135 (40), 125 (79), 105 (53), 91 (60), 79 (56), 67 (22), 55 (81), 41 (45), 39 (100), 29 (70), no other peaks >10%. IR (KBr): 1/λ=3451 (m), 3265 (m), 2964 (s), 2935 (s), 2875 (s), 2116 (w), 1772 (s), 1699 (s), 1435 (s), 1383 (s), 1333 (m), 1287 (s), 1209 (m), 1110 (s), 1076 (s), 1040 (m), 979 (m), 916 (w), 894 (w), 861 (w), 840 (w), 815 (w), 776 (w), 722 (w), 700 (w), 624 (w) 576 (w), 493 (w) cm^{-1}. HR-MS (EI): calcd for $C_{16}H_{21}NO_3$: 275.15214; found. 275.15208 [M]$^+$.

3.7.29. 3-Phenyl propynoic acid amide. Procedure E. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.11. Yield: 97%. Colorless solid. Mp: 99–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.15 and 7.67 (both s, both 1H, NH_2), 7.57–7.40 (m, 5H, 5 C*H*-Ar). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 153.9 (*C*O), 132.1 and 128.9 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 130.2 (*p*-*C*H-Ar), 119.9 (*i*-*C*-Ar), 84.3 (Ph*C*≡C), 82.9 (PhC≡*C*). MS (EI, 70 eV): *m/z* (%) = 145 (47) $[M]^+$, 129 (100) $[M-NH_2]^+$, 75 (21), no other peaks >10%. IR (KBr): 1/λ = 3383 (s), 3179 (s), 3048 (s), 2775 (m), 2526 (w), 2301 (w), 2223 (s) cm^{-1}. HR-MS (EI): calcd for C_9H_7NO: 145.05276; found. 145.05238 $[M]^+$.

3.7.30. Propynoic acid amide. Procedure E. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.05. Yield: 95%. Colorless solid. Mp: 73 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.06 and 7.65 (both s, both 1H, NH_2), 4.04 (s, 1H, *H*C≡CCO). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 153.3 (*C*O), 78.5 (H*C*≡C), 75.5 (HC≡*C*). MS (EI, 70 eV): *m/z* (%) = 69 (55) $[M]^+$, 54 (100) $[M-NH_2]^+$, 44 (29), 41 (75), no other peaks >10%. IR (KBr): 1/λ = 3295 (s), 3207 (s), 2791 (m), 2111 (s), 1664 (s), 1616 (s), 1388 (s), 1133 (s), 833 (m), 723 (m), 681 (s), 657 (s), 544 (m) cm^{-1}. Elemental analysis: calcd for C_3H_3NO: C (52.17%); H (4.38%); N (20.28%); found. C (52.43%); H (4.41%); N (20.38%).

3.7.31. Tetrolic acid amide. Procedure E. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.06. Yield: 70%. Colorless solid. Mp: 82 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.80 and 7.36 (both s, both 1H, NH_2), 1.91 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 154.2 (*C*O), 87.3 (CH_3C≡C), 75.9 (CH_3C≡*C*), 3.0 (CH_3). MS (EI, 70 eV): *m/z* (%) = 83 (81) $[M]^+$, 67 (100) $[M-NH_2]^+$, 56 (28), 44 (16), 39 (69), 28 (19), no other peaks >10%. IR (KBr): 1/λ = 3311 (s), 3160 (s), 2801 (w), 2253 (s), 2136 (w), 1667 (s), 1614 (s), 1401 (s), 1309 (w), 1137 (s), 748 (m), 719 (m), 589 (m), 478 (m) cm^{-1}. Elemental analysis: calcd for C_4H_5NO: C (57.82%); H (6.07%); N (16.86%); found. C (57.54%); H (6.11%); N (16.93%).

3.7.32. Pent-2-ynoic acid amide. Procedure E. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.06. Yield: 96%. Colorless solid. Mp: 88 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.81 and 7.36 (both s, both 1H, NH_2), 2.30 (q, J = 7.5 Hz, 2H, CH_2), 1.09 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 153.3 (*C*O), 78.5 (H*C*≡C), 75.5 (HC≡*C*), 23.6 (*C*H_2), 13.4 (*C*H_3). MS (EI, 70 eV): *m/z* (%) = 97 (79) $[M]^+$, 81 (80) $[M-NH_2]^+$, 54 (100), 44 (28), 39 (25), 27 (40), no other peaks >10%. IR (KBr): 1/λ = 3310 (s), 2986 (s), 2942 (m), 2881 (m), 2793 (m), 2241 (s), 1663 (s), 1391 (s), 1315 (s), 1133 (s), 1056 (w), 936 (w), 810 (m), 720 (s), 590 (m), 540 (m), 443 (m) cm^{-1}. HR-MS (EI): calcd for C_5H_7NO: 97.05276; gef. 97.05302 $[M]^+$.

3.7.33. Tris(prop-2-ynyloxy)methane. Procedure F. Yield: 47%. Colorless liquid. Bp: 123 °C (2.1×10^{-2} bar). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.63 (s, 1H, C*H*O), 4.37 (dd, J = 0.79, 1.58 Hz, 6H, 3 CH_2), 3.58 (m, 3H, C≡C*H*). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ = 110.2 (*C*HO), 79.3 (H*C*≡CCH$_2$), 77.4 (HC≡*C*CH$_2$), 52.0 (*C*H$_2$). MS (EI, 70 eV): *m/z* (%) = 178 (1) $[M]^+$, 123 (100), 39 (52), no other peaks >10%. IR (KBr): 1/λ = 3293 (s), 2934 (m), 2875 (m), 2122 (m), 1448 (m), 1345 (m), 1268 (m), 1142 (s), 1050 (s), 982 (m), 919 (m), 901 (m), 643 (s) cm^{-1}. HR-MS (EI): calcd for $C_{10}H_{10}O_3$: 178.06299; found. 178.06318 $[M]^+$.

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Straightforward synthesis of di-, tri- and tetracyclic lactams via catalytic Pauson–Khand and Alder–Ene reactions of MCR products

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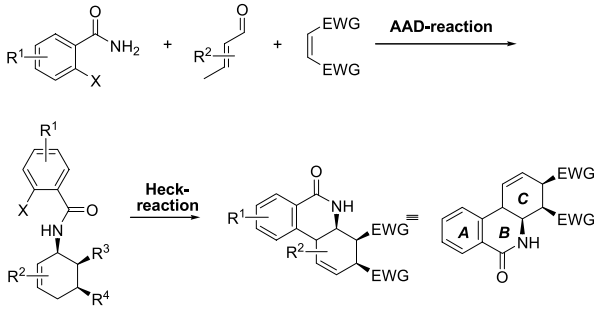
Abstract—Novel enynes have been synthesized by three-component coupling reactions of aldehydes, dienophiles and amides (AAD-reaction; see preceding manuscript) and were converted via catalytic Pauson–Khand- and Alder–Ene-reactions to give functionalized di-, tri- and tetracyclic lactam derivatives in good yields.

1. Introduction

Due to their increased efficiency and practicability, multi-component[1] and domino reactions[2] are more and more used in academia and industry.[3] Nowadays, a multitude of interesting building blocks is available by such reactions. Subsequent catalytic refinement reactions of suitably functionalized multicomponent products offer numerous possibilities for the synthesis of potentially biologically active compounds. Obviously, the combination of MCRs and catalytic methods allows also for the enhancement of structural diversity in an elegant and easy way.

In recent years, we have been interested in the development of transition metal-catalyzed three- and four-component coupling reactions. For instance, our investigations included hydroaminomethylation of olefins,[4] and amidocarbonylation of aldehydes.[5] With respect to the latter work,[6] we discovered novel multicomponent reactions, in which amides (AAD-reaction), or anhydrides (ANAD-reaction), or orthoesters (ALAD-reaction) react with aldehydes and dienophiles, respectively.[7] The synthetic utility of these multi-component reactions has been demonstrated in the preparation of highly substituted anilines,[8] luminols,[9] bicyclo[2.2.2]oct-2-enes,[10] enantiomerically pure cyclohexenols,[11] as well as cyclohexenylamino,[12] and phthalic acid derivatives.[13]

Very recently, our AAD-reaction protocol was also applied to the synthesis of suitably functionalized aryl halides, which were subsequently converted via palladium-catalyzed Heck reactions into phenanthridone derivatives (Scheme 1).[14] Following this synthetic strategy of combining MCRs with palladium-catalyzed coupling reactions, we became interested in the synthesis of cyclohexenes bearing a tethered alkyne moiety, which are commonly known as enyne-reaction precursors[15] (Scheme 2).



Scheme 1. Synthesis of phenanthridones via AAD–eck reaction sequence.

These compounds should give access to di-, tri- and tetracyclic lactam derivatives by applying transiton metal-catalyzed ring-closing reactions in the following step. Often lactams show interesting biological activity either themselves or they have been used as building block for the synthesis of biologically active molecules. Prominent compounds of this class, such as kainic acid,[16] dendrobine,[17] isocynometrine,[18] and isopilocapine[19] are exemplarly mentioned here (Fig. 1).

Keywords: Enynes; Multicomponent reactions; Pauson–Khand reactions; Alder-ene reactions.
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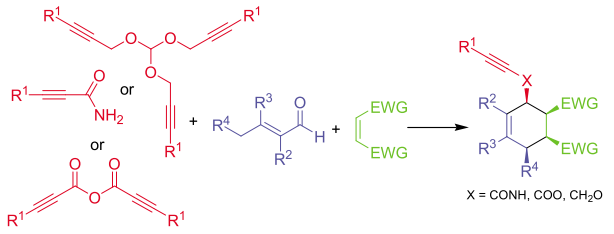


Scheme 2. Schematic representation of the AAD-, ANAD-, ALAD-reaction protocol for the synthesis of enyne-reaction precursors.

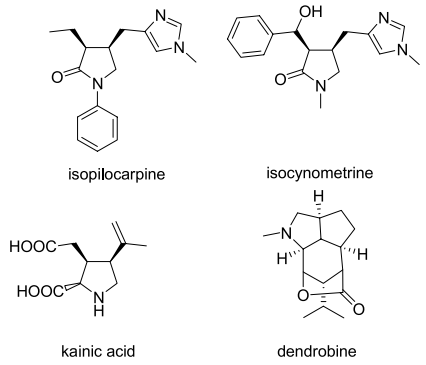
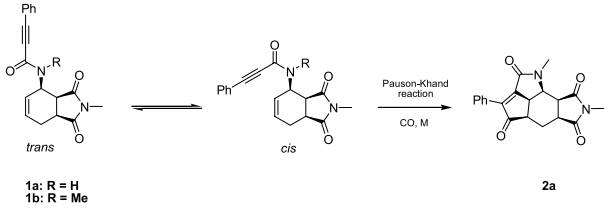


Figure 1. Selected examples of pharmaceutically interesting lactams.



Scheme 3. Cis/trans effect of AAD-enyne precursors.

Herein, we report for the first time on the application of alkyne-substituted MCR adducts as substrates in the intramolecular transition metal-catalyzed Pauson–Khand- and Alder–Ene-reaction.

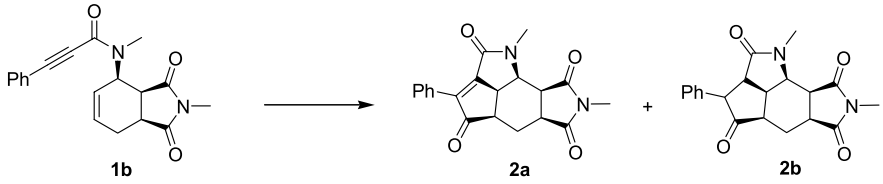
2. Results and discussion

The transition metal-catalyzed [2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide represents an elegant procedure for the preparation of cyclopentenones. Since its discovery by Pauson and Khand[20] in 1973 this reaction (PKR) has received much attention with regard to synthetic elaborations and mechanistic studies.[21] More specifically, a number of procedures using Co-,[22] Ru-,[23] Rh-,[24] and Ir[25]-catalysts have been developed. Taking into account the increase of structural diversity by the application of the Pauson–Khand methodology, we were interested in the use of MCR-enyne-precursors for the synthesis of highly fused lactam-containing ring systems. Initially, as a model reaction, the conversion of the unprotected reaction precursor **1a**[26] was studied (Scheme 3). Despite numerous variation of the catalysts (Co, Rh, and Ru complexes) and reaction conditions (80–140 °C, 3–20 bar CO) in no case, the desired cycloaddition product was obtained. In accordance with the results of other groups working in the field of enyne amide chemistry, we assume that the trans-conformer of the amide is predominant, which is unfavorable for cyclopentenone formation.[27]

Therefore, in the next set of experiments, we studied the conversion of the protected Pauson–Khand reaction precursor **1b**.[15] Among the various metal complexes screened, $Ru_3(CO)_{12}$ and $Co_2(CO)_8$ were found to be active catalysts. Thus, in the presence of 10 mol% $Co_2(CO)_8$ in THF at 80 °C and 3 bar of carbon monoxide the desired cycloaddition product **2a** was obtained in 11% yield (Table 1, entry 1).

Increasing the temperature to 100 °C slightly improves the yield of **2a** to 16% (Table 1, entry 2). A more significant improvement was achieved by raising the reaction temperature to 120 °C. In this case, apart from the isolation of the desired cyclopentenone **2a** (53% yield), we also observed the formation of the cyclopentanone **2b** in 26% yield (Table 1, entry 3).

Table 1. Screening of **1b** in the Pauson–Khand reaction



Entry	Catalyst	mol (%)	Solvent	*T* (°C)	p(CO) (bar)	Yield **2a** (%)	Yield **2b** (%)
1	$Co_2(CO)_8$	10	THF	80	3	11	0
2	$Co_2(CO)_8$	10	THF	100	3	16	0
3	$Co_2(CO)_8$	10	THF	120	3	53	26
4	$Co_2(CO)_8$	10	THF	80	6	15	0
5	$Co_2(CO)_8$	10	THF	120	6	20	33
6	$Co_2(CO)_8$	5	THF	120	3	40	18
7	$Co_2(CO)_8$	10	NMP	120	3	0	0
8	$Co_2(CO)_8$	10	Toluene	120	3	41	18
9	$Ru_3(CO)_{12}$	10	THF	120	3	23	0
10	$Ru_3(CO)_{12}$	10	THF	120	10	70	0
11	$Ru_3(CO)_{12}$	10	THF	120	20	61	0
12	$Ru_3(CO)_{12}$	5	THF	120	10	56	0
13	$Ru_3(CO)_{12}$	10	Toluene	120	10	36	0

Conditions: 2 mmol **1b**, catalyst, 30 mL solvent, CO, 16 h.

Table 2. Application of AAD-enyne-precursors in the Pauson–Khand reaction

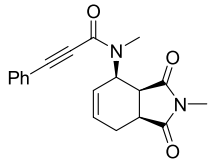
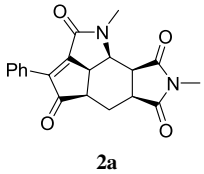
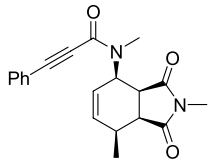
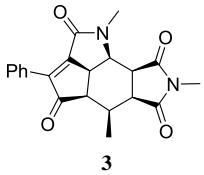
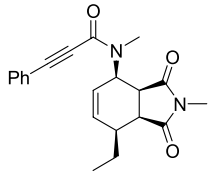
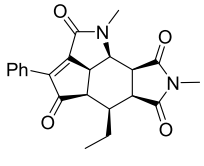
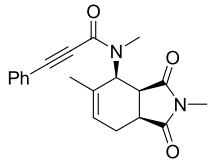
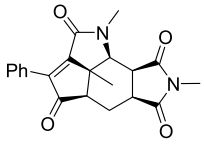
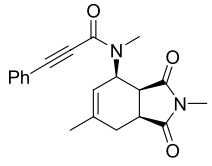
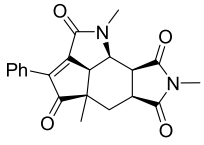
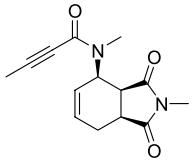
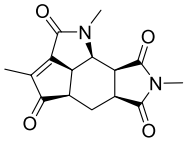
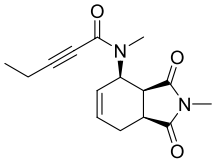
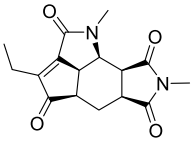
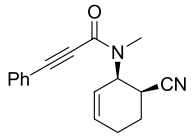
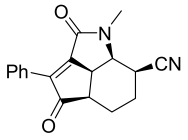
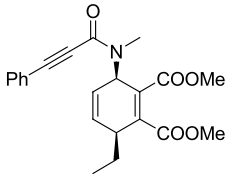
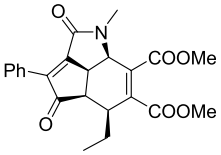
Entry	AAD-precursor	PKR-product	Yield proced. A[a] (%)	Yield proced. B[b] (%)
1	 **1b**	 **2a**	53	70
2	 **1c**	 **3**	68	61
3	 **1d**	 **4**	71	63
4	 **1e**		0	0
5	 **1f**		0	0
6	 **1g**	 **5**	42	0
7	 **1h**	 **6**	55	17
8	 **1i**	 **7**	68	66

Table 2 (*continued*)

Entry	AAD-precursor	PKR-product	Yield proced. A[a] (%)	Yield proced. B[b] (%)
9	 **1j**		0	0

[a] Conditions: AAD-precursor (2 mmol), 10 mol% $Co_2(CO)_8$, 30 mL THF, 120 °C, 3 bar CO, 16 h.
[b] Conditions: AAD-precursor (2 mmol), 10 mol% $Ru_3(CO)_{12}$, 30 mL THF, 120 °C, 10 bar CO, 16 h.

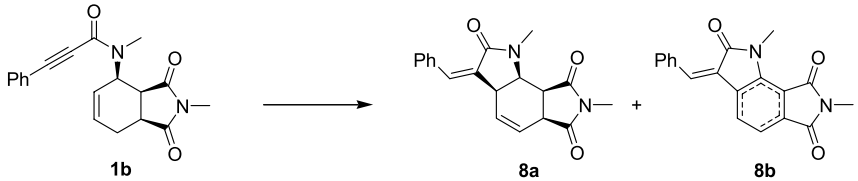
Next, we studied the influence of an increased pressure of CO (6 bar), but at 80 and 120 °C the cyclopentenone yield dropped (Table 1, entries 4–5). Furthermore, lowering the catalyst amount to 5 mol%, afforded **2a** in 40% yield (Table 1, entry 6). Finally, a change of the solvent to NMP and toluene resulted in yields of 0 and 41%, respectively (Table 1, entries 7–8). In a second approach, $Ru_3(CO)_{12}$ was used as a catalyst under the above mentioned best conditions. Here, only a low yield (23%) of **2a** was obtained (Table 1, entry 9). However, raising the carbon monoxide pressure to 10 bar led to the best yield of 70% (Table 1, entry 10). Further enhancement of the CO pressure to 20 bar, resulted in a slightly decreased yield of 61% (Table 1, entry 11). Again, lowering the catalyst amount to 5 mol% led to a decrease of the product yield (56%, Table 1, entry 12). Also the use of toluene as solvent resulted in a significant reduction of the cyclopentenone yield to 36% (Table 1, entry 13).

Next, we applied both catalytic systems under optimized reaction conditions for the conversion of a broader range of enynes. First, we examined the influence of the substitution pattern of different cyclohexene scaffolds. In the case of methyl- and ethyl-substituted compounds **1c** and **1d**, the cycloaddition products **3** and **4** were obtained in good yields, 68 and 71%, respectively, with the $Co_2(CO)_8$-method. Using the $Ru_3(CO)_{12}$-catalyst led to slightly lower yields of 61% (**3**) and 63% (**4**) (Table 2, entries 2–3). Then, we studied the conversion of enynes **1e**, **1f** possessing methyl-groups directly attached to the double bond. Surprisingly, in all experiments no cyclopentenone was obtained and the starting material was completely reisolated (Table 2, entries 4–5). To examine the tolerance of substituents directly attached to the alkyne terminus, precursors **1g** and **1h** were converted in the presence of both catalysts. In case of methyl- and ethyl-substitution the resulting cyclopentenones **5** and **6** were obtained in 42 and 55% yield, respectively, using $Co_2(CO)_8$ as the catalyst.

By contrast, with $Ru_3(CO)_{12}$, compound **5** was not obtained and **6** was isolated in only 17% yield (Table 2, entries 6–7). Finally, we studied the conversion of the cyclohexene-carbonitrile- **1i** and the dimethyl cyclohexadiene dicarboxylate- **1j** derived enyne precursors. While the cyclopentenone **7** was isolated in yields of 68 and 66% (Table 2, entry 8), the latter reaction did not give the desired cycloadduct (Table 2, entry 9).

Apart from Pauson–Khand reactions, enynes can be advantageously involved in other catalytic

Table 3. Screening of **1b** in the Alder–Ene reaction



Entry	$Pd(OAc)_2$ (mol%)	Ligand	(mol%)	Solvent	*t* (h)	*T* (°C)	Additive	Conversion (%)	Yield **8a** (%)	Yield **8b** (%)
1	5	PPh_3	10	Toluene	16	60	—	41	27	0
2	5	dppe	5	Toluene	16	60	—	20	11	0
3	5	dppp	5	Toluene	16	60	—	33	17	0
4	5	dppb	5	Toluene	16	60	—	45	32	0
5	5	dppb	5	Toluene	16	80	—	61	44	8
6	5	dppb	5	Toluene	16	100	—	100	53	21
7	5	dppb	5	Toluene	40	60	—	51	36	0
8	10	dppb	10	Toluene	24	60	—	100	62	0
9	10	dppb	10	Toluene	24	60	HOAc	98	0	0
10	10	dppb	10	Toluene	24	60	CF_3COOH	100	0	0
11	10	dppb	10	Toluene	24	60	*p*-TSA	100	0	0
12	10	dppb	10	THF	24	60	—	100	45	0

Reaction conditions: 1 mmol **1b**, catalyst, 10 mL solvent.

functionalizations. We were particularly interested in the application of our MCR-enyne-precursors in Alder–Ene reactions. Although the methodology of transition metal catalyzed Alder–Ene type reactions is well established,[28] only a few reports exist on amide tethered enyne-precursors.[29]

Starting with a screening of the reported Pd-, and Rh-sources, $Pd(OAc)_2$ was found to be an active catalyst. Again the conversion of **1b** was used as a model reaction. Applying 5 mol% $Pd(OAc)_2$/2 PPh_3 in toluene at 60 °C and 16 h led to the cyclization product **8a** in 27% yield (Table 3, entry 1). Further screening by changing the ligand to dppe, dppp, and dppb afforded **8a** in 11, 17, and 32% yield, respectively (Table 3, entries 2–4). Due to the low conversion rate (up to 45%, Table 3, entry 4), we raised the temperature to 80 and 100 °C in the presence of dppb as the ligand. Beside the formation of increased yields (44 and 53%, Table 3, entries 5–6), we also observed the formation of double bond regioisomers **8b** (8 and 21%, Table 3, entries 5–6).

Clearly, this is a result of the elevated temperatures. In order to achieve full conversion at a lower temperature, we increased the catalyst amount to 10 mol%. In this case, the desired lactam-derivative **8a** was isolated in 62% yield (Table 3, entry 8). The potential influence of acids in Alder–Ene reactions, was also examined. Unfortunately, in no case was the desired product **8a** obtained (Table 3, entries 9–11). Also changing the solvent to THF led to a lower yield of 45% (Table 3, entry 12).

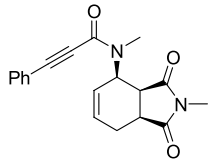
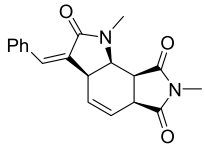
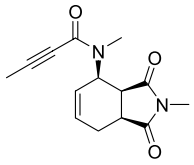
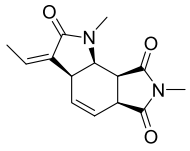
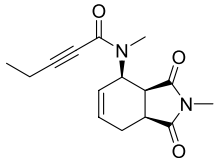
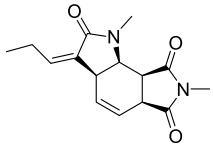
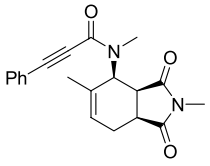
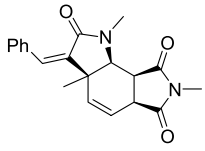
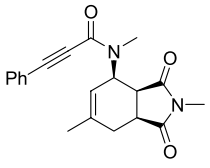
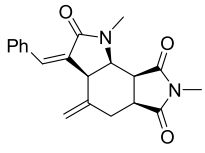
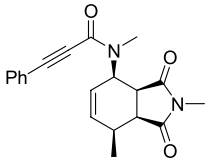
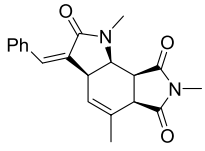
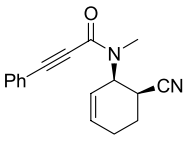
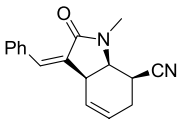
Next, we applied our best reaction conditions for the conversion of several enyne amides. To examine the influence of different alkyne moieties, again we tested the methyl- and ethyl-substituted AAD-adducts **1g** and **1h**.

The corresponding tricyclic lactams **9** and **10** were obtained in 44 and 53% yield (Table 4, entries 2–3). The lactamization reaction of substrates **1e** and **1f**, in which the double bond is substituted by a methyl group was also investigated. Whereas **1e** did not react, compound **1f** led to the Alder–Ene product **11** exclusively, possessing an exocyclic double bond in 62% yield (Table 4, entry 5). Moreover, cyclization of **1c** remained unsuccessful (Table 4, entry 6). On account of the all *syn*-relationship of all substituents attached to the cylohexene scaffold, β-hydride elimination cannot take place here. Finally, conversion of the carbonitrile derived enyne amide, gave the corresponding lactam **12** in 65% yield (Table 4, entry 7).

For all products, one- and two-dimensional NMR experiments unambiguously established the stereochemical structure. Analyses of the ^1H–^1H coupling constants of the amide moiety as well as the other alkyl substituents on the cyclohexene ring revealed the exclusive formation of the all-*syn* diastereomers. In case of products **8a**, **9**, **10**, **11** and **12** NOE-experiments unambiguously revealed the configuration of the exocyclic trisubstituted double bond. In general, the resulting cyclohexenes have a bowl- or crown-shaped structure.

In summary, we have synthesized a range of new fused lactam-containing ring systems, taking advantage of the three-component coupling reactions of aldehydes, amides, and dienophiles and subsequent conversion of the resulting products by transition metal catalyzed Pauson–Khand- and Alder–Ene reaction protocols.

Table 4. Application of AAD-enyne-precursors in the Alder–Ene reaction

Entry	AAD-precursor	Alder–Ene product	Yield (%)
1	 **1b**	 **8a**	62
2	 **1g**	 **9**	44
3	 **1h**	 **10**	53
4	 **1e**		0
5	 **1f**	 **11**	62
6	 **1c**		0
7	 **1i**	 **12**	65

Reaction conditions: AAD-precursor (2 mmol), 10 mol% $Pd(OAc)_2$, 10 mol% dppb, 20 mL toluene, 24 h, 60 °C.

3. Experimental

3.1. General

Solvents were distilled from CaH_2 and stored over 3 Å MS. Unless otherwise noted, all reagents were used as received from commercial suppliers. Silica gel column chromatography was performed with 230–400 mesh ASTM silica gel from Merck. Melting points were recorded on a Galen III (Cambridge Instruments) and are uncorrected. IR spectra as solids were recorded as nujol mulls using KBr plates or KBr pellets on a Nicolet Magna 550, liquids were analyzed as capillary films. MS were obtained on an AMD 402/3 from AMD Intectra (EI, 70 eV). NMR data were recorded on a Bruker ARX 400 with QNP probe head. (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at 25 °C. GC analyses were performed on a HP 6890 equipped with a HP-5 capillary column (5% phenylmethylsiloxane, $L=30$, $d=250$ μm, $d_{film}=0.25$ μm) and a FID detector. Quantitative GC analyses were referenced to internal hexadecane or dodecane.

3.2. Procedure A (Pauson–Khand reaction with $Co_2(CO)_8$)

Protected AAD-enyne precursor (2 mmol), $Co_2(CO)_8$ (10 mol%), and THF (20 mL) were combined in a Schlenk vessel and stirred for 30 min. Then, the reaction mixture was filled in an 100 mL autoclave. Afterwards, the reaction was stirred at 120 °C for 16 h under an initial CO pressure of 3 bar. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding products.

3.3. Procedure B (Pauson–Khand reaction with $Ru_3(CO)_{12}$)

Protected AAD-enyne precursor (2 mmol), $Ru_3(CO)_{12}$ (10 mol%), and THF (20 mL) were combined in a Schlenk vessel and stirred for 30 min. Then, the reaction mixture was filled in an 100 mL autoclave. Afterwards, the reaction was stirred at 120 °C for 16 h under an initial CO pressure of 10 bar. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding products.

3.4. Procedure C (Alder–Ene reaction)

Protected AAD-enyne precursor (2 mmol), $Pd(OAc)_2$ (10 mol%), dppb (10 mol%), and toluene (20 mL) were combined in a Schlenk vessel. Then, the reaction was stirred at 60 °C for 24 h. After cooling, all volatile compounds were removed under reduced pressure. Silica gel flash chromatography (*n*-heptane/EtOAc) afforded the corresponding products.

3.4.1. 1,7-Dimethyl-3-phenyl-4a,5,5a,8a,8b,8c-hexahydro-1*H*-1,7-diaza-cyclopenta[*cd*]-s-indacene-2,4,6,8-tetraone (2a). Procedure A, B. 16 h. R_f (SiO_2, *n*-heptane/EtOAc =1:1): 0.14. Yield (procedure A): 53%; yield (procedure B): 70%. Colorless solid. Mp: 186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.67$–7.41 (m, 5H, *H*-Ar), 4.28 (m, 1H, C*H*NCH$_3$), 4.08 (s, 3H, CHNC*H*$_3$), 3.45 (m, 1H, PhC=CC*H*), 3.39 (m, 1H, NCHC*H*CON), 3.18 (m, 1H, CH$_2$C*H*CON), 3.11 (m, 1H, COC*H*CH$_2$), 2.74 (s, 3H, CHCONC*H*$_3$), 2.18–2.09 (m, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): $\delta=208.3$ (C=C*C*OCH), 178.4 and 177.2 (2 *C*ONCH$_3$), 174.4 (C=C*C*ONCH$_3$), 158.3 (Ph*C*=C), 137.3 (PhC=*C*), 133.5 (*i*-*C*-Ar), 129.0 and 127.1 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 128.0 (*p*-*C*H-Ar), 59.4 (*C*HNCH$_3$), 55.9 (N*C*H$_3$), 48.2 (CH$_2$*C*HCOC=C), 44.0 (NCH*C*HC=C), 36.5 (NCH*C*HCON), 30.8 (CH$_2$*C*HCON), 27.4 (CHCONC*H*$_3$), 23.7 (COCH*C*H$_2$CH). MS (EI, 70 eV): *m*/*z* (%)=350 (100) [M]$^+$, 335 (22), 250 (20), 222 (16), 211 (13), 204 (25), 164 (16), 141 (13), 129 (26), 115 (27), 91 (18), 77 (30), 57 (13) 44 (16), no other peaks >10%. IR (KBr): $1/\lambda=3430$ (m), 2949 (m), 1777 (m), 1709 (s), 1638 (m), 1583 (s), 1496 (m), 1434 (s), 1376 (s), 1281 (s), 1236 (s), 1161 (m), 1071 (m), 1017 (m), 960 (m), 932 (w), 813 (w), 791 (w), 729 (m), 702 (m), 647 (w), 557 (w), 478 (w) cm^{-1}. HR-MS (EI): calcd for $C_{20}H_{18}N_2O_4$: 350.12666; found 350.12645 [M]$^+$.

3.4.2. 1,7-Dimethyl-3-phenyl-octahydro-1,7-diaza-cyclopenta[*cd*]-s-indacene-2,4,6,8-tetraone (2b). Procedure A, B. 16 h. R_f (SiO_2, *n*-heptane/EtOAc =1:1): 0.36. Yield (procedure A): 26%; yield (procedure B): 0%. Colorless solid. Mp: 152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.36$–7.05 (m, 5H, *H*-Ar), 4.54 (m, 1H, C*H*NCH$_3$), 3.79 (s, 3H, CHNC*H*$_3$), 3.71 (m, 1H, PhC*H*CH), 3.36 (m, 1H, NCHC*H*CO), 3.03 (m, 1H, CH$_2$C*H*CON), 2.93 (m, 1H, PhCHC*H*), 2.74 (s, 3H, CHCONC*H*$_3$), 2.65 (m, 1H, COCHC*H*CH), 2.49 (m, 1H, COC*H*CH$_2$), 2.49–2.39 and 2.29–2.19 (both m, both 1H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): $\delta=207.7$ (C=C*C*OCH), 179.8 and 178.4 (2 *C*ONCH$_3$), 174.4 (C=C*C*ONCH$_3$), 138.3 (*i*-*C*-Ar), 129.5 and 128.1 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 127.8 (*p*-*C*H-Ar), 62.7 (*C*HNCH$_3$), 57.0 (N*C*H$_3$), 53.9 (Ph*C*HCH), 53.6 (Ph*C*HCH), 45.5 (CH$_2$*C*HCOC=C), 41.7 (NCH*C*HCHCH), 38.0 (NCH*C*HCON), 30.6 (CH$_2$-*C*HCON), 27.4 (CHCONC*H*$_3$), 23.2 (COCH*C*H$_2$CH). MS (EI, 70 eV): *m*/*z* (%)=352 (100) [M]$^+$, 323 (14), 212 (11), 186 (18), 179 (12), 160 (10), 131 (29), 115 (11), 91 (13), 77 (21), no other peaks >10%. IR (KBr): $1/\lambda=3449$ (m), 3029 (w), 2947 (m), 1776 (m), 1701 (s), 1640 (s), 1497 (m), 1437 (s), 1384 (s), 1334 (m), 1281 (s), 1128 (m), 1070 (m), 1031 (m), 1001 (m), 951 (w), 916 (w), 875 (w), 734 (m), 699 (m), 649 (w), 631 (w), 487 (w) cm^{-1}. HR-MS (EI): calcd for $C_{20}H_{20}N_2O_4$: 352.14231; found 352.14236 [M]$^+$.

3.4.3. 1,5,7-Trimethyl-3-phenyl-4a,5,5a,8a,8b,8c-hexahydro-1*H*-1,7-diaza-cyclopenta[*cd*]-s-indacene-2,4,6,8-tetraone (3). Procedure A, B. 16 h. R_f (SiO_2, *n*-heptane/EtOAc =1:1): 0.12. Yield (procedure A): 68%; yield (procedure B): 61%. Colorless solid. Mp: 179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.65$–7.43 (m, 5H, *H*-Ar), 4.25 (m, 1H, C*H*NCH$_3$), 4.11 (s, 3H, CHNC*H*$_3$), 3.49 (m, 1H, PhC=CC*H*), 3.46 (m, 1H, NCHC*H*CON), 3.17 (m, 1H, CH$_3$CHC*H*CON), 3.17 (m, 1H, COC*H*CHCH$_3$), 2.72 (s, 3H, CHCONC*H*$_3$), 2.46 (m, 1H, CH$_3$C*H*CH), 1.31 (d, $J=7.33$ Hz, 3H, C*H*$_3$CHCH). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): $\delta=206.9$ (C=C*C*OCH), 179.1 and 178.6 (2 *C*ONCH$_3$), 173.9 (C=C*C*ONCH$_3$), 158.2 (Ph*C*=C), 137.1 (PhC=*C*), 133.7 (*i*-*C*-Ar), 129.2 and 127.3 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 128.4 (*p*-*C*H-Ar), 59.6 (*C*HNCH$_3$), 55.7 (N*C*H$_3$), 48.4 (CH*C*HCOC=C), 44.2 (NCH*C*HC=C), 36.7 (NCH*C*HCON), 32.1 (CH$_3$CH*C*HCON), 27.2 (CHCONC*H*$_3$),

24.6 (COCH*C*HCH$_3$), 17.6 (COCHCH*C*H$_3$). MS (EI, 70 eV): *m*/*z* (%)=364 (91) [M]$^+$, 337 (41), 321 (14), 307 (12), 247 (18), 225 (36), 211 (22), 193 (27), 178 (18), 165 (15), 129 (29), 118 (18), 105 (81), 94 (89), 77 (51), 55 (100), 43 (41), no other peaks >10%. IR (KBr): 1/λ=3448 (m), 2934 (m), 1744 (s), 1701 (s), 1620 (s), 1496 (m), 1436 (s), 1379 (s), 1283 (s), 1141 (m), 1086 (m), 1021 (m), 967 (m), 913 (w), 876 (w), 831 (w), 736 (w), 700 (m), 558 (w) cm^{-1}. HR-MS (EI): calcd for $C_{21}H_{20}N_2O_4$: 364.14231; found 364.14444 [M]$^+$.

3.4.4. 5-Ethyl-1,7-dimethyl-3-phenyl-4a,5,5a,8a,8b,8c-hexahydro-1*H*-1,7-diaza-cyclopenta[*cd*]-s-indacene-2,4,6,8-tetraone (4). Procedure A, B. 16 h. R_f (SiO_2, *n*-heptane/EtOAc =1:1): 0.15. Yield (procedure A): 71%; yield (procedure B): 63%. Colorless solid. Mp: 179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.72–7.41 (m, 5H, *H*-Ar), 4.26 (m, 1H, C*H*NCH$_3$), 4.12 (s, 3H, CHNC*H*$_3$), 3.49 (m, 1H, PhC=CC*H*), 3.45 (m, 1H, NCHC*H*CON), 3.18 (m, 1H, CH$_2$CHC*H*CON), 3.18 (m, 1H, COC*H*CHCH$_2$), 2.74 (s, 3H, CHCONC*H*$_3$), 2.48 (1H, m, CH$_2$C*H*CH), 1.95–1.78 (m, 2H, CH$_3$C*H*$_2$CH), 1.02 (t, *J*=6.93 Hz, 3H, C*H*$_3$CH$_2$CH). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ=208.0 (C=C*C*OCH), 178.1 and 178.5 (2 *C*ONCH$_3$), 173.6 (C=C*C*ONCH$_3$), 158.5 (Ph*C*=C), 137.3 (PhC=*C*), 133.6 (*i*-*C*-Ar), 129.3 and 127.3 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 128.5 (*p*-*C*H-Ar), 59.7 (*C*HNCH$_3$), 55.5 (NCH$_3$), 48.3 (CH*C*HCOC=C), 44.3 (NCH*C*HC=C), 36.6 (NCH*C*HCON), 32.2 (CH$_2$CH*C*HCON), 27.4 (CHCONC*H*$_3$), 24.5 (COCH*C*HCH$_2$), 22.7 (COCHCH*C*H$_2$), 13.6 (COCHCHCH$_2$*C*H$_3$). MS (EI, 70 eV): *m*/*z* (%)=378 (100) [M]$^+$, 362 (17), 250 (22), 233 (17), 179 (12), 165 (16), 129 (30), 91 (22), 77 (18), 57 (18), 44 (22), no other peaks >10%. IR (KBr): 1/λ=3447 (m), 2935 (m), 1748 (s), 1723 (s), 1625 (s), 1438 (s), 1381 (s), 1285 (s), 1144 (m), 1084 (m), 1028 (m), 964 (m), 922 (w), 853 (w), 741 (w), 654 (m), 446 (w) cm^{-1}. HR-MS (EI): calcd for $C_{22}H_{22}N_2O_4$: 378.15796; found 378.15822 [M]$^+$.

3.4.5. 1,3,7-Trimethyl-4a,5,5a,8a,8b,8c-hexahydro-1*H*-1,7-diaza-cyclopenta[*cd*]-s-indacene-2,4,6,8-tetraone (5). Procedure A, B. 16 h. R_f (SiO_2, *n*-heptane/EtOAc =1:1): 0.13. Yield (procedure A): 42%; yield (procedure B): 0%. Colorless solid. Mp: 221 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.25 (m, 1H, C*H*NCH$_3$), 4.11 (s, 3H, CHNC*H*$_3$), 3.45 (m, 1H, MeC=CC*H*), 3.42 (m, 1H, NCHC*H*CON), 3.22 (m, 1H, CH$_2$C*H*CON), 3.12 (m, 1H, COC*H*CH$_2$), 2.72 (s, 3H, CHCONC*H*$_3$), 2.22–2.13 (m, 2H, CHC*H*$_2$CH), 1.56 (s, 3H, *C*H$_3$C=C). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ=209.7 (C=C*C*OCH), 178.7 and 177.6 (2 *C*ONCH$_3$), 174.5 (C=C*C*ONCH$_3$), 158.1 (Me*C*=C), 135.8 (MeC=*C*), 59.5 (*C*HNCH$_3$), 55.2 (NCH$_3$), 48.7 (CH$_2$*C*HCOC=C), 44.4 (NCH*C*HC=C), 37.1 (NCH*C*HCON), 32.1 (CH$_2$-*C*HCON), 27.4 (CHCONC*H*$_3$), 23.8 (COCH*C*H$_2$CH), 9.7 (*C*H$_3$C=C). MS (EI, 70 eV): *m*/*z* (%)=288 (56) [M]$^+$, 262 (47), 164 (22), 149 (16), 140 (13), 98 (24), 79 (22), 55 (17), 44 (17), 28 (100), no other peaks >10%. IR (KBr): 1/λ=3315 (m), 2926 (m), 1777 (m), 1701 (s), 1435 (s), 1383 (s), 1345 (m), 1279 (s), 1262 (s), 1130 (m), 1083 (m), 1053 (m), 1017 (m), 968 (m), 920 (w), 842 (w), 732 (m), 684 (w), 649 (w), 601 (w), 551 (w) cm^{-1}. HR-MS (EI): calcd for $C_{15}H_{16}N_2O_4$: 288.19854; found 288.19868 [M]$^+$.

3.4.6. 3-Ethyl-1,7-dimethyl-4a,5,5a,8a,8b,8c-hexahydro-1*H*-1,7-diaza-cyclopenta[*cd*]-s-indacene-2,4,6,8-tetraone (6). Procedure A, B. 16 h. R_f (SiO_2, *n*-heptane/EtOAc = 1:1): 0.12. Yield (procedure A): 55%; yield (procedure B): 17%. Colorless solid. Mp: 208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.27 (m, 1H, C*H*NCH$_3$), 4.09 (s, 3H, CHNC*H*$_3$), 3.44 (m, 1H, EtC=CC*H*), 3.41 (m, 1H, NCHC*H*CON), 3.21 (m, 1H, CH$_2$C*H*CON), 3.13 (m, 1H, COC*H*CH$_2$), 2.74 (s, 3H, CHCONC*H*$_3$), 2.35 (m, 2H, C*H*$_2$C=C), 2.18–2.09 (m, 2H, CHC*H*$_2$CH), 1.23 (t, *J*=7.78 Hz, 3H, C*H*$_3$CH$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ=208.3 (C=C*C*OCH), 178.4 and 177.2 (2 *C*ONCH$_3$), 174.4 (C=C*C*ONCH$_3$), 155.4 (Et*C*=C), 136.4 (EtC=*C*), 59.2 (*C*HNCH$_3$), 55.7 (NCH$_3$), 48.3 (CH$_2$*C*HCOC=C), 44.2 (NCH*C*HC=C), 36.4 (NCH*C*HCON), 30.9 (CH$_2$*C*HCON), 27.3 (CHCONC*H*$_3$), 23.6 (COCH*C*H$_2$CH), 19.7 (CH$_3$*C*H$_2$), 11.6 (*C*H$_3$CH$_2$). MS (EI, 70 eV): *m*/*z* (%)=302 (100) [M]$^+$, 287 (16), 179 (34), 165 (12), 57 (13), no other peaks >10%. IR (KBr): 1/λ=3447 (m), 3091 (w), 2934 (m), 2877 (w), 1775 (m), 1694 (s), 1522 (w), 1436 (s), 1385 (s), 1347 (m), 1281 (s), 1222 (m), 1131 (m), 1087 (w), 1033 (m), 970 (w), 918 (w), 783 (w), 733 (m), 651 (w), 554 (w) cm^{-1}. HR-MS (EI): calcd for $C_{16}H_{18}N_2O_4$: 302.12666; found 302.12656 [M]$^+$.

3.4.7. 1,2,4,4a,5,6,7,7a-Octahydro-1-methyl-2,4-dioxo-3-phenyl-0*H*-cyclopenta[cd]indole-7-carbonitrile (7). Procedure A, B. 16 h. R_f (SiO_2, *n*-heptane/EtOAc =1:1): 0.41. Yield (procedure A): 68%; yield (procedure B): 66%. Colorless solid. Mp: 159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.66–7.35 (m, 5H, *H*-Ar), 4.25 (t, *J*=7.6 Hz, 1H, C*H*NCH$_3$), 4.05 (s, 3H, NC*H*$_3$), 3.45 (m, 1H, CH$_2$C*H*CN), 3.42 (m, 1H, CH$_2$C*H*CO), 3.04 (m, 1H, CHC*H*CH), 2.21 and 1.91 (both m, both 1H, CH$_2$C*H*$_2$CH), 1.65–1.51 (m, 2H, CHC*H*$_2$CH$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ=210.2 (C=C*C*OCH), 169.1 (*C*ONCH$_3$), 159.6 (Ph*C*=C), 135.4 (PhC=*C*), 130.6 (*i*-*C*-Ar), 129.6 and 128.1 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 129.2 (*p*-*C*H-Ar), 118.5 (*C*N), 59.2 (*C*HNCH$_3$), 56.6 (NCH$_3$), 46.7 (CH*C*HC=C), 45.6 (CH$_2$-*C*HCO), 33.6 (*C*HCN), 23.4 (COCH*C*H$_2$CH$_2$), 21.2 (COCHCH$_2$*C*H$_2$). MS (EI, 70 eV): *m*/*z* (%)=292 (100) [M]$^+$, 277 (10), 263 (14), 249 (15), 210 (16), 196 (17), 153 (12), 129 (31), 115 (20), 104 (32), 77 (15), 44 (11), 28 (14), no other peaks >10%. IR (KBr): 1/λ=3390 (w), 2940 (m), 2924 (m), 2860 (w), 2238 (w), 1705 (s), 1579 (s), 1443 (m), 1380 (m), 1312 (m), 1244 (m), 1163 (m), 1040 (m), 984 (m), 930 (m), 775 (m), 735 (m), 696 (m), 661 (w), 551 (w), 475 (w) cm^{-1}. HR-MS (EI): calcd for $C_{18}H_{16}N_2O_2$: 292.12119; found 292.12149 [M]$^+$.

3.4.8. (3*Z*)-3-Benzylidene-1,3,3a,8b-tetrahydro-1,7-dimethylpyrrolo[3,4-*g*]indole-2,6,8(5a*H*,7*H*,8a*H*)-trione (8a). Procedure C. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=1/1): 0.31. Yield: 62%. Colorless solid. Mp: 137–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.41–7.22 (m, 5H, *H*-Ar), 6.71 (s, 1H, PhC*H*=CH), 5.97 (m, 1H, CH=C*H*CHCO), 5.66 (m, 1H, CHC*H*=CH), 4.41 (t, *J*=5.54 Hz, 1H, N(CH$_3$)C*H*CH), 3.61 (s, 3H, CON(C*H*$_3$)CH), 3.50 (m, 1H, CHC*H*CH=CH), 3.35 (m, 1H, CH=CHC*H*CO), 3.19 (dd, *J*=6.14, 5.94 Hz, 1H, CHC*H*CO), 2.99 (s, 3H, CHCONC*H*$_3$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ=178.0 and 176.5 (2 CH*C*ON), 168.8 (*C*ON(CH$_3$)CH), 135.4 (CH*C*H=CH), 134.6 (*i*-*C*-Ar), 129.9 (CH=*C*CO), 129.3

(2 *o*-*C*H-Ar), 127.8 (Ph*C*H=C), 127.7 (*m*-*C*H-Ar), 127.6 (2 *p*-*C*H-Ar), 118.9 (CH*C*H=CH), 59.6 (CHC*C*HCH), 54.8 (CON(*C*H$_3$)CH), 46.4 (CH*C*HCH=CH), 41.1 (CH*C*HCO), 38.8 (CH=CH*C*HCO), 24.0 (CHCON*C*H$_3$). MS (EI, 70 eV): *m*/*z* (%)=322 (100) [M]$^+$, 307 (40), 265 (15), 222 (46), 209 (35), 204 (13), 194 (21), 179 (21), 115 (15), 91 (31), 77 (16), 52 (11), 28 (16), no other peaks >10%. IR (KBr): 1/λ=3443 (w), 2987 (m), 2934 (w), 1774 (m), 1709 (s), 1603 (s), 1438 (m), 1376 (m), 1283 (m), 1270 (m), 1128 (m), 1051 (m), 977 (s), 847 (w), 724 (m), 694 (m), 603 (w), 497 (w), 421 (w) cm^{-1}. HR-MS (EI): calcd for $C_{19}H_{18}N_2O_3$: 322.13174; found 322.13195 [M]$^+$.

3.4.9. (3*Z*)-3-Ethylidene-1,3,3a,8b-tetrahydro-1,7-dimethylpyrrolo[3,4-*g*]indole-2,6,8(5a*H*,7*H*,8a*H*)-trione (9). Procedure C. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.33. Yield: 44%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=5.83 (m, 1H, CH$_3$C*H*=C), 5.65 (m, 1H, CHC*H*=CHCHCO), 5.43 (m, 1H, CHCH=C*H*CHCO), 4.25 (m, 1H, C*H*NCH$_3$), 3.62 (s, 3H, CONC*H*$_3$), 3.26 (m, 1H, CH=CHC*H*C=CH), 3.25 (m, 1H, NCHC*H*CO), 3.12 (dd, *J*=1.79, 6.12 Hz, 1H, CH=CHC*H*CO), 2.94 (s, 3H, CONC*H*$_3$), 0.92 (d, *J*=4.51 Hz, 3H, C*H*$_3$CH=C). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=178.4 and 176.8 (2 CH*C*ON), 170.0 (CH=C*C*O), 134.5 (CH$_3$CH=*C*), 132.4 (CH$_3$*C*H=C), 130.7 (CHCH=*C*HCHCO), 118.3 (CHCH=*C*HCHCO), 59.9 (*C*HNCH$_3$), 54.9 (N*C*H$_3$), 44.5 and 44.4 (2 *C*HCONCH$_3$), 38.8 (CH=C*C*HCH=CH), 24.4 (CON*C*H$_3$), 15.1 (*C*H$_3$). MS (EI, 70 eV): *m*/*z* (%)=260 (100) [M]$^+$, 245 (36), 231 (22), 160 (32), 146 (18), 121 (17), 103 (18), 91 (23), no other peaks >10%. IR (KBr): 1/λ=3435 (m), 2951 (m) 1775 (m), 1701 (s), 1610 (m), 1474 (m), 1437 (s), 1383 (s), 1287 (s), 1193 (m), 1160 (m), 1132 (m), 1051 (m), 915 (w), 875 (w), 806 (w), 748 (w), 714 (w), 563 (w) cm^{-1}. HR-MS (EI): calcd for $C_{14}H_{16}N_2O_3$: 260.11609; found 260.11594 [M]$^+$.

3.4.10. (3*Z*)-1,3,3a,8b-Tetrahydro-1,7-dimethyl-3-propylidenepyrrolo[3,4-*g*]indole-2,6,8(5a*H*,7*H*,8a*H*)-trione (10). Procedure C. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.32. Yield: 53%. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ=5.85 (m, 1H, CH$_2$C*H*=C), 5.67 (t, *J*=7.72 Hz, 1H, CHC*H*=CHCHCO), 5.47 (dt, *J*=10.1, 2.47 Hz, 1H, CHCH=C*H*CHCO), 4.23 (t, *J*=5.65 Hz, 1H, C*H*NCH$_3$), 3.61 (s, 3H, CONC*H*$_3$), 3.28 (m, 1H, CH=CHC*H*C=CH), 3.24 (m, 1H, NCHC*H*CO), 3.10 (dd, *J*=1.78, 6.14 Hz, 1H, CH=CHC*H*CO), 2.93 (s, 3H, CONC*H*$_3$), 2.32 (m, 2H, C*H*$_2$), 0.92 (t, *J*=7.53 Hz, 3H, C*H*$_3$CH$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, DMSO-d_6): δ=178.2 and 176.6 (2 CH*C*ON), 169.8 (CH=C*C*O), 134.4 (CH$_2$CH=*C*), 132.1 (CH$_2$*C*H=C), 130.8 (CHCH=*C*HCHCO), 118.1 (CHCH=*C*HCHCO), 59.7 (*C*HNCH$_3$), 54.7 (N*C*H$_3$), 44.3 and 44.2 (2 *C*HCONCH$_3$), 38.6 (CH=C*C*HCH=CH), 24.0 (CON*C*H$_3$), 21.4 (*C*H$_2$), 14.1 (*C*H$_3$CH$_2$). MS (EI, 70 eV): *m*/*z* (%)=274 (100) [M]$^+$, 259 (40), 245 (17), 174 (34), 160 (14), 146 (21), 130 (14), 117 (16), 91 (13), 77 (10), 28 (30), no other peaks >10%. IR (KBr): 1/λ=3461 (s), 3031 (m), 2945 (s), 2251 (w), 1777 (m), 1704 (s), 1608 (m), 1435 (s), 1384 (m), 1281 (m), 1158 (w), 1123 (w), 1052 (w), 977 (m), 840 (w), 780 (w), 721 (w), 616 (w), 497 (w) cm^{-1}. HR-MS (EI): calcd for $C_{15}H_{18}N_2O_3$: 274.13174; found 274.13134 [M]$^+$.

3.4.11. (*Z*)-3-Benzylidene-hexahydro-1,7-dimethyl-4-methylenepyrrolo[3,4-*g*]indole-2,6,8(3*H*,7*H*,8a*H*)-trione (11). Procedure C. 24 h. R_f (SiO_2, *n*-heptan/EtOAc=1:1): 0.33. Yield: 62%. Colorless solid. Mp: 170–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40–7.21 (m, 5H, *H*-Ar), 6.64 (s, 1H, PhC*H*=C), 4.99 and 4.86 (both m, both 1H, C*H*$_2$=C), 4.62 (t, *J*=5.85 Hz, 1H, CHC*H*CH), 3.71 (d, *J*=6.73 Hz, 1H, CHC*H*C=CH$_2$), 3.66 (s, 3H, CON(C*H*$_3$)CH), 3.06 (m, 2H, 2 C*H*CON), 3.01 (s, 3H, CHCONC*H*$_3$), 2.52 and 2.18 (both m, both 1H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ=179.4 and 178.1 (2 CH*C*ON), 170.0 (*C*ON(CH$_3$)CH), 146.3 (CH$_2$=*C*CH), 134.8 (*i*-*C*-Ar), 134.6 (Ph*C*H=C), 129.8 (PhCH=*C*), 129.6 (2 *m*-*C*H-Ar), 127.8 (*p*-*C*H-Ar), 127.5 (2 *o*-*C*H-Ar), 111.2 (*C*H$_2$=C–H), 64.2 (CH*C*HCH), 55.3 (CH*C*HC=CH$_2$), 52.0 (CON(*C*H$_3$)-CH), 42.2 (CH*C*HCO), 40.4 (CH$_2$*C*HCO), 24.3 (CHCON*C*H$_3$), 22.6 (CH$_2$=C*C*H$_2$) MS (EI, 70 eV): *m*/*z* (%)=336 (100) [M]$^+$, 321 (28), 236 (19), 225 (18), 210 (22), 193 (11), 115 (20), 91 (20), no other peaks >10%. IR (KBr): 1/λ=3295 (s), 3207 (s), 2954 (w), 2791 (m), 2111 (s), 1665 (s), 1616 (s), 1572 (s), 1389 (s), 1134 (s), 807 (m), 775 (s), 681 (s), 597 (s), 545 (m) cm^{-1}. HR-MS (EI): calcd for $C_{20}H_{20}N_2O_3$: 336.14739; found 336.14714 [M]$^+$.

3.4.12. (3*Z*)-3-Benzylidene-2,3,3a,6,7,7a-hexahydro-1-methyl-2-oxo-1*H*-indole-7-carbonitrile (12). Procedure C. 24 h. R_f (SiO_2, *n*-heptane/EtOAc=1:1): 0.31. Yield: 65%. Colorless solid. Mp: 153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.27 (m, 5H, *H*-Ar), 6.59 (d, *J*=1.9 Hz, 1H, PhC*H*=CH), 5.75 (m, 2H, C*H*=C*H*), 4.26 (dd, *J*=4.1, 6.4 Hz, 1H, CHC*H*NCH$_3$), 3.83 (s, 3H, NC*H*$_3$), 3.54 (m, 1H, CHC*H*CN), 3.07 (m, 1H, CH=CHC*H*CH), 2.42 and 2.33 (both m, both 1H, C*H*$_2$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ=170.6 (*C*ON), 134.9 (*i*-*C*-Ar), 134.0 (CH=*C*CO), 129.3 and 127.8 (2 *o*-*C*H-Ar and 2 *m*-*C*H-Ar), 127.9 (*p*-*C*H-Ar), 127.5 (Ph*C*H=C), 127.4 (CH=*C*HCH), 124.2 (CH$_2$*C*H=CH), 120.6 (*C*N), 60.8 (CH*C*HN), 55.3 (N*C*H$_3$), 44.3 (CH*C*HCN), 29.8 (CH=CH*C*HCH), 24.2 (*C*H$_2$). MS (EI, 70 eV): *m*/*z* (%)=264 (100) [M]$^+$, 249 (26), 224 (45), 205 (24), 180 (10), 167 (17), 145 (18), 128 (11), 115 (20), 105 (42), 91 (25), 77 (34), 69 (13), 52 (17), 42 (30), 28 (21), no other peaks >10%. IR (KBr): 1/λ=3363 (m), 3028 (w), 2947 (m), 2228 (w), 1701 (m), 1600 (m), 1441 (s), 1319 (m), 1274 (m), 1068 (m), 987 (w), 879 (w), 697 (m) cm^{-1}. HR-MS (EI): calcd for $C_{17}H_{16}N_2O$: 264.12626; found 264.12680 [M]$^+$.

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A two-step four-component queuing cascade involving a Heck coupling, π-allylpalladium trapping and Diels–Alder reaction☆

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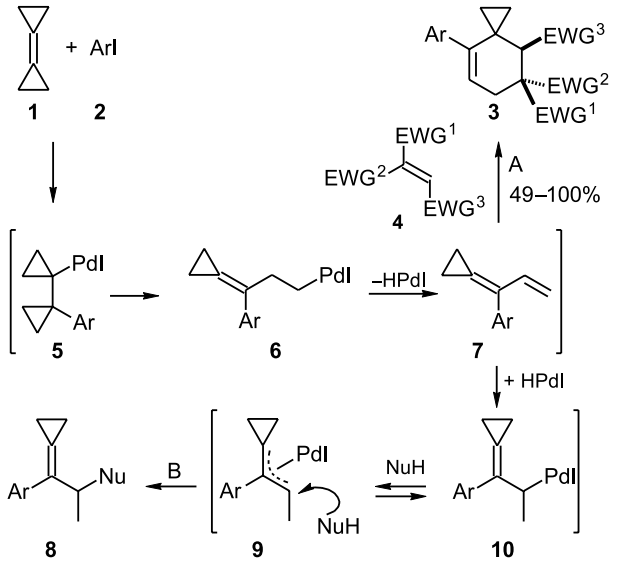
Abstract—Palladium-catalyzed cross-coupling of bicyclopropylidene (**1**) with iodoethene (**11**) in the presence of a secondary amine **12** provides allylidenecyclopropanes **13** which undergo immediate Diels–Alder reactions upon addition of dienophiles **14**–**18** to provide 8-(1′-aminoethyl)-substituted spiro[2.5]oct-7-ene derivatives **23a**–**26a** in 29–66% yield. The same one-pot, two-step queuing cascade can be carried out with other iodoalkenes including cyclic ones and with cyclic dienophiles such as *N*-arylmaleinamides **19**–**22** and *N*-phenyltriazolinedione **37** to furnish highly substituted spiro[2.5]oct-4-enes and spirocyclopropanated heterobicycles **47a**–**49a**, **41a**–**46a** (17–50%). Spirocyclopropanated heterobicycles such as **55**, **56** (25 and 38% yield, respectively) can also be obtained by an inter-intra-intra-intermolecular version of this queuing cascade involving 1-hydroxyethyl- and 1-aminoethyl-substituted iodoethenes **53**, **54**.

1. Introduction

One of the foremost aims in the development of modern organic synthetic methods is an increase in efficiency,[2] as expressed in the increase in molecular complexity in a minimum number of procedural steps. Both multicomponent[3] and cascade (or domino) reactions[4] bring about remarkable changes in molecular complexity. While multicomponent reactions by definition constitute a subgroup of cascade reactions,[5] not all cascade reactions do necessarily involve more than one component. Thus, multicomponent reactions in which one or more of the reaction partners are involved in more than one step of the overall transformation cascade, are particularly efficient in terms of increasing the molecular complexity.

In recent years, we have found several new examples of such multicomponent molecular queuing cascades,[6] in which palladium-catalyzed cross-couplings and the highly reactive C_6-building block bicyclopropylidene (**1**) play pivotal rules.[6] One of them is a cross-coupling between **1**, an aryl iodide **2** leading to an allylidenecyclopropane **7** which immediately reacts with a dienophile **4**, present in the mixture to yield a 4-arylspiro[2.5]oct-4-ene derivative **3** (Scheme 1).[7] The combinatorial potential of this process has been demonstrated with the automatized preparation of a structurally diverse set of these multifunctional biaryl mimics.[8] A related three-component sequence starts with the same carbopalladation of the unusually reactive double bond in bicyclopropylidene (**1**) and subsequent



Scheme 1. Two recently developed three-component reactions involving bicyclopropylidene (**1**), an aryl iodide and a cyclopropylcarbinyl to homoallylpalladium rearrangement. (A) $Pd(OAc)_2$, PPh_3, K_2CO_3, Et_4NCl, MeCN, 80 °C, 48 h. (B) $Pd(OAc)_2$, TFP, K_2CO_3, Et_4NCl, NuH, MeCN, 80 °C, 24 h.

☆ See Ref. 1.

Keywords: π-Allylpalladium species; Bicyclopropylidene; Cascade reactions; Cycloadditions; Small rings; Spiro[2.5]octenes.
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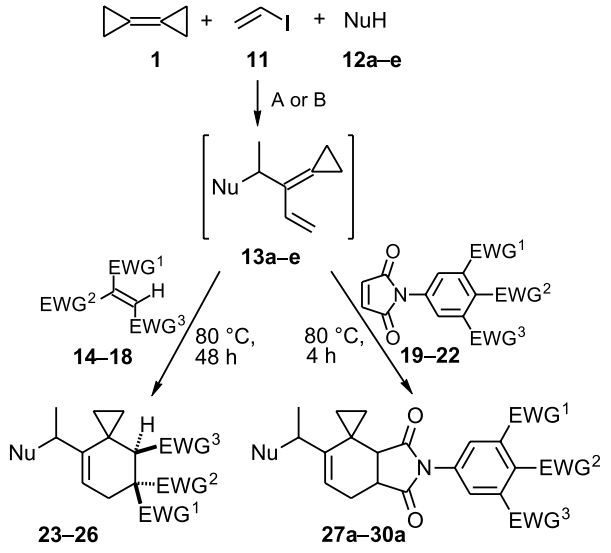
cyclopropylcarbinyl to homoallyl rearrangement of **5** affording the homoallylpalladium species **6**, which rapidly undergoes a β-hydride elimination to yield the diene **7**. In the absence of a dienophile **4** and favored by the presence of tris(2-furyl)phosphine (TFP) instead of triphenylphosphine, **7** undergoes hydridopalladation with the reverse regioselectivity to form the σ-allylpalladium intermediate **10**. Irrespective of the latter equilibrating with the π-allylpalladium species **9**,[9] it is trapped regioselectively by an added nucleophile, for example, lithium acetate or an amine, to furnish a 2-arylallyl derivative of type **8** (Scheme 1).[10] Since the cross coupling of **1** with an alkenyl iodide in the presence of a dienophile leads to a transmissive Diels–Alder adduct of an intermediately formed cross-conjugated triene, we conceived the possibility of extending the second reaction mode into an overall four-component queuing cascade by coupling an alkenyl iodide with bicyclopropylidene (**1**) in the presence of TFP. This would yield, after trapping of the formed π-allylpalladium intermediate with a nucleophile, a conjugated diene, which would undergo a Diels–Alder reaction with an added dienophile. This concept was tested, and here we present our first results.



Scheme 2. A new one-pot, two-step four-component queuing cascade involving bicyclopropylidene (**1**), iodoethene (**11**), nucleophiles **12a–e** and dienophiles **14–18**, **19–22**. (A) $Pd(OAc)_2$, TFP, NEt_3, 2 h, 80 °C, DMF. (B) $Pd(OAc)_2$, TFP, K_2CO_3, Et_4NCl, 2 h, 80 °C, MeCN. For further details see Table 1.

2. Results and discussion

The palladium-catalyzed cross-coupling with rearrangement and nucleophilic trapping cannot be carried out with the dienophile being present from the beginning, since a Michael addition of the nucleophile onto the dienophile would compete with the desired reaction. Therefore, bicyclopropylidene (**1**) and iodoethene (**11**) in the presence of a secondary amine **12** in dimethylformamide were treated with a typical palladium catalyst cocktail (e.g., $Pd(OAc)_2$, TFP, NEt_3) at 80 °C for 2 h, then a dienophile like methyl acrylate (**14**) was added, and the mixture was heated at 80 °C for 48 h (Scheme 2 and Table 1).

With morpholine (**12a**) as a secondary amine, well known to be a good nucleophile,[11] the yields in this one-pot, two-step queuing cascade were generally good (37–66%), irrespective of the nature of the dienophile (Table 1). With piperidine (**12b**), pyrrolidine (**12c**), *N*-benzylpiperazine (**12d**), and *N*-*tert*-butoxycarbonylpiperazine (**12e**) in combination with **1**, **11** and the best yielding *tert*-butyl acrylate (**15**), the cascade reaction gave the corresponding products **24b–e** mostly in moderate yield (29–49%). In all cases, the products from unsymmetrical dienophiles **14–16** were only 5-substituted spiro[2.5]oct-7-ene derivatives as assigned on the basis of their NMR spectra. This is in agreement with the previously observed regioselectivities in Diels–Alder additions of acrylates to allylidenecyclopropanes.[6a,12]

The reaction with dimethyl fumarate **17** and dimethyl maleate **18** both gave mixtures of dimethyl *cis*- and *trans*-spiro[2.5]octenedicarboxylates (*cis*- and *trans*-**26a**) in slightly different ratios (Table 1), irrespective of the conditions (A or B in Scheme 2) used. Control experiments confirmed that simple heating in dimethylformamide at 80 °C causes **18** to isomerize to **17**, (50% conversion after 1.5 h, ~98% conversion after 6 h), whereas heating of **18** in

Table 1. One-pot, two-step four-component queuing cascade involving bicyclopropylidene (**1**), iodoethene **11**, nucleophiles **12a–e**, dienophiles **14–18** and **19–22** (see Scheme 2)

Nucleophile **12** NuH	Cond.	Dienophile	EWG^1	EWG^2	EWG^3	Product	Yield (%)[a]	d.r.[b]
a Morpholine	B	**14**	CO_2Me	H	H	**23a**	65	1.1:1
a Morpholine	A	**15**	CO_2tBu	H	H	**24a**	66	1.3:1
a Morpholine	A	**16**	SO_2Ph	H	H	**25a**	62	1.2:1
a Morpholine	B	**17**	CO_2Me	H	CO_2Me	*cis*/*trans*-**26a**	58	1.2:1
a Morpholine	B	**18**	H	CO_2Me	CO_2Me	*cis*/*trans*-**26a**	52	1.7:1
a Morpholine	A	**17**	CO_2Me	H	CO_2Me	*cis*/*trans*-**26a**	39	1.3:1
b Piperidine	A	**15**	CO_2tBu	H	H	**24b**	33	1:1
c Pyrrolidine	A	**15**	CO_2tBu	H	H	**24c**	29	1:1
d *N*-Bn-Piperazine	B	**15**	CO_2tBu	H	H	**24d**	48	1.1:1
e *N*-Boc-piperazine	B	**15**	CO_2tBu	H	H	**24e**	49	1:1
a Morpholine	A	**19**	H	H	H	**27a**	40	1:1
a Morpholine	A	**20**	CF_3	H	H	**28a**	38	1.2:1
a Morpholine	A	**21**	H	CF_3	H	**29a**	44	1.1:1
a Morpholine	A	**22**	CF_3	H	CF_3	**30a**	37	1.6:1

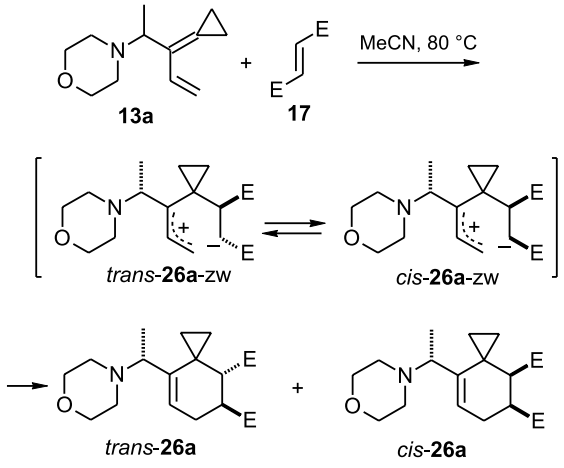
[a] Isolated yields are given.
[b] Diastereomeric ratios were determined by integration of relevant ^1H NMR signals in the spectra of the crude products.

acetonitrile at 80 °C did not lead to any isomerization even after 24 h.

Attention was then turned to the reaction of isolated diene **13a** with dimethyl maleate (**18**) to explain the formation of the *trans*-spirooctenedicarboxylate *trans*-**26a** along with *cis*-**26a** under conditions B (i.e., in acetonitrile), since isomerization of **18** to **17** during the course of the Heck reaction is well known.[13] In other words, in the absence of the catalyst ingredients, *cis*-**26a** would be expected as a single product if the cycloaddition of dimethyl maleate (**18**) to the 1,3-diene **13a** occurred in a concerted mode. Surprisingly, however, the reaction of a fourfold excess of dimethyl maleate (**18**) with diene **13a** in acetonitrile at 80 °C after 24 h again gave virtually the same mixture of *cis*- and *trans*-**26a** in a ratio of 1.4:1 in quantitave yield (based on the diene **13a**) along with a 3:1 mixture of **17** and **18**.

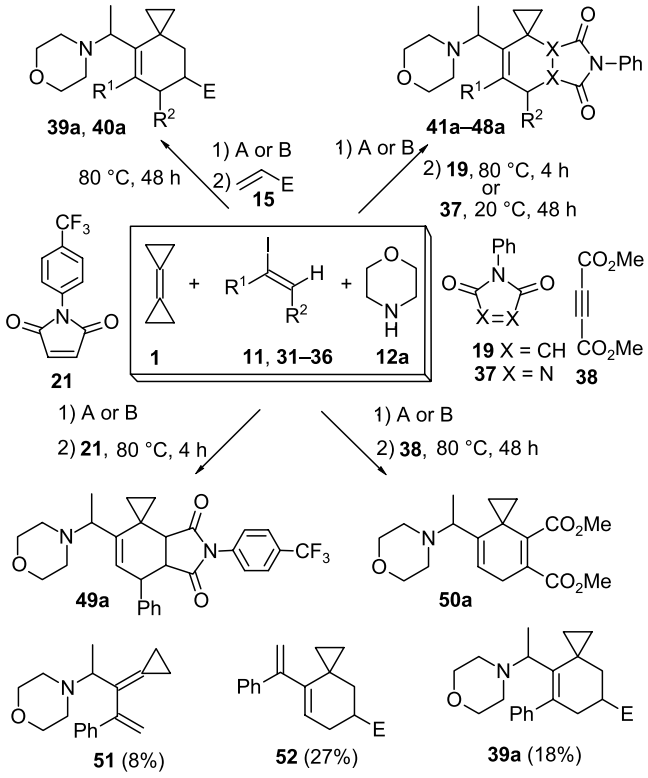
The reaction of **13a** with a twofold excess of **18** was also performed in deuterated acetonitrile and monitored by NMR spectroscopy. After 1 h, some dimethyl fumarate (**17**) was detectable, but none of the cycloadduct *cis*- or *trans*-**26a** from the diene **13a**. The concentration of **17** continued to increase until the formation of *cis*- and *trans*-**26a** set in. Thus, the second order rate of the cycloaddition of **17** to **13a** at the given temperature becomes comparable to that of the first order or pseudo-first order rate of isomerization of **18** to **17** only when the concentration of **17** has reached a certain level (almost one third of that of **18** after 7 h). It is well known that dimethyl fumarate (**17**) is more reactive as a dienophile than dimethyl maleate (**18**) by a factor of about 82.[14] Most probably, the diene **13a**, which is a tertiary amine, catalyzes the isomerization of **18** to **17**. Indeed, in a control experiment, *N*-allylmorpholine as a model for **13a** was shown to cause this isomerization.

Altogether these results imply that the cycloaddition of dimethyl fumarate (**17**) to **13a** must proceed in two steps through the zwitterionic intermediate *trans*-**26a**-zw, just as has been suggested for the reaction of (1′-arylallylidene)-cyclopropanes with **17** and **18** (Scheme 3).[6a] Rather than undergoing immediate cyclization, the initial zwitterion *trans*-**26a**-zw by internal rotation can go to *cis*-**26a**-zw and then cyclize to furnish the cycloadduct of dimethyl maleate (**18**). Since only two diastereomers were obtained from both **17** and **18**, the stereocenter present in the diene **13a** most probably controls the approach of the dienophile **17** in such a way as to only form the zwitterion *trans*-**26a**-zw as shown, and this undergoes rotation only to *cis*-**26a**-zw or ring closure to *trans*-**26a**.



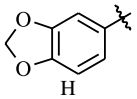
Scheme 3. Rationalizing the formation of both diastereomeric cycloadducts *trans*-**26a** and *cis*-**26a** from the allylidenecyclopropane **13a** and dimethyl fumarate (**17**). E = CO_2Me.

The complexity of the product structure was further increased by the use of heteroatom-containing dienophiles **19**, **21** and **37** with various substituted vinyl iodides **31**–**36** (Scheme 4 and Table 2), which were prepared according to published procedures.[15] In most of these cases, however, the yields were only moderate and, in general, lower than with iodoethene (**11**). In the reactions of α-iodostyrene (**31**) (entries 1, 8 and 10 in Table 2) and 5-(1-iodovinyl)benzo-[1,3]dioxole **32** (entry 2 in Table 2), more than one equivalent of morpholine had to be added, and the reaction mixture with the palladium catalyst had to be heated for more than two hours to drive the first section of the sequential reaction to completion. Indeed, when the reactions of iodoalkenes **31** and **32** were carried out with sterically encumbered dienophiles such as *tert*-butyl acrylate (**15**) (entries 1, 2 in Table 2), prolonged reaction times and higher temperatures than 80 °C were necessary for the Diels–Alder reaction in the second step to be successful. For example, the reaction of α-iodostyrene (**31**) with **1** and one equivalent of morpholine (**12a**) under the usual conditions (80 °C, 2 h for the first step and 80 °C, 48 h for the second step) yielded the diene **51** (8%) and the



Scheme 4. One-pot, two-step four-component queuing cascade involving bicyclopropylidene (**1**), iodoalkenes **11** and **31**–**36**, morpholine **12a** and dienophiles **15**, **19**, **21**, **37** and **38**. (A) $Pd(OAc)_2$, TFP, NEt_3, 80 °C, DMF. (B) $Pd(OAc)_2$, TFP, K_2CO_3, Et_4NCl, 80 °C, MeCN. E = CO_2tBu, For details see Table 2.

Table 2. One-pot, two-step four-component queuing cascade involving bicyclopropylidene (**1**), iodoalkenes **11** and **31–36**, morpholine **12a** and dienophiles **15**, **19**, **21**, **37** and **38** (see Scheme 4)

Entry	Cond.	Time [h]	Alkenyl Iodide	R^1	R^2	Dienophile	Product	Yield (%)	d.r.
1	B[a,b]	3	**31**	Ph	H	**15**	**39a**	36	1.1:1
2	B[a,b]	3	**32**		H	**15**	**40a**	44	1.2:1
3	A	3	**33**	H	2-Thienyl	**37**	**41a**	26	1:1
4	A[c]	5	**34**	$-(CH_2)_4-$		**37**	**42a**	33	4.6:1
5	B	3	**35**	$[(CH_2)_2NCH_2]$ Bn		**37**	**43a**	17	—[d]
6	A	2	**36**	H	Ph	**37**	**44a**	35	1.4:1
7	B	2	**11**	H	H	**37**	**45a**	50	—[d]
8	B[b]	3	**31**	Ph	H	**37**	**46a**	35	—[d]
9	A[e]	2	**36**	H	Ph	**19**	**47a**	42	2:1
10	A[b,f]	3	**31**	Ph	H	**19**	**48a**	40	1.18:1
11	A[e]	2	**36**	H	Ph	**21**	**49a**	37	2:1
12	B[f]	2	**11**	H	H	**38**	**50a**	30	—[d]

[a] 100 °C, 65 h for the second step.
[b] 1.5 equiv of morpholine (**12a**) used in the first step.
[c] 100 °C for the first step.
[d] Only one diastereomer was isolated.
[e] 80 °C, 4 h for the second step.
[f] 80 °C, 48 h for the second step.

styryl[2.5]spirooctene derivative **52** (27%) along with the expected product **39a** (18%) (Scheme 4). Formation of the by-products **51** and **52** could only be eliminated by applying 1.5 equiv of **12a** in the first step and prolonged heating (65 h) at elevated temperature (100 °C) for the second step (entry 1 in Table 2). Interestingly, however, in the case of (*E*)-1-iodo-2-phenylethene (**36**) (entries 6, 9 and 11 in Table 2) 2 h without using more than one equivalent of morpholine were enough to complete the first step of the reaction.

Yet, even spirocyclopropanated heterooligocyclic systems **42a** and **43a** (entries 4 and 5 in Table 2) were accessible by the use of iodocyclohexene **34** and *N*-benzyl-4-iodotetrahydropyridine **35**, respectively. For the first step of the sequential reaction of iodocyclohexene (**34**), the mixture had to be heated exceptionally long, that is, for 5 h at 100 °C, to reach the maximum yield, whereas the reactions of other iodoalkenes gave lower yields when the temperature for the first steps exceeded 80 °C. The configuration of the major diastereomer **42a** was rigorously proved by an X-ray crystal structure analysis (Fig. 1). A heterocyclic substituent could also be attached to the spirooctene core as in **41a** by means of 2-(2-iodovinyl)thiophene **33** in the cross-coupling step (entry 3 in Table 2).

Furthermore, heteroatoms could be incorporated in the spirooctene moiety of the Diels–Alder products by employing the highly reactive dienophile *N*-phenyltriazolinedione (PTAD) **37**. Whereas with *N*-phenylmaleimide (**19**) the cycloaddition could be completed at 80 °C in 4 h, the reaction with **37** gave better yields when carried out at 20 °C for prolonged times (up to 2 days).

To extend the scope of this cascade reaction even further, functionalized vinyl iodides **53** and **54** were employed to provide, by intramolecular π-allylpalladium trapping in the first step after the cross-coupling and rearrangement, spirocyclopropanated heterobicycles **55**, **56**, albeit in moderate yields only (at best 25 and 38%, respectively) (Scheme 5).[17] Although this is not a four-component reaction, this inter-intra-intra-intermolecular queuing cascade proceeds by the same number of individual steps and with formation of the same number of carbon–carbon and carbon-heteroatom bonds (altogether four) as the four-component cascades discussed above.

Interestingly, the iodohomoallyl alcohol **53** gave the best results under conditions B in acetonitrile with potassium carbonate and the phase transfer agent (Et_4NCl), whereas the *N*-tosylhomoallylamine **54** gave the best yield of 38% under conditions A ($Pd(OAc)_2$, TFP, NEt_3, DMF, 80 °C, 3 h), and the product **56** was obtained as a single diastereomer along with the tosylaminobutenylspiro[2.5]-octenecarboxylate **57** resulting from β-hydride elimination in the intermediate of type **6** and immediate Diels–Alder addition of **15**. The configuration of **56** was also rigorously proved by an X-ray crystal structure analysis (Fig. 2). All

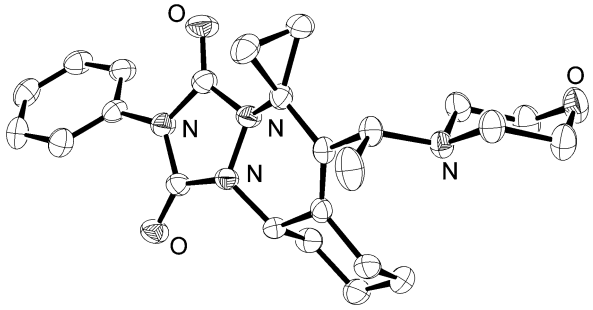
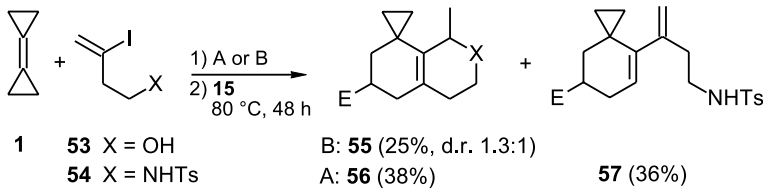


Figure 1. Structure of compound **42a** in the crystal.[16] $C_{24}H_{30}N_4O_3$ (422.52); crystal size $0.50\times0.50\times0.50\ mm^3$, orthorhombic, $a=919.67$ (18), $b=1352.8$ (3), $c=1733.3$ (4) pm, $\alpha=90°$ $\beta=90°$, $\gamma=90°$, $V=2.1565$ (7) nm^3; $Z=4$, space group $P2_1/2_1/2_1$, $T=200$ (2) K, $\rho=1.301\ mg\ m^{-3}$, absorption coefficient $=0.087\ mm^{-1}$, $F_o=904$, θ range for data collection $=3.56–24.96°$, reflection collected $=2892$, $R_{int}=2575[0.0374]$, data/restraints/parameters $=2575/0/281$, Goof on $F^2=1.037$, Final R indices $[I>2\sigma(I)]=R_1$ (0.0374), wR_2 (0.0912), R indices (all data) $=R_1$ (0.0400), wR_2 (0.0943), Largest diff. peak and hole $=0.144$ and $-0.227\ e\ Å^{-3}$.



Scheme 5. An inter-intra-intra-intermolecular queuing cascade involving bicyclopropylidene (**1**) a functionalized iodoalkene **53**, **54**, and a dienophile **15**. (A) $Pd(OAc)_2$, TFP, NEt_3, 80 °C, DMF. (B) $Pd(OAc)_2$, TFP, K_2CO_3, Et_4NCl, 80 °C, MeCN. E=CO_2tBu.

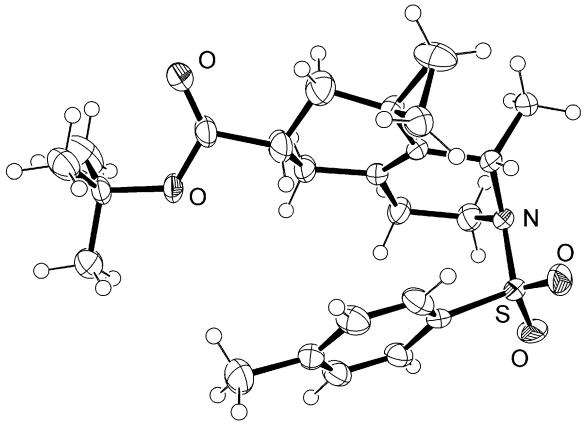


Figure 2. Structure of compound **56** in the crystal.[16] $C_{24}H_{33}NO_4S$ (431.57); crystal size 0.30×0.20×0.20 mm^3, monoclinic, a=1135.4(2), b=1289.1(3), c=1632.3(3) pm, α=90° β=108.0(3)°, γ=90°, V=2.2723(8) nm^3; Z=4, space group $P2_1/c$, T=133(2) K, ρ=1.262 mg m^{-3}, absorption coefficient =0.172 mm^{-1}, F_o=928, θ range for data collection=1.89–24.82°, reflection collected =33280, R_{int}=3897[0.0774], data/restraints/parameters=3897/0/276, Goof on F^2=1.021, Final R indices [$I>2\sigma(I)$]=R_1(0.0536), wR_2(0.1333), R indices (all data)=R_1(0.0873), wR_2(0.1439), Largest diff. peak and hole=0.974 and −0.403 e $Å^{-3}$.

attempts to suppress the formation of **57** by increasing the reaction temperature or the time were unsuccessful.

3. Conclusion

In conclusion, another dimension of diversity has been added to an already powerful combinatorial approach to libraries of spiro[2.5]octene derivatives. The new one-pot, two-step four-component queuing cascade leads to a particularly rich pattern of substituents by variation of the iodoalkenes, the nucleophiles and the dienophiles, exceeding those of the previously described spirocyclopropanated carbo- and heterocyclic skeletons.[6] This sequential transformation may also open up new approaches to natural products containing spiro[2.5]octane substructures.[18]

4. Experimental

4.1. General

NMR spectra were recorded with a Varian Mercury 200 (200 MHz for ^1H and 50.3 MHz for ^{13}C), a Bruker AM 250 (250 MHz for ^1H and 62.9 MHz for ^{13}C NMR), a Varian UNITY-300 (300 MHz for ^1H and 75.5 MHz for ^{13}C NMR) or a Varian Inova 600 (600 MHz for ^1H and 151 MHz for ^{13}C NMR) instruments. Chemical shifts δ are given in ppm relative to residual peaks of deuterated solvents and coupling constants, J, are given in Hertz. Multiplicities were determined by DEPT (distortionless enhancement by polarization transfer): +=primary or tertiary (positive DEPT signal), −=secondary (negative DEPT Signal), C_{quat}=quaternary carbon atoms] or APT (attached proton test) measurements. HMQC (heteronuclear multiple quantum coherence) spectra were also measured. IR spectra were recorded on a Bruker IFS 66 spectrometer and measured as KBr pellets or as oils between KBr plates. Low resolution mass spectra (EI at 70 eV or DCI with NH_3) were obtained on a Finnigan MAT 95 spectrometer. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95 spectrometer by preselected-ion peak matching at $R\approx$10,000 to be within ±2 ppm of the exact masses. Elemental analyses were carried out by the Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen. Chromatographic separations were performed with Merck Silica 60 (200–400 or 70–230 mesh). The dimensions of the columns are given as 'diameter×height of the silica gel column'. TLC was performed with Macherey-Nagel TLC Alugram® Sil G/UV 254 plates, detection was under UV light at 254 nm and development with MOPS reagent (10% molybdophosphoric acid in ethanol). Melting points were obtained with a Büchi apparatus according to Dr. Tottoli; values are uncorrected. All reagents were used as purchased from commercial suppliers without further purification. Acetonitrile was dried over P_2O_5, DMF and CH_2Cl_2 were distilled from CaH_2. Ether and THF were freshly distilled from sodium/benzophenone ketyl. Solvents for column chromotography, ethyl acetate and light petroleum were distilled in a rotatory evaporator.

Starting materials: bicyclopropylidene (**1**),[19] iodoalkenes **11**,[20] **31**, **32**, **34**,[15a] **33**,[15c] **35**,[21] **36**,[15e,j] and functionalized iodoalkenes **53**,[15b] **54**,[22] pyrrole-2,5-dione derivatives **19–22**[23] were prepared according to published procedures.

4.2. General procedure for the one-pot, two-step queuing cascade involving bicyclopropylidene (1) an iodoalkene, a secondary amine 12 and a dienophile under conditions A (GP-A)

Palladium acetate (22.4 mg, 100 μmol, 5 mol%) and tri-2-furylphosphine (46.4 mg, 200 μmol, 10 mol%), were suspended in anhydrous DMF (1 mL) in a screw-cap pyrex bottle. Argon was bubbled through the mixture for 5 min, and then the respective amine (2.00 or 2.50 mmol), triethylamine (202 mg, 2.00 mmol), iodoalkene (2.00 mmol) and bicyclopropylidene (**1**) (320 mg, 4.00 mmol) were added. After having stirred the mixture for the given time at the stated temperature the bottle was cooled to ambient temperature, the respective dienophile

(4.00 mmol) was added, (*N*-phenyltriazolinedione was added to the ice-cooled mixture), and then the mixture was stirred for an additional time as stated at the given temperature in a preheated oil bath. After cooling to room temperature, the reaction mixture was taken up in 20 mL of diethyl ether. The solution was washed with water (2× 20 mL). The aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic phases were dried ($MgSO_4$). After removal of the solvent in a rotatory evaporator, the residue was subjected to chromatography on silica gel.

4.3. General procedure for the one-pot, two-step queuing cascade involving bicyclopropylidene (1) an iodoalkene, a secondary amine 12 and a dienophile under conditions B (GP-B)

A screw-cap Pyrex bottle was charged with anhydrous acetonitrile (2 mL), K_2CO_3 (556 mg, 4.00 mmol) and Et_4NCl (332 mg, 2.00 mmol). Argon was bubbled through the mixture for 5 min, $Pd(OAc)_2$ (22.4 mg, 100 μmol, 5 mol%), and tri-2-furylphosphine (46.4 mg, 200 μmol, 10 mol%) were added, and the mixture was stirred once more for an additional 5 min with argon bubbling through, before the respective iodoalkene (2.00 mmol), the nucleophile (2.00 or 2.50 mmol) and bicyclopropylidene (**1**) (320 mg, 4.00 mmol) were added. The bottle was tightly closed, and the mixture was stirred for the given period of time at the stated temperature. After the bottle was cooled to ambient temperature, the respective dienophile (4.00 mmol) was added, (*N*-phenyltriazolinedione was added to the ice-cooled mixture), and then the mixture was stirred for the additional time at the given temperature in a preheated oil bath. After cooling to room temperature, the reaction mixture was taken up in 20 mL of diethyl ether. The solution was washed with water (2×20 mL), the aqueous phase was extracted with diethyl ether (2×20 mL), and the combined organic phases were dried ($MgSO_4$). After removal of the solvent in a rotatory evaporator, the residue was subjected to chromatography on silica gel.

4.3.1. Methyl 8-(1-morpholin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (23a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. After cooling the mixture to room temperature methyl acrylate (**14**, 344 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **23a** (363 mg, 65%, yellowish oil) as a mixture of two diastereomers (ratio 1.1:1 according to NMR).

Major diastereomer. R_f=0.27 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3076, 2973, 2851, 2809, 1738, 1653, 1456, 1329, 1160, 1120, 911, 866 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.32–0.39 (m, 1H, *c*Pr-H), 0.47–0.54 (m, 1H, *c*Pr-H), 0.77–0.95 (m, 2H, *c*Pr-H), 1.02 (d, J=6.23 Hz, 3H, CH_3), 1.24 (ddd, J=12.75, 2.72, 1.2 Hz, 1H, 4- or 6-H), 2.03 (ddd, J=12.5, 12.5, 1.7 Hz, 1H, 4- or 6-H), 2.12 (q, J=6.23 Hz, 1H, 1′-H), 2.29–2.45 (m, 6H, CH_2NCH_2, 4- or 6-H), 2.67–2.80 (m, 1H, 5-H), 3.63–3.69 (m, 4H, CH_2OCH_2), 3.66 (s, 3H; OCH_3), 5.77 (dd, J=4.4, 2.9 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.74 (−, *c*Pr-C), 13.23 (−, *c*Pr-C), 17.78 (+, CH_3), 19.47 (C_{quat}, *c*Pr-C), 28.34 (−, C-4 or -6), 38.56 (−, C-4 or -6), 39.29 (+, C-5), 50.74 (−, CH_2NCH_2), 51.56 (+, OCH_3), 59.17 (+, C-1′), 67.20 (−, CH_2OCH_2), 124.8 (+, C-7), 140.73 (C_{quat}, C-8), 176.09 (C_{quat}, C=O); MS (70 eV, EI), *m*/*z* (%): 279 (29) [M^+], 264 (100) [M^+-CH_3], 250 (11) [$M^+-C_2H_5$], 133 (21), 114 (86), 91 (24), 86 (12); $C_{16}H_{25}NO_3$ (279.38): calcd 279.1834 (correct HRMS); elemental analysis calcd (%) for $C_{16}H_{25}NO_3$: C 68.79, H 9.02; found: C 68.63, H 9.10.

Minor diastereomer. R_f=0.23 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3079, 2952, 2851, 2805, 1740, 1650, 1457, 1257, 1194, 1172, 945, 861 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.35–0.51 (m, 2H, *c*Pr-H), 0.59–0.66 (m, 1H, *c*Pr-H), 1.03 (d, J=6.8 Hz, 3H, CH_3), 1.02–1.14 (m, 1H, *c*Pr-H), 1.48 (dd, J=12.8, 3.1 Hz, 1H, 4- or 6-H), 1.90 (dd, J=10.2, 13 Hz, 1H, 4- or 6-H), 2.20 (q, J=6.8 Hz, 1H, 1′-H), 2.32–2.48 (m, 6H, CH_2NCH_2, 4- or 6-H), 2.69–2.80 (m, 1H, 5-H), 3.63–3.71 (m, 4H, CH_2OCH_2), 3.66 (s, 3H, OCH_3), 5.71 (t, J=3.8 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=11.75 (−, *c*Pr-C), 12.39 (−, *c*Pr-C), 16.99 (+, CH_3), 18.51 (C_{quat}, *c*Pr-C), 27.80 (−, C-4 or -6), 38.16 (−, C-4 or -6), 38.72 (+, C-5), 50.38 (−, CH_2NCH_2), 51.42 (+, OCH_3), 58.51 (+, C-1′), 67.24 (−, CH_2OCH_2), 121.4 (+, C-7), 143.67 (C_{quat}, C-8), 175.84 (C_{quat}, C=O); MS (70 eV, EI), *m*/*z* (%): 279 (26) [M^+], 264 (100) [M^+-CH_3], 250 (16) [$M^+-C_2H_5$], 133 (19), 114 (94), 91 (22), 86 (16); $C_{16}H_{25}NO_3$ (279.38): calcd 279.1834 (correct HRMS).

4.3.2. *tert*-Butyl 8-(1-morpholin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (24a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 3:1) to yield **24a** (426 mg, 66%, yellowish oil) as a mixture of two diastereomers (ratio 1.3:1 according to NMR).

Major diastereomer. R_f=0.34 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3077, 2977, 2851, 2809, 2689, 1731, 1455, 1367, 1339, 1253, 1150, 1119, 942, 855 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.32–0.39 (m, 1H, *c*Pr-H), 0.47–0.54 (m, 1H, *c*Pr-H), 0.77–0.92 (m, 2H, *c*Pr-H), 1.02 (d, J=6.2 Hz, 3H, CH_3), 1.19 (ddd, J=12.4, 2.7, 1.2 Hz, 1H, 4- or 6- H), 1.43 [s, 9H, $C(CH_3)_3$], 1.98 (t, J=12.7 Hz, 1H, 4- or 6-H), 2.09 (q, J=6.4 Hz, 1H, 1′-H), 2.27–2.42 (m, 6H, CH_2NCH_2, 4- or 6-H), 2.53–2.68 (m, 1H, 5-H), 3.65 (t, J=4.4 Hz, 4H, CH_2OCH_2), 5.76 (t, J=3.6 Hz, 1H, 7-H);

^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.75 (−, *c*Pr-C), 13.16 (−, *c*Pr-C), 17.87 (+, CH_3), 19.45 (C_{quat}, *c*Pr-C), 28.00 [+, $C(CH_3)_3$], 28.53 (−, C-4 or -6), 38.51 (−, C-4 or -6), 40.32 (+, C-5), 50.75 (−, CH_2NCH_2), 59.11 (+, C-1′), 67.15 (−, CH_2OCH_2), 79.78 [C_{quat}, $C(CH_3)_3$], 120.7 (+, C-7), 140.64 (C_{quat}, C-8), 174.98 (C_{quat}, C=O); MS (70 eV, EI) *m/z* (%): 321 (46) [M^+], 306 (68) [M^+-CH_3], 250 (60) [$M^+-C_2H_5$], 133 (30), 114 (100), 100 (22), 86 (20); elemental analysis calcd (%) for $C_{19}H_{31}NO_3$ (321.5): C 70.99, H 9.72; found: C 70.78, H 9.52.

Minor diastereomer. R_f=0.29 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3079, 2977, 2851, 2804, 2689, 1730, 1454, 1367, 1329, 1256, 1150, 1119, 945, 863 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.35–0.42 (m, 1H, *c*Pr-H), 0.46–0.54 (m, 1H, *c*Pr-H), 0.57–0.64 (m, 1H, *c*Pr-H), 1.03 (d, *J*=6.6 Hz, 3H, CH_3), 1.08–1.17 (m, 1H, *c*Pr-H), 1.43 [s, 10H, $C(CH_3)_3$, 4- or 6-H*], 1.87 (t, *J*=12.9 Hz, 1H, 4- or 6-H), 2.20 (q, *J*=6.5 Hz, 1H, 1′-H), 2.31–2.42 (m, 6H, CH_2NCH_2, 4- or 6-H), 2.57–2.68 (m, 1H, 5-H), 3.64 (t, *J*=4.6 Hz, 4H, CH_2OCH_2), 5.71 (t, *J*=3.6 Hz, 1H, 7-H). *The peak of this proton sits under the broad singlet of the *tert*-butyl group, thus the spin coupling constant of this proton could not be determined. This proton correlates clearly with the carbon peak at 38.14 ppm in the HMQC spectrum.^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.13 (−, *c*Pr-C), 12.43 (−, *c*Pr-C), 17.15 (+, CH_3), 18.63 (C_{quat}, *c*Pr-C), 28.01 [+, $C(CH_3)_3$], 28.01 (−, C-4 or -6), 38.14 (−, C-4 or -6), 39.85 (+, C-5), 50.47 (−, CH_2NCH_2), 58.58 (+, C-1′), 67.17 (−, CH_2OCH_2), 79.88 [C_{quat}, $C(CH_3)_3$], 120.68 (+, C-7), 140.58 (C_{quat}, C-8), 174.81 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 321 (49) [M^+], 306 (94) [M^+-CH_3], 250 (80) [$M^+-C_2H_5$], 133 (30), 114 (100), 100 (26), 86 (22); elemental analysis calcd (%) for $C_{19}H_{31}NO_3$: C 70.99, H 9.72; found: C 70.72, H 9.98. $C_{19}H_{31}NO_3$ (321.46): calcd 321.2304 (correct HRMS).

4.3.3. 4-[1-(7-Benzenesulfonylspiro[2.5]oct-4-en-4-yl)-ethyl]morpholine (25a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. After cooling the mixture to room temperature phenyl vinyl sulfone (**16**, 672 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield **25a** (450 mg, 62%, yellowish oil) as a mixture of two diastereomers (ratio 1.2:1 according to NMR).

Major diastereomer. R_f=0.45 (light petroleum/ethyl acetate, 1:1); IR (KBr): $\tilde{\nu}$=3064, 2972, 2955, 2856, 2814, 1448, 1311 (S=O), 1275 (S=O), 1152 (S=O), 1116 (S=O), 1023, 938, 861, 726 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.30–0.39 (m, 1H, *c*Pr-H), 0.52–0.62 (m, 1H, *c*Pr-H), 0.74–0.84 (m, 1H, *c*Pr-H), 0.92–1.00 (m, 1H, *c*Pr-H), 0.99 (d, *J*=6.3 Hz, 3H, CH_3), 1.38 (ddd, *J*=12.4, 2.7, 1.2 Hz, 1H, 6- or 8-H), 2.04–2.17 (m, 2H, 1′-H, 6- or 8-H), 2.29–2.41 (m, 6H, CH_2NCH_2, 6- or 8-H), 3.28–3.45 (m, 1H, 7-H), 3.65 (t, *J*=4.56 Hz, 4H, CH_2OCH_2), 5.72 (t, *J*=3.8 Hz, 1H, 5-H), 7.52–7.70 (m, 3H, Ph), 7.86–7.90 (m, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.74 (−, *c*Pr-C), 13.37 (−, *c*Pr-C), 17.34 (+, CH_3), 19.49 (C_{quat}, *c*Pr-C), 25.57 (−, C-6 or -8), 34.67 (−, C-6 or -8), 50.46 (−, CH_2NCH_2), 59.00 (+, C-1′), 59.77 (+, C-7), 66.99 (−, CH_2OCH_2), 118.60 (+, C-5), 128.71 (+, Ph-C), 128.99 (+, Ph-C), 133.56 (+, Ph-C), 137.02 (C_{quat}), 141.18 (C_{quat}); MS (70 eV, EI), *m/z* (%): 361 (11) [M^+], 346 (38) [M^+-CH_3], 204 (35), 117 (28), 114 (100), 91 (33); elemental analysis calcd (%) for $C_{20}H_{27}NO_3S$ (361.5): C 66.45, H 7.53; found: C 66.24, H 7.61.

Minor diastereomer. R_f=0.38 (light petroleum/ethyl acetate, 1:1); IR (film): $\tilde{\nu}$=3057, 2967, 2858, 2812, 1447, 1306 (S=O), 1273 (S=O), 1147 (S=O), 1114 (S=O), 944, 751, 725 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.24–0.38 (m, 1H, *c*Pr-H), 0.45–0.55 (m, 2H, *c*Pr-H), 0.92 (d, *J*=6.6 Hz, 3H, CH_3), 1.17–1.23 (m, 1H, *c*Pr-H), 1.33 (ddd, *J*=12.7, 2.7, 1.4 Hz, 1H, 6- or 8-H), 2.04 (t, *J*=12.1 Hz, 1H, 6- or 8-H), 2.16–2.45 (m, 7H, CH_2NCH_2, 1′-H, 6- or 8-H), 3.20–3.36 (m, 1H, 7-H), 3.54 (t, *J*=4.6 Hz, 4H, CH_2OCH_2), 5.72 (dd, *J*=5.5, 4.9 Hz, 1H, 5-H), 7.44–7.63 (m, 3H, Ph), 7.77–7.82 (m, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=11.83 (−, *c*Pr-C), 13.85 (−, *c*Pr-C), 16.31 (+, CH_3), 19.06 (C_{quat}, *c*Pr-C), 25.65 (−, C-6 or -8), 34.36 (−, C-8 or -6), 50.19 (−, CH_2NCH_2), 58.56 (+, C-1′), 59.67 (+, C-7), 67.25 (−, CH_2OCH_2), 120.09 (+, C-5), 128.82 (+, Ph-C), 129.13 (+, Ph-C), 133.68 (+, Ph-C), 137.23 (C_{quat}), 141.61 (C_{quat}); MS (70 eV, EI), *m/z* (%): 361 (13) [M^+], 346 (47) [M^+-CH_3], 204 (42), 117 (37), 114 (100), 91 (33) 77 (61); elemental analysis calcd (%) for $C_{20}H_{27}NO_3S$ (361.5): C 66.45, H 7.53; found: C 66.21, H 7.62.

4.3.4. 4,5-Dimethyl 8-(1-morpholin-4-ylethyl)spiro[2.5]oct-7-ene-carboxylate (*cis*-/*trans*-26a). (a) According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL), at 80 °C for 2 h. After cooling the mixture to room temperature, dimethyl fumarate (**17**, 576 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying over $MgSO_4$, the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield *cis*-/*trans*-**26a** (391.7 mg, 58%, yellowish oil) as a mixture of two diastereomers (ratio 1.2:1 according to NMR).

*Major and minor diastereomers**. R_f=0.27 (light petroleum/ethyl acetate, 3:1); IR (film): $\tilde{\nu}$=3083, 2953, 2850, 2809, 2691, 1739, 1466, 1349, 1265, 1197, 1172, 1119, 1021, 945, 918, 864 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.43–0.50 (m, 1H, *c*Pr-H), 0.59–0.68 (m, 3H, *c*Pr-H), 0.70–0.81 (m, 2H, *c*Pr-H), 0.93–0.99 (m, 2H, *c*Pr-H), 1.04 (d, *J*=6.5 Hz, 3H, CH_3), 1.04 (d, *J*=6.5 Hz, 3H, CH_3), 2.08 (q, *J*=6.7 Hz, 1H, 1′-H), 2.19–2.52 (m, 13H, 2×

(CH_2NCH_2), 2×6-H, 1′-H), 2.58 (d, J=4.3 Hz, 1H, 4-H), 2.82 (d, J=7.3 Hz, 1H, 4-H), 3.12 (q, J=7.0 Hz, 1H, 5-H), 3.21–3.26 (m, 1H, 5-H), 3.62–3.68 (m, 8H, 2×CH_2OCH_2), 3.65 (s, 3H, OCH_3), 3.67 (s, 9H, 3×OCH_3), 5.75 (q, J= 3.5 Hz, 2H, 2×7-H); ^{13}C NMR (75.5 MHz, $CDCl_3$, DEPT): δ=9.77 (−, *c*Pr-C), 9.86 (−, *c*Pr-C), 10.65 (−, *c*Pr-C), 11.61 (−, *c*Pr-C), 16.95 (+, CH_3), 17.22 (+, CH_3), 18.61 (C_{quat}, *c*Pr-C), 19.29 (C_{quat}, *c*Pr-C), 24.51 (−, C-6), 26.51 (−, C-6), 40.56 (+, C-5), 41.33 (+, C-5), 49.77 (+, C-4), 50.52 (−, CH_2NCH_2), 50.66 (−, CH_2NCH_2), 50.77 (+, C-4), 51.59 (+, 4×OCH_3), 58.93 (+, C-1′), 59.56 (+, C-1′), 67.22 (−, 2×CH_2OCH_2), 120.04 (+, C-7), 121.09 (+, C-7), 138.76 (C_{quat}, C-8), 139.65 (C_{quat}, C-8), 173.11 (C_{quat}, C=O), 173.24 (C_{quat}, C=O), 174.04 (C_{quat}, C=O), 174.72 (C_{quat}, C=O); MS (70 eV, EI), m/*z* (%): 337 (10) [M^+], 322 (47) [M^+-CH_3], 262 (5), 191 (11), 131 (24), 114 (100), 91 (24) 59 (26); elemental analysis calcd (%) for $C_{18}H_{27}NO_5$ (337.4): C 64.07, H 8.07; found: C 64.26, H 7.86. *Proton and carbon chemical shifts were given for both diastereomers together because ^{1}H NMR and ^{13}C NMR spectra were not proper to classify all of the peaks for major and minor diastereomers. IR, EI mass and elemental analysis were carried out for the mixture of diastereomers.

(b) From the same quantities of reagents, but dimethyl maleate (**18**) instead of dimethyl fumarate (**17**), compound *cis*-/*trans*-**26a** (351 mg, 52%) was obtained as a mixture of two diastereomers (ratio 1.7:1 according to NMR) according to GP-B after column chromatography.

4.3.5. *tert*-Butyl 8-(1-piperidin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (24b). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), piperidine (**12b**, 170.3 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. After cooling the mixture to room temperature *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 1:1) to yield **24b** (209 mg, 33%, yellowish oil) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. R_f=0.28 (light petroleum/ethyl acetate, 1:1); IR (film): $\tilde{\nu}$=3075, 2975, 2932, 2852, 2793, 2747, 1729, 1456, 1391, 1367, 1320, 1255, 1153, 1060, 932, 851 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.29–0.34 (m, 1H, *c*Pr-H), 0.45–0.49 (m, 1H, *c*Pr-H), 0.82–0.91 (m, 2H, *c*Pr-H), 0.99 (d, J=6.7 Hz, 3H, CH_3), 1.13–1.19 (m, 1H, 4- or 6-H), 1.36–1.51 (m, 6H, piperidine), 1.43 [s, 9H, $C(CH_3)_3$], 1.98 (t, J=11.9 Hz, 1H, 4- or 6-H), 2.19–2.45 (m, 7H, 4- or 6-H, piperidine, 1′-H), 2.58–2.71 (m, 1H, 5-H), 5.68–5.71 (m, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.77 (−, *c*Pr-C), 13.70 (−, *c*Pr-C), 16.41 (+, CH_3), 19.91 (C_{quat}, *c*Pr-C), 24.75 (−, piperidine), 26.19 (−, piperidine), 28.02 [+, $C(CH_3)_3$], 28.64 (−, C-4 or -6), 38.79 (−, C-4 or -6), 40.41 (+, C-5), 50.91 (−, piperidine), 59.49 (+, C-1′), 79.71 [C_{quat}, $C(CH_3)_3$], 120.29 (+, C-7), 141.16 (C_{quat}, C-8), 175.21 (C_{quat}, C=O); MS (70 eV, EI), m/*z* (%): 319 (18) [M^+], 304 (58) [M^+-CH_3], 248 (60), 234 (12), 112 (100), 84 (26); elemental analysis calcd (%) for $C_{20}H_{33}NO_2$ (319.5): C 75.19, H 10.41; found: C 74.97, H 10.66.

Diastereomer II. R_f=0.18 (light petroleum/ethyl acetate 1:1); IR (film): $\tilde{\nu}$=3078, 2975, 2932, 2852, 2790, 2748, 1729, 1456, 1391, 1367, 1332, 1257, 1153, 1117, 933, 850 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.27–0.34 (m, 1H, *c*Pr-H), 0.40–0.48 (m, 1H, *c*Pr-H), 0.51–0.58 (m, 1H, *c*Pr-H), 0.98 (d, J=6.7 Hz, 3H, CH_3), 1.09–1.19 (m, 1H, *c*Pr-H), 1.29–1.51 (m, 7H, 4- or 6-H, piperidine), 1.37 [s, 9H, $C(CH_3)_3$], 1.79–1.89 (m, 1H, 4- or 6-H), 2.18–2.40 (m, 7H, 4- or 6-H, piperidine, 1′-H), 2.51–2.63 (m, 1H, 5-H), 5.68 (d, J= 3.9 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.24 (−, *c*Pr-C), 12.60 (−, *c*Pr-C), 16.36 (C_{quat}, *c*Pr-C), 18.76 (+, CH_3), 24.62 (−, piperidine), 26.12 (−, piperidine), 27.94 [+, $C(CH_3)_3$], 28.09 (−, C-4 or -6), 38.25 (−, C-4 or -6), 39.92 (+, C-5), 50.75 (−, piperidine), 58.76 (+, C-1′), 79.68 [C_{quat}, $C(CH_3)_3$], 121.45 (+, C-7), 141.00 (C_{quat}, C-8), 174.87 (C_{quat}, C=O); MS (70 eV, EI), m/*z* (%): 319 (18) [M^+], 304 (58) [M^+-CH_3], 248 (60), 234 (12), 112 (100), 84 (26); elemental analysis calcd (%) for $C_{20}H_{33}NO_2$ (319.5): C 75.19, H 10.41; found: C 74.97, H 10.66.

4.3.6. *tert*-Butyl 8-(1-pyrrolidin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (24c). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), pyrrolidine (**12c**, 142 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. After cooling the mixture to room temperature *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate/methanol 3:1:1) to yield **24c** (176 mg, 29%, yellowish oil) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. R_f=0.33 (light petroleum/ethyl acetate/methanol, 3:1:1); IR (film): $\tilde{\nu}$=3075, 2971, 2932, 2875, 2776, 2712, 1728, 1478, 1457, 1256, 1152, 985, 850 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.34–0.38 (m, 1H, *c*Pr-H), 0.46–0.49 (m, 1H, *c*Pr-H), 0.62–0.66 (m, 1H, *c*Pr-H), 0.80–0.84 (m, 1H, *c*Pr-H), 1.07 (d, J=6.2 Hz, 3H, CH_3), 1.14–1.17 (m, 1H, 4- or 6-H), 1.39 [s, 9H, $C(CH_3)_3$], 1.66–1.71 (m, 4H, pyrrolidine), 1.81 (q, J=6.11 Hz, 1H, 1′-H), 1.96 (td, J=1.8, 12.5 Hz, 1H, 4- or 6-H), 2.21 (ddd, J=17.5, 11.5, 2.5 Hz, 1H, 4- or 6-H), 2.33–2.38 (m, 3H, 4- or 6-H, pyrrolidine), 2.42–2.44 (m, 2H, pyrrolidine), 2.55–2.60 (m, 1H, 5-H), 5.79 (dd, J=2.4, 4.9 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.59 (−, *c*Pr-C), 13.17 (−, *c*Pr-C), 18.66 (C_{quat}, *c*Pr-C), 22.72 (+, CH_3), 23.35 (−, pyrrolidine), 28.04 [+, $C(CH_3)_3$], 28.55 (−, C-4 or -6), 38.30 (−, C-4 or -6), 40.43 (+, C-5), 52.66 (−, pyrrolidine), 59.31 (+, C-1′), 79.78 [C_{quat}, $C(CH_3)_3$], 119.74 (+, C-7), 142.42 (C_{quat}, C-8), 175.16 (C_{quat}, C=O); MS (70 eV, EI), m/*z* (%): 305 (20) [M^+], 290 (56) [M^+-CH_3], 234 (44), 220 (10), 98 (100), 70 (22); elemental analysis calcd (%) for $C_{19}H_{31}NO_2$ (305.5): C 74.71, H 10.23; found: C 74.41, H 10.01.

Diastereomer II. R_f=0.25 (light petroleum/ethyl acetate/methanol, 3:1:1); IR (film): $\tilde{\nu}$=3078, 2971, 2875, 2776, 2710, 1728, 1478, 1457, 1391, 1367, 1256, 1054, 947, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.36–0.42 (m, 1H, *c*Pr-H), 0.44–0.51 (m, 1H, *c*Pr-H), 0.55–0.61 (m, 1H, *c*Pr-H), 0.96–1.03 (m, 1H, *c*Pr-H), 1.07 (d, J=6.5 Hz, 3H, CH_3), 1.40–1.47 (m, 1H, 4- or 6-H), 1.41 [s, 9H, $C(CH_3)_3$], 1.67–1.71 (m, 4H, pyrrolidine), 1.82–1.89 (m, 1′ H, 4- or 6-H), 1.98 (q, J=6.4 Hz, 1H, 1′-H), 2.27–2.34 (m, 2H, 4- or 6-H), 2.43–2.54 (m, 4H, pyrrolidine), 2.54–2.63 (m, 1H, 5-H), 5.79 (t, J=4.0 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.11 (−, *c*Pr-C), 12.27 (−, *c*Pr-C), 18.42 (C_{quat}, *c*Pr-C), 22.64 (+, CH_3), 23.33 (−, pyrrolidine), 28.03 [+, $C(CH_3)_3$], 38.07 (−, C-4 or -6), 39.88 (+, C-5), 52.67 (−, pyrrolidine), 58.19 (+, C-1′), 79.80 [C_{quat}, $C(CH_3)_3$], 120.97 (+, C-7), 142.54 (C_{quat}, C-8), 174.86 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 305 (4) [M^+], 290 (24) [M^+-CH_3], 234 (28), 220 (12), 98 (100), 70 (35), 57 (30), 41 (18); elemental analysis calcd (%) for $C_{19}H_{31}NO_2$ (305.5): C 74.71, H 10.23; found: C 74.41, H 10.01.

4.3.7. *tert*-Butyl 8-[1-(4-benzylpiperazin-1-yl)ethyl] spiro[2.5]oct-7-ene-5-carboxylate (24d). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), *N*-benzylpiperazine (**12d**, 352.5 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. After cooling the mixture to room temperature *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **24d** (395 mg, 48%, yellowish oil) as a mixture of two diastereomers (ratio 1.1:1 according to NMR).

Major diastereomer. R_f=0.39 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3063, 2975, 2932, 2808, 2689, 1727, 1495, 1391, 1367, 1330, 1258, 1153, 1013, 910, 849, 823, 734 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.33–0.40 (m, 1H, *c*Pr-H), 0.45–0.52 (m, 1H, *c*Pr-H), 0.56–0.64 (m, 1H, *c*Pr-H), 1.03 (d, J=6.6 Hz, 3H, CH_3), 1.11–1.18 (m, 1H, *c*Pr-H), 1.36–1.43 (m, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.88 (t, J=11.6 Hz, 1H, 4- or 6-H), 2.09 (q, J=6.2 Hz, 1H, 1′-H), 2.31–2.42 (m, 10H, piperazine, 4- or 6-H), 2.56–2.67 (m, 1H, 5-H), 3.48 (s, 2H, Bn), 5.68 (t, J=3.8 Hz, 1H, 7-H), 7.21–7.30 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.11 (−, *c*Pr-C), 12.61 (−, *c*Pr-C), 17.37 (+, CH_3), 18.73 (C_{quat}, *c*Pr-C), 28.03 [+, $C(CH_3)_3$], 28.12 (−, C-4 or -6), 38.30 (−, C-4 or -6), 39.99 (+, C-5), 49.81 (−, piperazine), 53.51 (−, piperazine), 58.23 (+, C-1′), 63.10 (−, Bn), 79.77 [C_{quat}, $C(CH_3)_3$], 121.5 (+, C-7), 126.87 (+, Ph-C), 128.08 (+, Ph-C), 129.21 (+, Ph-C), 138.21 (C_{quat}), 141.16 (C_{quat}), 174.88 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 410 (26) [M^+], 395 (6) [M^+-CH_3], 203 (10), 175 (100), 91 (42); elemental analysis calcd (%) for $C_{26}H_{38}N_2O_2$ (410.6): C 76.06, H 9.33; found: C 75.81, H 9.14.

Minor diastereomer. R_f=0.55 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3063, 3026 2974, 2931, 2807, 1727, 1495, 1455, 1391, 1367, 1318, 1256, 1150, 1013, 906, 849, 825, 736 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.29–0.35 (m, 1H, *c*Pr-H), 0.47–0.52 (m, 1H, *c*Pr-H), 0.80–0.89 (m, 2H, *c*Pr-H), 1.02 (d, J=6.4 Hz, 3H, CH_3), 1.15–1.21 (m, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.98 (t, J=12.30 Hz, 1H, 4- or 6-H), 2.17 (q, J=6.42 Hz, 1H, 1′-H), 2.24–2.56 (m, 10H, piperazine, 4- or 6-H), 2.56–2.68 (m, 1H, 5-H), 3.48 (s, 2H, Bn), 5.73 (t, J=3.8 Hz, 1H, 7-H); 7.21–7.30 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.79 (−, *c*Pr-C), 13.38 (−, *c*Pr-C), 17.71 (+, CH_3), 19.62 (C_{quat}, *c*Pr-C), 28.05 [+, $C(CH_3)_3$], 28.59 (−, C-4 or -6), 38.68 (−, C-4 or -6), 40.41 (+, C-5), 49.99 (−, piperazine), 53.43 (−, piperazine), 58.88 (+, C-1′), 63.09 (−, Bn), 79.76 [C_{quat}, $C(CH_3)_3$], 120.48 (+, C-7), 126.88 (+, Ph-C), 128.09 (+, Ph-C), 129.18 (+, Ph-C), 138.22 (C_{quat}), 141.04 (C_{quat}), 175.09 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 410 (36) [M^+], 395 (8) [M^+-CH_3], 337 (19), 203 (14), 175 (100), 91 (35); elemental analysis calcd (%) for $C_{26}H_{38}N_2O_2$ (410.6): C 76.06, H 9.33; found: C 75.81, H 9.14.

4.3.8. *tert*-Butyl 4-[1-(7-*tert*-butoxycarbonylspiro[2.5] oct-4-en-4-yl)ethyl]piperazinecarboxylate (24e). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), *N*-Boc-piperazine (**12e**, 372 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL), at 80 °C for 2 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **24e** (410.7 mg, 49%, yellowish oil) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. R_f=0.54 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3076, 2976, 2931, 2814, 1727, 1698, 1455, 1422, 1366, 1291, 1248, 1170, 1003, 923, 733 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.31–0.38 (m, 1H, *c*Pr-H), 0.47–0.54 (m, 1H, *c*Pr-H), 0.77–0.92 (m, 2H, *c*Pr-H), 1.02 (d, J=6.4 Hz, 3H, CH_3), 1.16–1.21 (m, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.44 [s, 9H, $C(CH_3)_3$], 1.98 (t, J=12.3 Hz, 1H, 4- or 6-H), 2.18 (q, J=6.3 Hz, 1H, 1′-H), 2.25–2.38 (m, 6H; piperazine, 4- or 6-H), 2.57–2.69 (m, 1H, 5-H), 3.35 (t, J=4.8 Hz, 4H, piperazine), 5.75 (dd, J=2.7, 4.6 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.65 (−, *c*Pr-C), 13.19 (−, *c*Pr-C), 17.22 (+, CH_3), 19.46 (C_{quat}, *c*Pr-C), 27.85 [+, $C(CH_3)_3$], 28.21 [+, $C(CH_3)_3$], 28.39 (−, C-4 or -6), 38.41 (−, C-4 or -6), 40.13 (+, C-5), 43.19 (−, piperazine)*, 49.59 (−, piperazine), 58.60 (+, C-1′), 79.08 [C_{quat}, $C(CH_3)_3$], 79.58 [C_{quat}, $C(CH_3)_3$], 120.63 (+, C-7), 140.59 (C_{quat}), 154.51 (C_{quat}, C=O). 174.79 (C_{quat}, C=O); *It appears as a multiplet of low intensity. This carbon correlates clearly with the triplet at 3.35 ppm in the HMQC spectrum. MS (70 eV, EI), *m/z* (%): 420 (3) [M^+], 397 (8), 284 (17), 213 (52), 157 (100), 57 (48), 41 (14); elemental analysis calcd

(%) for $C_{24}H_{40}N_2O_4$ (420.6): C 68.54, H 9.59; found: C 68.30, H 9.42.

Diastereomer II. R_f=0.48 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3078, 2975, 2931, 2811, 2756, 1727, 1699, 1455, 1422, 1366, 1291, 1248, 1167, 1003, 923, 733 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.34–0.42 (m, 1H, *c*Pr-H), 0.46–0.54 (m, 1H, *c*Pr-H), 0.56–0.64 (m, 1H, *c*Pr-H), 1.02 (d, J=6.6 Hz, 3H, CH_3), 1.08–1.21 (m, 1H, *c*Pr-H), 1.38–1.44 (m, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.44 [s, 9H, $C(CH_3)_3$], 1.88 (dd, J=10.7, 12.8 Hz, 1H, 4- or 6-H), 2.22–2.43 (m, 7H, piperazine, 4- or 6-H, 1′-H), 2.57–2.69 (m, 1H, 5-H), 3.35 (t, J=4.9 Hz, 4H, piperazine), 5.68 (t, J=3.8 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.10 (−, *c*Pr-C), 12.39 (−, *c*Pr-C), 16.43 (+, CH_3), 18.51 (C_{quat}, *c*Pr-C), 27.89 [+, $C(CH_3)_3$], 27.89 (−, C-4 or -6), 28.27 [+, $C(CH_3)_3$], 38.09 (−, C-4 or -6), 39.75 (+, C-5), 43.58 (−, piperazine)*, 49.32 (−, piperazine), 59.74 (+, C-1′), 79.14 [C_{quat}, $C(CH_3)_3$], 79.69 [C_{quat}, $C(CH_3)_3$], 121.65 (+, C-7), 140.58 (C_{quat}), 154.61 (C_{quat}, C=O), 174.64 (C_{quat}, C=O). *It appears as a multiplet of low intensity. This carbon correlates clearly with the triplet at 3.35 ppm in the HMQC spectrum. MS (70 eV, EI), *m/z* (%): 420 (13) [M^+], 405 (18) [M^+-CH_3], 293 (22), 279 (10), 213 (18), 157 (32), 133 (50), 57 (100), 41 (34); elemental analysis calcd (%) for $C_{24}H_{40}N_2O_4$ (420.6): C 68.54, H 9.59; found: C 68.30, H 9.42.

4.3.9. 5-[1′-(Morpholin-4″-yl)ethyl]-2-phenylspiro[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (27a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature, 1-phenyl-pyrrole-2,5-dione (**19**, 693 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield **27a** (290 mg, 40%, yellow solid) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. Mp 127 °C, R_f=0.42 (light petroleum/ethyl acetate 1:1); IR (KBr): $\tilde{\nu}$=3087, 3022, 2955, 2906, 2847, 2809, 1708, 1595, 1494, 1456, 1435, 1368, 1298, 1183, 1170, 1135, 1111, 855, 759 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.300.34 (m, 1H, *c*Pr-H), 0.72–0.80 (m, 1H, *c*Pr-H), 1.58 (d, J=6.7 Hz, 3H, CH_3), 1.20–1.26 (m, 1H, *c*Pr-H), 1.75–1.83 (m, 1H, *c*Pr-H), 2.21–2.47 (m, 6H, CH_2NCH_2, 3a-H, 7-H), 2.65 (q, J=6.7 Hz, 1H, 1′-H), 2.81 (ddd, J=2.0, 7.2, 14.8 Hz, 1H, 7-H), 3.29–3.36 (m, 1H, 7a-H), 3.50 (t, J=4.6 Hz, 4H, CH_2OCH_2), 5.85 (dd, J=2.9, 6.9 Hz, 1H, 6-H), 7.18–7.21 (m, 2H, Ph), 7.32–7.45 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.65 (−, *c*Pr-C), 13.04 (−, *c*Pr-C), 15.04 (+, CH_3), 20.05 (C_{quat}, *c*Pr-C), 24.19 (−, C-7), 41.59 (+, C-3a), 50.19 (+, C-7a), 50.57 (−, CH_2NCH_2), 64.02 (+, C-1′), 66.96 (−, CH_2OCH_2), 125.95 (+, Ph-C, C-6), 128.26 (+, Ph), 128.88 (+, Ph-C), 131.89 (C_{quat}), 144.11 (C_{quat}), 177.07 (C_{quat}, C=O), 178.88 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 366 (46) [M^+], 351 (93) [M^+-CH_3], 152 (6), 133 (8), 117 (18), 114 (100), 91 (16), 86 (27); elemental analysis calcd (%) for $C_{22}H_{26}N_2O_3$ (366.5): C 72.11, H 7.15; found: C 71.96, H 7.02.

Diastereomer II. Mp 140 °C, R_f=0.38 (light petroleum/ethyl acetate 1:1); IR (KBr): $\tilde{\nu}$=3064, 2965, 2891, 2846, 2815, 1773, 1702, 1597, 1500, 1455, 1435, 1390, 1301, 1189, 1172, 1115, 1040, 944, 923, 754 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.35–0.43 (m, 1H, *c*Pr-H), 0.79–0.87 (m, 1H, *c*Pr-H), 0.98 (d, J=6.7 Hz, 3H, CH_3), 1.06–1,18 (m, 1H, *c*Pr-H), 1.47–1.55 (m, 1H, *c*Pr-H), 2.31–2.50 (m, 6H, CH_2NCH_2, 3a-H, 7-H), 2.80–2.92 (m, 2H, 1′-H, 7-H), 3.32–3.40 (m, 1H, 7a-H), 3.52–3.63 (m, 4H, CH_2OCH_2), 5.93 (br s, 1H, 6-H), 7.13–7.17 (m, 2H, Ph), 7.34–7.45 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.71 (−, *c*Pr-C), 11.87 (+, CH_3), 12.73 (−, *c*Pr-C), 22.29 (C_{quat}, *c*Pr-C), 24.56 (−, C-7), 41.60 (+, C-7a), 49.16 (−, CH_2NCH_2), 50.05 (+, C-3a), 60.80 (+, C-1′), 67.28 (−, CH_2OCH_2), 123.30 (+, C-6), 126.33 (+, Ph-C), 128.49 (+, Ph-C), 129.05 (+, Ph-C), 131.98 (C_{quat}), 143.59 (C_{quat}), 177.74 (C_{quat}, C=O), 178.96 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 366 (25) [M^+], 351 (77) [M^+-CH_3], 133 (6), 114 (100), 86 (16); elemental analysis calcd (%) for $C_{22}H_{26}N_2O_3$ (366.5): C 72.11, H 7.15; found: C 71.96, H 7.02.

4.3.10. 5-[1′-(Morpholin-4″-yl)ethyl]-2-(3‴-trifluoromethyl)phenylspiro[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (28a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature 1-(3′-trifluoromethylphenyl)-2,5-dihydro-pyrrole-2,5-dione (**20**, 965 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 2:3) to yield **28a** (327.4 mg, 38%, pale yellow solid) as a mixture of two diastereomers (ratio 1.2:1 according to NMR).

Major diastereomer. Mp 147 °C; R_f=0.51 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=3067 (C–H), 1721 (C=O), 1705, 1616, 1526, 1415, 1340, 1223, 1163 (C–F), 1129, 1110, 1071, 842, 824, 818 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.30–0.44 (m, 1H, *c*Pr-H), 0.74–0.89 (m, 1H, *c*Pr-H), 1.06 (d, J=6.9 Hz, 3H, CH_3), 1.19–1.33 (m, 1H, *c*Pr-H), 1.82 (m_c, 1H, *c*Pr-H), 2.19–2.39 (m, 4H, CH_2NCH_2), 2.35 (d, J=9.1 Hz, 1H, 3a-H), 2.45 (ddd, J=15.0, 6.6, 3.3 Hz, 1H, 7-H), 2.67 (q, ^3J=6.9 Hz, 1H, 1′-H), 2.84 (ddd, J=15.0, 6.9, 1.8 Hz, 1H, 7-H), 3.33–3.45 (m, 1H, 7a-H), 3.45–3.59 (m, 4H, CH_2OCH_2), 5.86 (dd, J=7.3, 3.3 Hz, 1H, 6-H), 7.40–7.75 (m, 4H, Ar-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.73 (−, *c*Pr-C), 13.3 (−, *c*Pr-C), 15.0 (+, CH_3), 20.6 (C_{quat}, C-4), 24.2 (−, C-7), 41.7 (+, C-7a), 50.3 (+, C-1′), 50.6 (−, CH_2NCH_2), 63.9 (+, C-3a), 67.0 (−, CH_2OCH_2), 123.0 (+, C-6), 123.5 (C_{quat}, q, ^1J(C,F)=247 Hz, CF_3), 125.0 (+, C-5‴), 125.5 (+, Ar-C), 125.9 (+, Ar-C), 129.2 (+, Ar-C), 131.4 (C_{quat},

q, ^2J(C,F)=33.3 Hz, C-3‴), 132.4 (C_{quat}, Ar-C), 144.2 (C_{quat}, C-5), 176.8 (C_{quat}, C=O), 178.5 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 434 (48) [M^+], 419 (100) [M^+-CH_3], 114 (100), 86 (14) [morpholine$^+$−H]; HRMS (EI): calcd for $C_{23}H_{25}F_3N_2O_3$ [M^+] 434.1817, correct HRMS.

Minor diastereomer. Mp 146 °C; R_f=0.44 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=3068 (C–H), 1723 (C=O), 1702, 1618, 1529, 1413, 1342, 1225, 1164 (C–F), 1126, 1113, 1074, 841, 823, 817 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.35 (m_c, 1H, *c*Pr-H), 0.74–0.85 (m, 1H, *c*Pr-H), 1.05 (d, ^3J=6.7 Hz, 3H, CH_3), 1.18–1.31 (m, 1H, *c*Pr-H), 1.81 (m_c, 1H, *c*Pr-H), 2.17–2.39 (m, 5H, CH_2NCH_2, 3a-H), 2.45 (ddd, *J*=15.0, 6.6, 3.3 Hz, 1H, 7-H), 2.67 (q, *J*=6.90 Hz, 1H, 1′-H) 2.83 (ddd, *J*=15.0, 6.9, 1.8 Hz, 1H, 7-H), 3.39 (m_c, 1H, 7a-H), 3.44–3.57 (m, 4H, CH_2OCH_2), 5.87 (dd, *J*=7.3, 3.4 Hz, 1H, 6-H), 7.39–7.70 (m, 4H, Ar-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.68 (−, *c*Pr-C), 11.8 (+, CH_3), 12.8 (−, *c*Pr-C), 22.9 (C_{quat}, C-4), 24.5 (−, C-7), 41.6 (+, C-7a), 49.1 (−, CH_2NCH_2), 50.1 (+, C-1′), 60.7 (+, C-3a), 67.3 (−, CH_2OCH_2), 123.2 (+, C-6), 123.4 (C_{quat}, q, ^1J(C,F)=245 Hz, CF_3), 125.1 (+, Ar-C), 125.2 (+, Ar-C), 129.5 (+, Ar-C), 129.6 (+, Ar-C), 131.8 (C_{quat}, q, ^2J(C,F)=33.3 Hz, C-3‴), 132.4 (C_{quat}, Ar-C), 143.7 (C_{quat}, C-5), 177.4 (C_{quat}, C=O), 178.6 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 434 (48) [M^+], 419 (100) [M^+-CH_3], 114 (100), 86 (14) [morpholine$^+$−H]; HRMS (EI): calcd for $C_{23}H_{25}F_3N_2O_3$ [M^+]: 434.1817, correct HRMS.

4.3.11. 5-[1′-(Morpholin-4″-yl)ethyl]-2-(4‴-trifluoromethyl)phenylspiro[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (29a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature 1-(4′-trifluoromethylphenyl)-2,5-dihydropyrrole-2,5-dione (**21**, 965 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (130 g, 3×40 cm, light petroleum/ethyl acetate 2:3) to yield **29a** (384 mg, 44%, pink crystals) as a mixture of two diastereomers (ratio 1.1:1, according to NMR).

Major diastereomer. Mp 158 °C; R_f=0.51 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=2966, 2852, 1714 (C=O), 1616, 1519, 1384 (CH_3), 1326, 1172 (C–F), 1115, 1067, cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.41 (m_c, 1H, *c*Pr-H), 0.79–0.90 (m, 1H, *c*Pr-H), 0.97 (d, *J*=6.8 Hz, 3H, CH_3), 1.04–1.20 (m, 1H, *c*Pr-H), 1.52 (m_c, 1H, *c*Pr-H), 2.31–2.41 (m, 4H, CH_2NCH_2), 2.41–2.47 (m, 1H, 3a-H), 2.47–2.54 (m, 2H, 1′-H, 7-H), 2.86 (m_c, 1H, 7-H), 3.37 (m_c, 1H, 7a-H), 3.61 (m_c, 4H, CH_2OCH_2), 5.94 (d, *J*=7.3, 3.1 Hz, 1H, 6-H), 7.36 (d, *J*=8.5 Hz, 2H, Ar), 7.70 (d, *J*=8.5 Hz, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.66 (−, *c*Pr-C), 11.9 (+, CH_3), 12.8 (−, *c*Pr-C), 22.8 (C_{quat}, C-4), 24.4 (−, C-7), 41.6 (+, C-7a), 49.1 (−, CH_2NCH_2), 50.1 (+, C-1′), 60.7 (+, C-3a), 67.3 (−, CH_2OCH_2), 123.2 (+, C-6), 126.1 (C_{quat}, q, ^2J(C,F)=33.3 Hz, C-4‴), 126.5 (+, 4×Ar-C), 127.8 (C_{quat}, q, ^1J(C,F)=272 Hz, CF_3), 135.0 (C_{quat}, Ar-C), 143.8 (C_{quat}, C-5), 177.8 (C_{quat}, C=O), 178.7 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 435/434 (10/42) [M^+], 420/419 (22/89) [M^+-CH_3], 117 (13), 114 (100), 91 (12), 86 (13) [morpholine$^+$−H]; HRMS (EI): calcd for $C_{23}H_{25}F_3N_2O_3$ [M^+]: 434.1817, correct HRMS.

Minor diastereomer. Mp 149 °C; R_f=0.57 (light petroleum/ethyl acetate 2:3); IR (KBr): $\tilde{\nu}$=2958, 2853, 2810, 1710 (C=O), 1702 (C=O), 1613, 1518, 1384 (CH_3), 1325, 1173 (C–F), 1124, 1066, 1020, 845 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.36 (m_c, 1H, *c*Pr-H), 0.80 (m_c, 1H, *c*Pr-H), 1.06 (d, *J*=6.7 Hz, 3H, CH_3), 1.19–1.31 (m, 1H, *c*Pr-H), 1.85 (m_c, 1H, *c*Pr-H), 2.19–2.40 (m, 4H, CH_2NCH_2), 2.36 (d, *J*=9.2 Hz, 1H, 3a-H), 2.46 (ddd, *J*=15.0, 6.6, 3.3 Hz, 1H, 7-H), 2.67 (q, *J*=6.7 Hz, 1H, 1′-H), 2.84 (ddd, *J*=15.0, 6.9, 1.8 Hz, 1H, 7-H), 3.39 (m_c, 1H, 7a-H), 3.52 (m_c, 4H, CH_2OCH_2), 5.87 (dd, *J*=7.4, 2.9 Hz, 1H, 6-H), 7.42 (d, *J*=8.5 Hz, 2H, Ar), 7.70 (d, *J*=8.5 Hz, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.72 (−, *c*Pr-C), 13.3 (−, *c*Pr-C), 15.2 (+, CH_3), 20.6 (C_{quat}, C-4), 24.6 (−, C-7), 41.8 (+, C-7a), 50.4 (+, C-1′), 50.7 (−, CH_2NCH_2), 64.2 (+, C-3a), 67.0 (−, CH_2OCH_2), 126.1 (+, C-6), 126.1 (C_{quat}, q, ^2J(C,F)=33.3 Hz, C-4‴), 126.2 (+, 4×Ar), 127.8 (C_{quart}, q, ^1J(C,F)=272 Hz, CF_3), 135.0 (C_{quat}, Ar-C), 144.3 (C_{quat}, C-5), 176.8 (C_{quat}, C=O), 178.5 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 435/434 (10/42) [M^+], 420/419 (22/89) [M^+-CH_3], 117 (13), 114 (100), 91 (12), 86 (13) [morpholine$^+$−H]; HRMS (EI): calcd for $C_{23}H_{25}F_3N_2O_3$ [M^+]: 434.1817, correct HRMS.

4.3.12. 5-[1′-(Morpholin-4″-yl)ethyl]-2-[bis-(3‴,5‴-trifluoromethyl)]phenylspiro[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (30a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature, 1-[3′,5′-bis(trifluoromethyl)phenyl]-2,5-dihydropyrrole-2,5-dione (**22**, 1236 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (130 g, 3×40 cm, light petroleum/ethyl acetate, 2:3) to yield **30a** (376 mg, 37%, pale yellow crystals) as a mixture of two diastereomers (ratio 1.6:1, according to NMR).

Major diastereomer. Mp 94 °C; R_f=0.60 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=2962, 1791 (C=O), 1628, 1472, 1395 (C–F), 1280, 1176 (C–F), 1137, 892 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.37 (m_c, 1H, *c*Pr-H), 0.82 (m_c, 1H, *c*Pr-H), 1.05 (d, *J*=6.7 Hz, 3H, CH_3), 1.19–1.30 (m, 1H, *c*Pr-H), 1.76–1.90 (m, 1H, *c*Pr-H), 2.19–2.43 (m, 5H, 3a-H, CH_2NCH_2), 2.43–2.55 (m, 1H, 7-H), 2.66 (q, ^3J=6.7 Hz, 1H, 1′-H), 2.84 (ddd, *J*=15.0, 7.8, 1.8 Hz, 1H, 7-H), 3.41 (m_c, 1H, 7a-H), 3.50 (m_c, 4H, CH_2OCH_2), 5.94 (dd, *J*=7.3, 3.2 Hz, 1H, 6-H), 7.75 (s, 2H, Ar), 7.86 (s, 1H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.74 (−, *c*Pr-C), 11.8 (+, CH_3), 13.0 (−, *c*Pr-C), 22.9 (C_{quat}, C-4), 24.5 (−, C-7), 41.7 (+, C-7a), 49.1 (−, CH_2NCH_2), 50.2

(+, C-1′), 60.7 (+, C-3a), 67.2 (−, CH_2OCH_2), 121.9 (+, Ar-C), 122.7 (C_{quat}, q, ^1J(C,F)=271 Hz, 2×CF_3), 123.2 (+, C-6), 126.3 (+, 2×Ar-C), 132.4 (C_{quat}, q, ^2J(C,F)=33.3 Hz, C-3‴, C-5‴), 133.4 (C_{quat}, Ar-C), 143.9 (C_{quat}, C-5), 177.0 (C_{quat}, C=O), 178.2 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 502 (27) [M^+], 488/487 (24/100) [M^+-CH_3], 229 (13), 114 (48), 43 (35); HRMS (EI): calcd for $C_{24}H_{24}F_6N_2O_3$ [M^+]: 502.1691, correct HRMS.

Minor diastereomer. Mp 69 °C; R_f=0.59 (light petroleum/ethyl acetate, 2:3); IR (KBr): $\tilde{\nu}$=3105 (C–H), 2967, 1720 (C=O), 1627, 1472, 1396 (C–F), 1280, 1176 (C–F), 1135, 892 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.43 (m_c, 1H, *c*Pr-H), 0.77–0.93 (m, 1H, *c*Pr-H), 0.96 (d, *J*=6.8 Hz, 3H, CH_3), 1.02–1.18 (m, 1H, *c*Pr-H), 1.55 (m_c, 1H, *c*Pr-H), 2.20–2.42 (m, 5H, 3a-H, CH_2NCH_2), 2.44–2.59 (m, 1H, 7-H), 2.80–2.94 (m, 2H, 1′-H, 7-H), 3.43 (m_c, 1H, 7a-H), 3.56–3.70 (m, 4H, CH_2OCH_2), 5.88 (dd, *J*=7.1, 3.2 Hz, 1H, 6-H), 7.75 (br s, 1H, Ar), 7.80 (br s, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.87 (−, *c*Pr-C), 12.1 (+, CH_3), 12.8 (−, *c*Pr-C), 22.9 (C_{quat}, C-4), 24.5 (−, C-7), 41.8 (+, C-3a), 49.2 (−, CH_2NCH_2), 50.2 (+, C-1′), 60.9 (+, C-7a), 67.1 (−, CH_2OCH_2), 119.3 (+, Ar-C), 122.1 (+, C-6), 122.7 (C_{quat}, q, ^1J(C,F)=273 Hz, 2×CF_3), 126.4 (+, 2×Ar-C), 132.4 (C_{quat}, q, ^2J(C,F)=33.5 Hz, C-3‴, C-5‴), 133.3 (C_{quat}, Ar-C), 139.3 (C_{quat}, C-5), 177.0 (C_{quat}, C=O), 178.1 (C_{quat}, C=O); MS (70 eV), *m/z* (%): 502 (27) [M^+], 488/487 (24/100) [M^+-CH_3], 229 (13), 114 (48), 43 (35); HRMS (EI): calcd for $C_{24}H_{24}F_6N_2O_3$ [M^+]: 502.1691, correct HRMS).

4.3.13. *tert*-Butyl 8-(1-morpholin-4-ylethyl)-7-phenylspiro[2.5]oct-7-ene-5-carboxylate (39a). (a) According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 261 mg, 3.00 mmol), (1-iodovinyl)benzene (**31**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 3 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 100 °C for 65 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 10:1) to yield **39a** (286 mg, 36%, yellowish oil) as a mixture of two diastereomers (ratio 1.1:1 according to NMR).

Major diastereomer. R_f=0.48 (light petroleum/ethyl acetate, 10:1); IR (film): $\tilde{\nu}$=3003, 2980, 2951, 2853, 2803, 1723, 1450, 1263, 1149, 1113, 943, 849, 705 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.29–0.36 (m, 1H, *c*Pr-H), 0.59–0.66 (m, 1H, *c*Pr-H), 0.83–0.95 (m, 1H, *c*Pr-H), 1.05–1.13 (m, 1H, 4- or 6-H), 1.11 (d, *J*=7.0 Hz, 3H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$), 1.63–1.70 (m, 1H, *c*Pr-H), 2.02–2.37 (m, 5H, CH_2NCH_2, 4- or 6-H), 2.37–2.59 (m, 2H, 4- or 6-H), 2.75–2.93 (m, 2H, 5-H, 1-H), 3.57 (t, *J*=4.1 Hz, 4H, CH_2OCH_2), 7.05 (d, *J*=9.1 Hz, 2H, Ph), 7.19–7.34 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=13.78 (−, *c*Pr-C), 14.83 (−, *c*Pr-C), 18.04 (+, CH_3), 19.14 (C_{quat}, *c*Pr-C), 28.02 [+, $C(CH_3)_3$], 36.85 (−, C-4 or -6), 40.35 (−, C-4 or -6), 40.99 (+, C-5), 51.86 (−, CH_2NCH_2), 61.86 (+, C-1′), 67.00 (−, CH_2OCH_2), 79.98 [C_{quat}, $C(CH_3)_3$], 126.12 (+, Ph-C), 128.09 (+, Ph-C), 128.17 (+, Ph-C), 135.69 (C_{quat}), 136.43 (C_{quat}), 144.11 (C_{quat}), 174.77 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 397 (30) [M^+], 382 (8) [M^+-CH_3], 254 (36), 209 (31), 114 (100), 100 (26), 57 (39); elemental analysis calcd (%) for $C_{25}H_{35}NO_3$ (397.6): C 75.53, H 8.87; found: C 75.59, H 8.64.

Minor diastereomer. R_f=0.44 (light petroleum/ethyl acetate 10:1); IR (film): $\tilde{\nu}$=3077, 2975, 2851, 2806, 1726, 1450, 1367, 1265, 1151, 1122, 943, 864, 703 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.37–0.45 (m, 1H, *c*Pr-H), 0.54–0.62 (m, 1H, *c*Pr-H), 1.00 (d, *J*=7.1 Hz, 3H, CH_3), 1.02–1.09 (m, 1H, *c*Pr-H), 1.32 (dd, *J*=12.7, 3.6 Hz, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.83–1.98 (m, 2H, 4- or 6-H, *c*Pr-H), 2.22 (br s, 4H, CH_2NCH_2), 1.83–1.98 (m, 2H, 4- or 6-H), 2.73–2.88 (m, 2H, 5-H, 1-H), 3.55 (t, *J*=4.6 Hz, 4H, CH_2OCH_2), 7.04 (d, *J*=8.1 Hz, 2H, Ph), 7.18–7.33 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=13.07 (−, *c*Pr-C), 14.13 (−, *c*Pr-C), 18.78 (C_{quat}, *c*Pr-C), 19.07 (+, CH_3), 27.97 [+, $C(CH_3)_3$], 36.56 (−, C-4 or -6), 39.69 (−, C-4 or -6), 40.56 (+, C-5), 51.55 (−, CH_2NCH_2), 61.11 (+, C-1′), 67.06 (−, CH_2OCH_2), 79.93 [C_{quat}, $C(CH_3)_3$], 125.91 (+, Ph-C), 127.98 (+, Ph-C), 128.17 (+, Ph-C), 135.63 (C_{quat}), 136.66 (C_{quat}), 144.35 (C_{quat}), 174.65 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 397 (22) [M^+], 382 (8) [M^+-CH_3], 254 (32), 209 (28), 114 (100), 100 (25), 57 (30); elemental analysis calcd (%) for $C_{25}H_{35}NO_3$ (397.6): C 75.53, H 8.87; found: C 75.57, H 8.56.

(b) According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (1-iodovinyl)benzene (**31**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 10:1) to yield **39a** (142.5 mg, 18%, yellowish oil) as a mixture of two diastereomers (ratio 1:1 according to NMR), **51** (45.6 mg, 8%, yellowish oil) and **52** (170 mg, 27%, yellowish oil).

4.3.14. 4-(2-Cyclopropylidene-1-methyl-3-phenyl-but-3-enyl)morpholine (51). R_f=0.33 (light petroleum/ethyl acetate, 10:1); IR (film): $\tilde{\nu}$=3078, 3052, 2972, 2851, 2807, 1724, 1597, 1492, 1445, 1265, 1118, 1009, 942, 777, 701 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.76 (t, *J*=7.8 Hz, 2H, *c*Pr-H), 1.18 (t, *J*=7.8 Hz, 2H, *c*Pr-H), 1.28 (d, *J*=7.1 Hz, 3H, CH_3), 2.38–2.55 (m, 4H, CH_2NCH_2), 3.39 (q, *J*=6.7 Hz, 1H, 1-H), 3.65 (t, *J*=4.7 Hz, 4H, CH_2OCH_2), 5.25 (d, *J*=1.9 Hz, 1H, vinyl), 5.60 (d, *J*=1.88 Hz, 1H, vinyl), 7.21–7.32 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=2.98 (−, *c*Pr-C), 3.82 (−, *c*Pr-C), 14.70 (+, CH_3), 50.04 (−, CH_2NCH_2), 63.22 (+, C-1), 67.34 (−, CH_2OCH_2), 114.04 (−, vinyl), 125.49 (C_{quat}), 126.66 (+, Ph-C), 127.56 (+, Ph-C), 127.80 (+, Ph-C), 129.78 (C_{quat}), 142.56 (C_{quat}), 149.51 (C_{quat}); MS

(70 eV, EI) *m/z* (%): 269 (18) [M^+], 268 (37), 183 (4) [M^+ −morpholinyl], 114 (100).

4.3.15. *tert*-Butyl 8-(1-phenylvinyl)spiro[2.5]oct-7-ene-5-carboxylate (52). R_f=0.76 (light petroleum/ethyl acetate, 10:1); IR (film): $\tilde{\nu}$=3081, 2977, 2931, 1726, 1367, 1255, 1152, 903, 780 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ= 0.29–0.61 (m, 4H, *c*Pr-H), 1.37 (dd, *J*=2.9, 13.1 Hz, 1H, 4- or 6-H), 1.46 [s, 9H, $C(CH_3)_3$], 2.09 (t, *J*=12.2 Hz, 1H, 4- or 6-H), 2.47 (dd, *J*=3.7, 7.9 Hz, 2H, 4- or 6-H), 2.71–2.86 (m, 1H, 5-H), 4.94 (d, *J*=1.8 Hz, 1H, vinyl), 5.42 (d, *J*= 1.8 Hz, 1H, vinyl), 5.65 (t, *J*=3.8 Hz, 1H, 7-H), 7.23–7.32 (m, 3H, Ph), 7.37–7.41 (m, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=12.80 (−, *c*Pr-C), 13.69 (−, *c*Pr-C), 19.44 (C_{quat}, *c*Pr-C), 28.07 [+, $C(CH_3)_3$], 28.47 (−, C-4 or -6), 37.29 (−, C-4 or -6), 40.37 (+, C-5), 79.97 [C_{quat}, $C(CH_3)_3$], 114.22 (−, vinyl), 124.82 (+, C-7), 126.04 (+, Ph-C), 127.48 (+, Ph-C), 128.22 (+, Ph-C), 140.16 (C_{quat}), 142.22 (C_{quat}), 147.56 (C_{quat}), 174.88 (C_{quat}, C=O); MS (70 eV, EI) *m/z* (%): 310 (3) [M^+], 254 (60), 209 (41), 181 (30), 167 (39), 115 (19), 103 (32), 91 (46), 77 (27), 57 (100), 41 (52).

4.3.16. *tert*-Butyl 7-(benzo[1,3]dioxol-5-yl)-8-(1-morpholin-4-ylethyl)spiro[2.5]oct-7-ene-5-carboxylate (40a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 261 mg, 3.00 mmol), 5-(1-iodovinyl)benzo[1,3]-dioxole (**32**, 548.1 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL), at 80 °C for 3 h. After cooling the mixture to room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated with stirring at 80 °C for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 4:1) to yield **40a** (386 mg, 44%, yellowish oil) as a mixture of two diastereomers (ratio 1.2:1 according to NMR).

Major diastereomer. R_f=0.44 (light petroleum/ethyl acetate 4:1); IR (KBr): $\tilde{\nu}$=2976, 2952, 2806, 1726, 1606, 1485, 1452, 1433, 1367, 1266, 1238, 1211, 1152, 1121, 1039, 939, 810 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.2–0.34 (m, 1H, *c*Pr-H), 0.57–0.65 (m, 1H, *c*Pr-H), 0.78–0.95 (m, 1H, *c*Pr-H), 1.05 (dd, *J*=12.7, 3.3 Hz, 1H, 4- or 6-H), 1.11 (d, *J*=7.0 Hz, 3H, CH_3), 1.41 [s, 9H, $C(CH_3)_3$], 1.62–1.69 (m, 1H, *c*Pr-H), 2.03 (td, *J*=12.0, 2.0 Hz, 1H, 4- or 6-H), 2.22 (br s, 4H, CH_2NCH_2), 2.34–2.55 (m, 2H, 4- or 6-H), 2.77–2.89 (m, 2H, 5-H, 1-H), 3.57 (br s, 4H, CH_2OCH_2), 5.94–5.96 (m, 2H, OCH_2O), 6.47 (dd, *J*=7.8, 1.7 Hz, 1H, Ph), 6.53 (d, *J*=1.6 Hz, 1H, Ph), 6.76 (d, *J*=7.6 Hz, 1H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=13.69 (−, *c*Pr-C), 14.78 (−, *c*Pr-C), 17.96 (+, CH_3), 19.04 (C_{quat}, *c*Pr-C), 27.93 [+, $C(CH_3)_3$], 36.81 (−, C-4 or -6), 40.18 (−, C-4 or -6), 40.84 (+, C-5), 51.80 (−, CH_2NCH_2), 61.77 (+, C-1), 66.89 (−, CH_2OCH_2), 79.86 [C_{quat}, $C(CH_3)_3$], 100.72 (−, OCH_2O), 108.05 (+, Ph-C), 108.59 (+, Ph-C), 120.94 (+, Ph-C), 135.79 (C_{quat}, Ph-C), 136.05 (C_{quat}, Ph-C), 137.70 (C_{quat}, Ph-C), 145.69 (C_{quat}), 147.27 (C_{quat}), 174.64 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 441 (12) [M^+], 426 (5) [M^+ −CH_3], 298 (56), 131 (22), 114 (95), 100 (28), 57 (100), 41 (45); elemental analysis calcd (%) for $C_{26}H_{35}NO_5$ (441, 6): C 70.72, H 7.99; found: C 70.55, H 7.72.

Minor diastereomer. R_f=0.39 (light petroleum/ethyl acetate 4:1); IR (KBr): $\tilde{\nu}$=3077, 2975, 2852, 2805, 1725, 1505, 1485, 1433, 1367, 1239, 1150, 1121, 1039, 938, 810 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.36–0.44 (m, 1H, *c*Pr-H), 0.53–0.61 (m, 1H, *c*Pr-H), 0.77–0.90 (m, 1H, *c*Pr-H), 0.99 (d, *J*=6.9 Hz, 3H, CH_3), 1.30 (dd, *J*=12.7, 3.6 Hz, 1H, 4- or 6-H), 1.43 [s, 9H, $C(CH_3)_3$], 1.85–1.94 (m, 2H, *c*Pr-H, 4- or 6-H), 2.24 (br s, 4H, CH_2NCH_2), 2.35–2.58 (m, 2H, 4- or 6-H), 2.72–2.89 (m, 2H, 5-H, 1-H), 3.58 (t, *J*=4.3 Hz, 4H, CH_2OCH_2), 5.92–5.97 (m, 2H, OCH_2O), 6.48 (dd, *J*=8.1, 1.0 Hz, 1H, Ph), 6.54 (d, *J*=1.5 Hz, 1H, Ph), 6.76 (d, *J*= 8.0 Hz, 1H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ= 13.14 (−, *c*Pr-C), 14.17 (−, *c*Pr-C), 18.76 (+, CH_3), 19.03 (C_{quat}, *c*Pr-C), 27.97 [+, $C(CH_3)_3$], 36.55 (−, C-4 or -6), 37.67 (−, C-4 or -6), 40.51 (+, C-5), 51.59 (−, CH_2NCH_2), 61.18 (+, C-1), 67.12 (−, CH_2OCH_2), 79.98 [C_{quat}, $C(CH_3)_3$], 100.74 (−, OCH_2O), 107.98 (+, Ph-C), 108.80 (+, Ph-C), 121.14 (+, Ph-C), 136.07 (C_{quat}, 2× Ph-C), 138.06 (C_{quat}, Ph-C), 145.62 (C_{quat}), 147.24 (C_{quat}), 174.67 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 441 (29) [M^+], 426 (14) [M^+ −CH_3], 298 (100), 253 (17), 131 (14), 114 (42), 100 (13), 57 (22), 41 (5); elemental analysis calcd (%) for $C_{26}H_{35}NO_5$ (441.6): C 70.72, H 7.99; found: C 70.55, H 7.72.

4.3.17. 6′-(1-Morpholin-4-ylethyl)-2′-phenyl-8′-(thiophen-2-yl)spiro[cyclopropane-1,5′(8′*H*)-[1,2,4]triazolo-[1,2-a]pyridazine]-1′,3′-dione (41a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), 2-(2-iodovinyl)thiophene (**33**, 472 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 3 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture, and then it was stirred again at room temperature for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **41a** (232 mg, 26%, colorless solid) as a mixture of two diastereomers (ratio 1:1 according to NMR).

Diastereomer I. Mp 160 °C, R_f=0.15 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3102, 3088, 2963, 2859, 2815, 1769, 1715, 1502, 1409, 1310, 1165, 1116, 767, 731 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.14–1.21 (m, 1H, *c*Pr-H), 1.19 (d, *J*=6.8 Hz, 3H, CH_3), 1.59–1.74 (m, 2H, *c*Pr-H), 2.46–2.64 (m, 6H, *c*Pr-H CH_2NCH_2, 1-H), 3.70 (t, *J*= 4.6 Hz, 4H, CH_2OCH_2), 5.88 (d, *J*=5.2 Hz, 1H, 8′-H), 6.17 (d, *J*=5.2 Hz, 1H, 7′-H), 6.99 (dd, *J*=3.6, 5.1 Hz, 1H, thiophene), 7.21 (d, *J*=3.8 Hz, 1H, thiophene), 7.27–7.42 (m, 6H, Ph, thiophene); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.36 (−, *c*Pr-C), 11.32 (−, *c*Pr-C), 16.08 (+, CH_3), 41.85 (C_{quat}, *c*Pr-C), 50.14 (−, CH_2NCH_2), 53.57 (−, C-8′), 57.28 (+, C-1), 67.07 (−, CH_2OCH_2), 121.17 (+, C-7′), 125.45 (+, Ph), 126.38 (+, thiophene), 126.93 (+, thiophene), 127.87 (+, Ph or thiophene), 128.01 (+, Ph or thiophene), 128.87 (+, Ph), 130.76 (C_{quat}), 138.93

(C_{quat}), 139.48 (C_{quat}), 149.94 (C_{quat}, C=O), 152.08 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 450 (27) [M^+], 364 (100) [M^+ −morpholine], 348 (8), 173 (17), 114 (30), 100 (90); elemental analysis calcd (%) for $C_{24}H_{26}N_4O_3S$ (450.6): C 63.98, H 5.82, N 12.43; found: C 63.76, H 5.71, N 12.68.

Diastereomer II. Mp 122 °C, R_f=0.15 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3108, 3062, 2963, 2858, 2796, 1775, 1714, 1502, 1411, 1112, 766, 713 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.17–1.44 (m, 3H, *c*Pr-H), 1.25 (d, *J*=6.4 Hz, 3H, CH_3), 2.32 (q, *J*=6.4 Hz, 1H, 1-H), 2.47 (br s, 4H, *c*Pr-H, CH_2NCH_2), 2.81–2.90 (m, 1H, *c*Pr-H), 3.69 (t, *J*=4.5 Hz, 4H, CH_2OCH_2), 5.89 (d, *J*=5.0 Hz, 1H, 8′-H), 6.29 (d, *J*=4.86 Hz, 1H, 7′-H), 6.98 (dd, *J*=3.5, 5.1 Hz, 1H, thiophene), 7.19 (d, *J*=3.4 Hz, 1H, thiophene), 7.27–7.42 (m, 6H, Ph, thiophene); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=9.37 (−, *c*Pr-C), 11.56 (−, *c*Pr-C), 18.22 (+, CH_3), 41.92 (C_{quat}, *c*Pr-C), 50.76 (−, CH_2NCH_2), 53.19 (−, C-8′), 58.27 (+, C-1), 67.04 (−, CH_2OCH_2), 120.19 (+, C-7′), 125.47 (+, Ph), 126.49 (+, Ph or thiophene), 126.83 (+, thiophene), 127.76 (+, thiophene), 128.06 (+, Ph or thiophene), 128.91 (+, Ph), 130.75 (C_{quat}), 138.75 (C_{quat}), 139.31 (C_{quat}), 150.45 (C_{quat}, C=O), 152.15 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 450 (9) [M^+], 363 (32) [M^+ −morpholine-H], 348 (4), [M^+ − morpholine–H–CH_3], 173 (11), 114 (36), 100 (100); elemental analysis calcd (%) for $C_{24}H_{26}N_4O_3S$(450.6): C 63.98, H 5.82; found: C 63.90, H 6.06.

4.3.18. 6′-[1-Morpholin-4-ylethyl]-2′-phenylspiro[cyclopropane-1,5′(10a'*H*)-5′,7′,8′,9′,10′,10a′-hexahydro-[1,2,4]triazolo[1,2-a]cinnoline]-1,3-dione (42a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), 1-iodo-cyclohexene (**34**, 416 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 100 °C for 5 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture, and then it was stirred again at room temperature for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **42a** (280 mg, 33%, colorless solid) as a mixture of two diastereomers (ratio 4.6:1 according to NMR).

Major diastereomer. Mp 151 °C, R_f=0.446 (light petroleum/ethyl acetate, 3:1); IR (KBr): $\tilde{\nu}$=3033, 2961, 2926, 2856, 1762, 1709, 1504, 1459, 1415, 1301, 1270, 1128, 1117, 1069, 1033, 866, 765 cm^{-1}; ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ=1.22–1.36 (m, 1H, *c*Pr-H), 1.28 (d, *J*=6.8 Hz, 3H, CH_3), 1.37–1.48 (m, 1H, *c*Pr-H), 1.51–1.67 (m, 1H, cychex), 1.75 (dt, *J*=3.6, 13.1 Hz, 1H, cychex), 1.88–2.00 (m, 5H, *c*Pr-H, cychex), 2.06–2.14 (m, 1H, *c*Pr-H), 2.47–2.54 (m, 1H, 1-H), 2.49 (t, *J*=4.4 Hz, 4H, CH_2NCH_2), 2.65–2.71 (m, 1H, cychex), 3.71 (t, *J*=4.7 Hz, 4H, CH_2OCH_2), 3.77 (br s, 1H, cychex), 4.23 (dd, *J*=4.2, 10.8 Hz, 1H, cychex), 7.35–7.52 (m, 5H, Ph); ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C, DEPT): δ=10.03 (−, *c*Pr-C), 10.48 (−, *c*Pr-C), 18.04 (+, CH_3), 24.28 (−, cychex), 26.80 (−, cychex), 29.91 (−, cychex), 31.99 (−, cychex), 40.88 (C_{quat}, *c*Pr-C), 51.88 (−, CH_2NCH_2), 57.68 (+, C-1), 58.66 (+, cychex), 66.79 (−, CH_2OCH_2), 125.46 (+, Ph-C), 127.66 (+, Ph-C), 127.85 (C_{quat}), 128.62 (+, Ph-C), 131.36 (C_{quat}), 133.92 (C_{quat}), 149.51 (C_{quat}, C=O), 151.98 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 422 (54) [M^+], 393 (16), 337 (22), 336 (100), 217 (16), 114 (14), 100 (42); elemental analysis calcd (%) for $C_{24}H_{30}N_4O_3$ (422.5): C 68.22, H 7.16; found: C 67.91, H 7.07.

Minor diastereomer. R_f=0.108 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3071, 2932, 2853, 1772, 1714, 1546, 1504, 1413, 1295, 1264, 1130, 1117, 1029, 985, 766 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): δ=0.60–0.67 (m, 1H, *c*Pr-H), 0.70–0.77 (m, 1H, *c*Pr-H), 0.82–0.89 (m, 1H, *c*Pr-H), 0.99–1.06 (m, 1H, *c*Pr-H), 1.13–1.29 (m, 1H, cychex), 1.36 (d, *J*=6.3 Hz, 3H, CH_3), 1.46 (td, *J*=3.2, 12.0 Hz, 1H, cychex), 1.57 (tt, *J*=3.5, 13.0 Hz, 1H, cychex), 1.71 (td, *J*=3.5, 13.7 Hz, 1H, cychex), 1.82–1.86 (m, 2H, cychex), 2.56 (t, *J*=4.6 Hz, 4H, CH_2NCH_2), 2.98–3.03 (m, 1H, cychex), 3.25 (d, *J*=13.60 Hz, 1H, cychex), 3.58 (q, *J*=3.9 Hz, 4H, CH_2OCH_2), 4.17 (dd, *J*=4.1, 11.2 Hz, cychex), 4.67 (q, *J*=6.3 Hz, 1H, 1-H), 7.29–7.34 (m, 1H, Ph), 7.46–7.51 (m, 4H, Ph); ^{13}C NMR (75.478 MHz, $CDCl_3$, DEPT): δ=11.25 (−, *c*Pr-C), 13.51 (−, *c*Pr-C), 19.87 (+, CH_3), 23.83 (−, cychex), 27.25 (−, cychex), 30.26 (−, cychex), 34.44 (−, cychex), 44.07 (C_{quat}, *c*Pr-C), 49.66 (−, CH_2NCH_2), 51.37 (+, C-1), 58.39 (+, cychex), 67.30 (−, CH_2OCH_2), 125.37 (+, Ph-C), 126.99 (C_{quat}), 127.80 (+, Ph-C), 128.95 (+, Ph-C), 131.33 (C_{quat}), 136.57 (C_{quat}), 149.67 (C_{quat}, C=O), 152.78 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 422 (79) [M^+], 407 (11) [M^+ −CH_3], 336 (55), 261 (18), 247 (30), 246 (100), 232 (27), 218 (24), 178 (20), 119 (39), 91 (42), 77 (20), 41 (22) for $C_{24}H_{30}N_4O_3$ (422.53); HRMS(EI):calcd 422.2318 (correct HRMS).

4.3.19. 6′-[1-Morpholin-4-ylethyl]-9′-(*N*)-benzyl-2′-phenylspiro[cyclopropane-1,5′(10a'*H*)-5′,7′,8′,9′,10′,10a′-hexahydro[1,2,4]triazolo[1,2-a]cinnoline]-1,3-dione (43a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), 1-benzyl-4-iodo-1,2,3,6-tetrahydropyridine (**35**, 600 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL), at 80 °C for 3 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture, and then it was stirred at room temperature for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **43a** (180 mg, 17%, colorless oil), R_f=0.17 (light petroleum/ethyl acetate 3:1); IR (film): $\tilde{\nu}$=3028, 2956, 2850, 2798, 1770, 1713, 1503, 1456, 1412, 1361, 1265, 1120, 1071, 1029, 936, 863, 736, 739 cm^{-1}; ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ=1.24–1.33 (m, 1H, *c*Pr-H), 1.29 (d, *J*=6.8 Hz, 3H, CH_3), 1.36–1.43 (m, 1H, *c*Pr-H), 1.79–1.87 (m, 1H, *c*Pr-H), 2.02–2.15 (m, 2H, tetrahydropyridine), 2.24 (t, *J*=10.3 Hz, 1H, tetrahydropyridine), 2.29–2.35 (m, 1H, *c*Pr-H), 2.39–2.51 (m, 1H, 1-H), 2.47 (q, *J*=4.3 Hz, 4H, CH_2NCH_2), 2.94–2.99 (m, 1H, tetrahydropyridine), 3.56–3.78 (AB system: δ_A=3.6, δ_B=3.8, J_{AB}= 13.3 Hz, 2H, Bn), 3.56–3.78 (1H, tetrahydropyridine)*, 3.68

(t, J=4.6 Hz, 4H, CH_2OCH_2), 3.98–4.02 (m, 1H, tetrahydropyridine), 4.47 (dd, J=4.4, 9.9 Hz, 1H, tetrahydropyridine), 7.28–7.48 (m, 10H, Ph); * The peak of this proton sits under the peaks of the AB system, thus the spin couplings of this proton could not be determined. This proton correlates clearly with the carbon peak at 28.49 ppm in the HMQC spectrum. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C, DEPT): δ=9.40 (−, *c*Pr-C), 10.67 (−, *c*Pr-C), 17.85 (+, CH_3), 28.49 (−, tetrahydropyridine), 40.74 (C_{quat}, *c*Pr-C), 51.80 (−, CH_2NCH_2), 52.61 (−, tetrahydropyridine), 57.06 (+, tetrahydropyridine), 57.32 (−, tetrahydropyridine), 57.71 (+, C-1), 61.61 (−, Bn), 66.70 (−, CH_2OCH_2), 125.52 (+, Ph), 126.86 (+, Ph), 127.77 (+, Ph), 127.98 (+, Ph), 128.53 (+, Ph), 128.66 (+, Ph), 128.81 (C_{quat}), 130.99 (C_{quat}), 131.19 (C_{quat}), 137.72 (C_{quat}), 149.24 (C_{quat}, C=O), 152.27 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 513 (34) [M^+], 427 (26) [M^+ −morpholinyl], 397 (9), 307 (6), 134 (46), 100 (46), 91 (100), 42 (14); elemental analysis calcd (%) for $C_{30}H_{35}N_5O_3$ (513.6): C 70.15, H 6.87; found: C 69.98, H 6.71.

4.3.20. 6′-(1-Morpholin-4-ylethyl)-2′,8′-diphenylspiro-[cyclopropane-1,5′(8′*H*)-[1,2,4]triazolo-[1,2-a]pyridazine]-1′,3′-dione (44a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (*E*)-1-iodo-2-phenylethene (**36**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. *N*-phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture and then it was stirred at room temperature for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield **44a** (310 mg, 35%, colorless solid) as a mixture of two diastereomers (ratio 1.4:1 according to NMR).

Major diastereomer. Mp 171 °C, R_f=0.47 (light petroleum/ethyl acetate 1:1); IR (KBr): $\tilde{\nu}$=3106, 3058, 3026, 2977, 2857, 2818, 1763, 1706, 1506, 1411, 1290, 1174, 1112, 768 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.18 (d, J=6.7 Hz, 3H, CH_3), 1.21–1.31 (m, 1H, *c*Pr-H), 1.55–1.65 (m, 1H, *c*Pr-H), 1.90–2.00 (m, 1H, *c*Pr-H), 2.32–2.65 (m, 6H, *c*Pr-H, CH_2NCH_2, 1-H), 3.66 (t, J=4.6 Hz, 4H, CH_2OCH_2), 5.54 (d, J=4.6 Hz, 1H, 8′-H), 5.99 (d, J=4.7 Hz, 1H, 7′-H), 7.25–7.44 (m, 10H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$, DEPT): δ=10.96 (−, *c*Pr-C), 11.33 (−, *c*Pr-C), 15.02 (+, CH_3), 41.54 (C_{quat}, *c*Pr-C), 49.86 (−, CH_2NCH_2), 57.92 (+, C-1), 58.98 (−, C-8′), 67.00 (−, CH_2OCH_2), 121.82 (+, C-7′), 125.39 (+, Ph-C), 127.90 (+, Ph-C), 127.98 (+, Ph-C), 128.57 (+, Ph-C), 128.64 (+, Ph-C), 128.82 (+, Ph-C), 130.85 (C_{quat}), 137.07 (C_{quat}), 137.80 (C_{quat}), 149.68 (C_{quat}, C=O), 151.83 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 444 (11) [M^+], 358 (46) [M^+ −morpholinyl], 167 (12), 114 (26), 100 (100) 91 (14); elemental analysis calcd (%) for $C_{26}H_{28}N_4O_3$ (444.5): C 70.25, H 6.35; found: C 70.54, H 6.26.

Minor diastereomer. Mp 170 °C, R_f=0.47 (light petroleum/ethyl acetate, 1:1); IR (KBr): $\tilde{\nu}$=3065, 2962, 2854, 2811, 1769, 1711, 1502, 1414, 1301, 1265, 1116, 765 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.24 (d, J=6.3 Hz, 3H, CH_3), 1.31–1.39 (m, 2H, *c*Pr-H), 1.43–1.51 (m, 1H, *c*Pr-H), 2.36–2.49 (m, 5H, CH_2NCH_2, 1-H), 2.74–2.82 (m, 1H, *c*Pr-H), 3.69 (t, J=4.4 Hz, 4H, CH_2OCH_2), 5.60 (d, J=4.9 Hz, 1H, 8′-H), 6.15 (d, J=5.0 Hz, 1H, 7′-H), 7.29–7.44 (m, 10H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=9.61 (−, *c*Pr-C), 11.59 (−, *c*Pr-C), 17.83 (+, CH_3), 41.97 (C_{quat}, *c*Pr-C), 50.61 (−, CH_2NCH_2), 58.18 (+, C-1), 58.29 (−, C-8′), 67.09 (−, CH_2OCH_2), 120.47 (+, C-7′), 125.43 (+, Ph-C), 128.00 (+, Ph-C), 128.43 (+, Ph-C), 128.59 (+, Ph-C), 128.72 (+, Ph-C), 128.89 (+, Ph-C), 130.81 (C_{quat}), 134.48 (C_{quat}), 138.44 (C_{quat}), 150.56 (C_{quat}, C=O), 151.60 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 444 (25) [M^+], 358 (80) [M^+ −morpholinyl], 357 (94), 167 (14), 119 (15), 114 (26), 100 (100), 91 (16); elemental analysis calcd (%) for $C_{26}H_{28}N_4O_3$ (444.5): C 70.25, H 6.35; found: C 70.43, H 6.07.

4.3.21. 6′-(1-Morpholin-4-ylethyl)-2′-phenylspiro[cyclopropane-1,5′(8′*H*)-[1,2,4]triazolo[1,2-a]pyridazine]-1′,3′-dione (45a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the ice-cooled mixture, and then it was stirred at room temperature for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, CH_2Cl_2/ethyl acetate, 1:1) to yield **45a** (367.2 mg, 50%, colorless solid), mp 130 °C, R_f=0.25 (CH_2Cl_2/ethyl acetate 1:1); IR (KBr): $\tilde{\nu}$=2962, 2953, 2852, 2813, 1771, 1709, 1699, 1504, 1421, 1313, 1268, 1142, 1123, 916, 860, 767 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.17 (d, J=6.5 Hz, 3H, CH_3), 1.18–1.26 (m, 1H, *c*Pr-H), 1.34–1.43 (m, 1H, *c*Pr-H), 1.69–1.78 (m, 1H, *c*Pr-H), 2.31–2.52 (m, 6H, *c*Pr-H, CH_2NCH_2, 1-H), 3.68 (t, J=4.6 Hz, 4H, CH_2OCH_2), 4.18–4.40 (m, 2H, 8′-H), 6.01 (t, J=6.6 Hz, 1H, 7′-H), 7.32–7.46 (m, 5H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=9.76 (−, *c*Pr-C), 11.58 (−, *c*Pr-C), 15.91 (+, CH_3), 41.36 (C_{quat}, *c*Pr-C), 44.28 (−, C-8′), 49.94 (−, CH_2NCH_2) 58.20 (+, C-1), 66.93 (−, CH_2OCH_2), 116.49 (+, C-7′), 125.29 (+, Ph), 127.92 (+, Ph), 128.87 (+, Ph), 130.83 (C_{quat}), 138.72 (C_{quat}), 149.66 (C_{quat}, C=O), 152.62 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 368 (20) [M^+], 281 (100) [M^+ −morpholine], 266 (6) [M^+ −morpholine–CH_3], 178 (16), 114 (10), 100 (64); elemental analysis calcd (%) for $C_{20}H_{24}N_4O_3$ (368.4): C 65.20, H 6.57; found: C 64.90, H 6.25.

4.3.22. 6′-(1-Morpholin-4-ylethyl)-2′,7′-diphenylspiro-[cyclopropane-1,5′(8′*H*)-[1,2,4]triazolo[1,2-a]pyridazine]-1′,3′-dione (46a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 261 mg, 3.00 mmol), (1-iodovinyl)benzene (**31**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 3 h. *N*-Phenyltriazolinedione (**37**, 700 mg, 4.00 mmol) was added to the

ice-cooled mixture and then it was stirred at room temperature for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 3:1) to yield **46a** (311 mg, 35%, colorless solid), mp 70 °C, R_f=0.30 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3050, 2956, 2850, 2805, 1772, 1713, 1598, 1503, 1407, 1265, 1143, 1119, 942, 863 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.25 (d, J=7.0 Hz, 3H, CH_3), 1.29–1.37 (m, 1H, *c*Pr-H), 1.53–1.62 (m, 1H, *c*Pr-H), 2.14–2.22 (m, 2H, *c*Pr-H), 2.30 (br s, 4H, CH_2NCH_2), 3.08 (q, J=6.7 Hz, 1H, 1-H), 3.61 (t, J=4.4 Hz, 4H, CH_2OCH_2), 4.50 (s, 2H, 8′-H), 7.10–7.14 (m, 2H, Ph), 7.33–7.42 (m, 4H, Ph), 7.45–7.50 (m, 4H, Ph); ^{13}C NMR (75.5 MHz, $CDCl_3$, DEPT): δ=11.77 (−, *c*Pr-C), 13.69 (−, *c*Pr-C), 17.51 (+, CH_3), 38.24 (C_{quat}, *c*Pr-C), 48.67 (−, C-8′), 51.50 (−, CH_2NCH_2), 59.79 (+, C-1), 66.77 (−, CH_2OCH_2), 125.33 (+, Ph-C), 127.63 (+, Ph-C), 127.89 (+, Ph-C), 128.56 (+, Ph-C), 128.88 (+, Ph-C), 131.22 (C_{quat}), 133.44 (C_{quat}), 136.70 (C_{quat}), 137.78 (C_{quat}), 150.39 (C_{quat}, C=O), 152.97 (C_{quat}, C=O); MS (70 eV, EI) *m/z* (%): 444 (22) [M^+], 357 (52) [M^+ −morpholinyl], 254 (7), 167 (16), 114 (27), 100 (100); elemental analysis calcd (%) for $C_{26}H_{28}N_4O_3$ (444.5): C 70.25, H 6.35, N 12.60; found: C 69.98, H 6.52, N 12.42.

4.3.23. 5-(1′-(Morpholin-4″-yl)ethyl)-2,7-diphenylspiro-[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (47a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (*E*)-1-iodo-2-phenylethene (**36**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature 1-phenyl-2,5-dihydropyrrole-2,5-dione (**19**, 693 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 2:3) to yield **47a** (370 mg, 42%, pale yellow solid) as a mixture of two diastereomers (ratio 2:1 according to NMR). R_f=0.51 (light petroleum/ethyl acetate, 2:3); IR (KBr)*: $\tilde{\nu}$=3095 (C–H), 1723 (C=O), 1499, 1456, 1393, 1376 (CH_3), 1314, 1163, 1149, 1123, 1110, 1076, 1057, 1036, 838 cm^{-1}; MS (70 eV, EI)*, *m/z* (%): 442 (14) [M^+], 427 (26) [$M^+ - CH_3$], 173 (63), 88 (14) [morpholinyl$^+$ +H], 70 (24), 61 (38), 43 (100); HRMS (EI)*: calcd for $C_{28}H_{30}N_2O_3$ (442.6): 442.2256, correct HRMS. *IR, low and high resolution mass measurements were carried out for the mixture of diastereomers.

Major diastereomer. ^1H NMR (250 MHz, $CDCl_3$): δ= 0.41–0.56 (m, 1H, *c*Pr-H), 0.90–1.04 (m, 1H, *c*Pr-H), 1.19 (d, J=6.6 Hz, 3H, CH_3), 1.22–1.32 (m, 1H, *c*Pr-H), 1.61–1.71 (m, 1H, *c*Pr-H), 2.29–2.51 (m, 4H, CH_2NCH_2), 2.46 (d, J=8.6 Hz, 1H, 3a-H), 3.03 (q, J=6.9 Hz, 1H, 1′-H), 3.53–3.70 (m, 5H, CH_2NCH_2, 7-H), 4.00–4.07 (m, 1H, 7a-H), 6.30 (d, J=3.5 Hz, 1H, 6-H), 7.10–7.60 (m, 10H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.56 (−, *c*Pr-C), 11.6 (+, CH_3), 13.7 (−, *c*Pr-C), 21.5 (C_{quat}, C-4), 23.9 (+, C-7), 41.9 (+, C-7a), 50.6 (+, C-1′), 60.7 (−, CH_2NCH_2), 64.7 (+, C-3a), 67.3 (−, CH_2OCH_2), 126.2 (+, C-6), 126.5 (+, Ph-C), 126.9 (+, Ph-C), 128.2 (+, Ph-C), 128.3 (+, Ph-C), 128.9 (+, Ph-C), 129.4 (+, Ph-C), 131.8 (C_{quat}), 139.7 (C_{quat}), 144.2 (C_{quat}), 175.3 (C_{quat}, C=O), 176.9 (C_{quat}, C=O).

Minor diastereomer. ^1H NMR (250 MHz, $CDCl_3$): δ= 0.41–0.56 (m, 1H, *c*Pr-H), 0.90–1.04 (m, 1H, *c*Pr-H), 1.09 (d, J=6.7 Hz, 3H, CH_3), 1.22–1.32 (m, 1H, *c*Pr-H), 1.61–1.71 (m, 1H, *c*Pr-H), 2.29–2.51 (m, 4H, CH_2NCH_2), 2.45 (d, J=8.6 Hz, 1H, 3a-H), 2.78 (q, J=6.7 Hz, 1H, 1′-H), 3.53–3.70 (m, 5H, CH_2OCH_2, 7-H), 4.00–4.07 (m, 1H, 7a-H), 6.30 (d, J=3.5 Hz, 1H, 6-H), 7.10–7.60 (m, 10H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.62 (−, *c*Pr-C), 13.0 (−, *c*Pr-C), 14.1 (+, CH_3), 21.5 (C_{quat}, C-4), 23.9 (+, C-7), 41.8 (+, C-7a), 48.2 (+, C-1′), 60.3 (−, CH_2NCH_2), 64.2 (+, C-3a), 67.0 (−, CH_2OCH_2), 126.0 (+, C-6), 126.5 (+, Ph-C), 126.9 (+, Ph-C), 128.2 (+, Ph-C), 128.3 (+, Ph-C), 128.9 (+, Ph-C), 129.4 (+, Ph-C), 131.8 (C_{quat}), 139.5 (C_{quat}), 143.7 (C_{quat}), 175.3 (C_{quat}, C=O), 176.4 (C_{quat}, C=O).

4.3.24. 5-(1′-(Morpholin-4″-yl)ethyl)-2,6-diphenylspiro-[cyclopropane-1′,4-(3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (48a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (1-iodovinyl)benzene (**31**, 460 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL) at 80 °C for 2 h. After cooling the mixture to room temperature, 1-Phenyl-2,5-dihydropyrrole-2,5-dione (**19**, 693 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 3:1) to yield **48a** (353 mg, 40%, colorless solid) as a mixture of two diastereomers (ratio 1.18:1 according to NMR).

Major diastereomer. Mp 165 °C, R_f=0.18 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=2969, 2847, 2802, 1777, 1713, 1597, 1493, 1388, 1185, 1115, 862 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.41–0.49 (m, 1H, *c*Pr-H), 0.78–0.86 (m, 1H, *c*Pr-H), 1.15 (d, J=6.8 Hz, 3H, CH_3), 1.21–1.28 (m, 1H, *c*Pr-H), 2.17 (br s, 4H, CH_2NCH_2), 2.31 (d, J=9.2 Hz, 1H, 3a-H), 2.41–2.49 (m, 1H, *c*Pr-H), 2.95–2.98 (m, 2H, 7-H), 3.08 (q, J=7.0 Hz, 1H, 1′-H), 3.42–3.49 (m, 1H, 7a-H), 3.55 (t, J=4.45 Hz, 4H, CH_2OCH_2), 6.94–6.97 (m, 2H, Ph), 7.22–7.52 (m, 8H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=8.44 (−, *c*Pr-C), 13.47 (−, *c*Pr-C), 16.75 (+, CH_3), 21.33 (C_{quat}, *c*Pr-C), 31.72 (−, C-7), 42.07 (+, C-7a), 51.11 (+, C-3a), 51.42 (−, CH_2NCH_2), 59.89 (+, C-1′), 67.01 (−, CH_2OCH_2), 126.11 (+, Ph), 126.66 (+, Ph), 127.58 (+, Ph), 128.26 (+, Ph), 128.43 (+, Ph), 129.15 (+, Ph), 131.99 (C_{quat}), 138.10 (C_{quat}), 139.28 (C_{quat}), 141.69 (C_{quat}), 177.43 (C_{quat}, C=O), 178.44 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 442 (35) [M^+], 427 (33) [$M^+ - CH_3$], 355 (20) [M^+ −morpholinyl–H], 209 (14), 165 (15), 114 (100), 88 (10); elemental analysis calcd (%) for $C_{28}H_{30}N_2O_3$ (442.6): C 75.99, H 6.83; found: C 75.70, H 7.03.

Minor diastereomer. Mp 168 °C, R_f=0.22 (light petroleum/ethyl acetate 3:1); IR (KBr): $\tilde{\nu}$=3077, 3051, 2965, 2852,

2791, 1779, 1709, 1596, 1492, 1390, 1181, 1151, 1120, 1113, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=0.41–0.49 (m, 2H, *c*Pr-H), 1.08 (d, J=7.4 Hz, 3H, CH_3), 1.21–1.29 (m, 1H, *c*Pr-H), 1.61 (q, J=7.1 Hz, 1H, *c*Pr-H), 2.12 (br s, 4H, CH_2NCH_2), 2.53 (d, J=9.2 Hz, 1H, 3a-H), 2.83–2.99 (m, 2H, 7-H) 3.05 (q, J=7.0 Hz, 1H, 1′-H), 3.28–3.46 (m, 5H, CH_2OCH_2, 7a-H), 7.05–7.07 (m, 2H, Ph), 7.24–7.49 (m, 8H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ= 9.28 (−, *c*Pr-C), 12.94 (−, *c*Pr-C), 17.53 (+, CH_3), 21.10 (C_{quat}, *c*Pr-C), 32.11 (−, C-7), 42.40 (+, C-7a), 49.71 (+, C-3a), 51.45 (−, CH_2NCH_2), 60.62 (+, C-1′), 66.84 (−, CH_2OCH_2), 126.07 (+, Ph-C), 126.59 (+, Ph-C), 127.75 (+, Ph-C), 128.17 (+, Ph-C), 128.46 (+, Ph-C), 129.07 (+, Ph-C), 131.82 (C_{quat}), 138.98 (C_{quat}), 139.27 (C_{quat}), 141.98 (C_{quat}), 177.60 (C_{quat}, C=O), 178.57 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 442 (34) [M^+], 427 (66) [M^+ − CH_3], 355 (30) [M^+ − morpholinyl–H], 208 (16), 165 (15), 114 (100), 88 (16); elemental analysis calcd (%) for $C_{28}H_{30}N_2O_3$ (442.6): C 75.99, H 6.83; found: C 75.70, H 6.90.

4.3.25. 5-[1′-(Morpholine-4″-yl)ethyl]-2-(4‴-trifluoromethylphenyl)spiro[cyclopropane-1′,4-(7-phenyl-3a,4,7,7a-tetrahydroisoindole)]-1,3-dione (49a). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), (*E*)-1-iodo-2-phenylethene (**36**) (460 mg, 2.00 mmol), and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (1 mL), at 80 °C for 2 h. After cooling the mixture to room temperature 1-(4′-trifluoromethylphenyl)-2,5 dihydropyrrole-2,5-dione (**21**, 964 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 4 h. After work-up and drying over $MgSO_4$, the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 2:3) to yield **49a** (380 mg, 37%, pink crystals) as a mixture of two diastereomers (ratio 2:1 according to NMR). R_f=0.60 (light petroleum/ethyl acetate 2:3); IR (KBr)*: $\tilde{\nu}$=2966, 2853 (C–H), 1717 (C=O), 1376 (CH_3), 1326 (C–F), 1170 (C–F), 1117 (C–F), 1068, 1021 cm^{-1} MS (70 eV, EI)*, *m/z* (%): 511/510 (12/55) [M^+], 497/496 (26/100) [M^+ +H–CH_3], 114 (95), 86 (26) [morpholinyl–H], 56 (11), 43 (29), 42 (10), 41 (13); HRMS (EI)*: calcd for $C_{29}H_{29}F_3N_2O_3$ (510.6): 510.2130, correct HRMS. *IR, low and high resolution mass spectrometric measurements were carried out for the mixture of diastereomers.

Major diastereomer. ^1H NMR (250 MHz, $CDCl_3$): δ= 0.43–0.61 (m, 1H, *c*Pr-H), 0.91–1.05 (m, 1H, *c*Pr-H), 1.08 (d, J=6.6 Hz, 3H, CH_3), 1.23–1.34 (m, 1H, *c*Pr-H), 1.62–1.75 (m, 1H, *c*Pr-H), 2.25–2.56 (m, 5H, CH_2NCH_2, 3a-H), 3.02 (q, J=6.6 Hz, 1H, 1′-H), 3.47–3.78 (m, 5H, CH_2OCH_2, 7-H), 4.01–4.11 (m, 1H, 7a-H), 6.27–6.37 (m, 1H, 6-H), 7.24–7.49 (m, 7H, Ar-H), 7.67 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=6.73 (−, *c*Pr-C), 11.7 (+, CH_3), 13.0 (−, *c*Pr-C), 23.8 (C_{quat}, C-4), 41.9 (+, C-7a), 48.3 (+, C-7), 50.7 (+, C-1′), 60.7 (−, CH_2NCH_2), 64.7 (+, C-3a), 67.2 (−, CH_2OCH_2), 126.0 (+, Ar-C), 126.1 (+, Ar-C), 126.3 (+, C-6), 127.1 (+, Ar-C), 127.5 (C_{quat}, q, ^1J(C,F)=273 Hz, CF_3), 128.2 (+, 3× Ar-C), 128.8 (+, Ar-C), 129.3 (+, 2×Ar-C), 130.1 (C_{quart}, q, ^2J(C,F)=33 Hz, C-4‴), 134.7 (C_{quat}), 139.4 (C_{quat}), 143.9 (C_{quat}, C-5), 174.9 (C_{quat}, C=O), 176.4 (C_{quat}, C=O) .

Minor diastereomer. ^1H NMR (250 MHz, $CDCl_3$): δ= 0.43–0.61 (m, 1H, *c*Pr-H), 0.91–1.05 (m, 1H, *c*Pr-H), 1.18 (d, J=6.6 Hz, 3H, CH_3), 1.23–1.34 (m, 1H, *c*Pr-H), 1.62–1.75 (m, 1H, *c*Pr-H), 2.25–2.56 (m, 5H, CH_2NCH_2, 3a-H), 2.79 (q, J=6.6 Hz, 1H, 1′-H), 3.47–3.78 (m, 5H, CH_2NCH_2, 7-H), 4.01–4.11 (m, 1H, 7a-H), 6.27–6.37 (m, 1H, 6-H), 7.24–7.49 (m, 7H, Ar), 7.67 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=7.62 (−, *c*Pr-C), 13.7 (−, *c*Pr-C), 16.0 (+, CH_3), 21.4 (C_{quat}, C-4), 41.6 (+, C-7a), 48.3 (+, C-7), 50.8 (+, C-1′), 60.3 (−, CH_2NCH_2), 64.7 (+, C-3a), 67.0 (−, CH_2OCH_2), 125.9 (+, Ar-C), 126.0 (+, Ar-C), 127.1 (+, Ar-C), 127.5 (C_{quat}, q, ^1J(C,F)=273 Hz, CF_3), 128.2 (+, 3×Ar-C), 128.8 (+, Ar-C), 129.3 (+, 2×Ar-C), 130.1 (C_{quat}, q, ^2J(C,F)= 33 Hz, C-4‴), 134.7 (C_{quat}), 139.2 (C_{quat}), 144.3 (C_{quat}, C-5), 175.1 (C_{quat}, C=O), 175.9 (C_{quat}, C=O).

4.3.26. Dimethyl 8-(1-morpholin-4-ylethyl)spiro[2.5]octa-4,7-diene-4,5-dicarboxylate (50a). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), morpholine (**12a**, 174 mg, 2.00 mmol), iodoethene (**11**, 308 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (2 mL) at 80 °C for 2 h. After cooling the mixture to room temperature dimethyl acetylenedicarboxylate (**38**, 568 mg, 4.00 mmol) was added, and then the mixture was heated again with stirring at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 1:1) to yield **50a** (200 mg, 30%, yellowish oil). R_f=0.5 (light petroleum/ethyl acetate, 1:1), IR (film): $\tilde{\nu}$=3056, 2953, 2895, 2857, 2824, 1733, 1630, 1587, 1436, 1371, 1266, 1162, 1118, 1033, 737, 704 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.00–1.15 (m, 3H, *c*Pr-H), 1.06 (d, J=6.7 Hz, 3H, CH_3), 1.25–1.35 (m, 1H, *c*Pr-H), 2.22 (q, J=6.5 Hz, 1H, 1-H), 2.35–2.50 (m, 4H, CH_2NCH_2), 3.15 (d, J=3.6 Hz, 2H, 6-H), 3.65 (t, J= 4.5 Hz, 4H, CH_2OCH_2), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.85 (t, J=3.7 Hz, 1H, 7-H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=13.46 (−, *c*Pr-C), 14.15 (−, *c*Pr-C), 17.14 (+, CH_3), 22.21 (C_{quat}, *c*Pr-C), 26.51 (−, C-6), 50.31 (−, CH_2NCH_2), 51.93 (+, OCH_3), 52.13 (+, OCH_3), 57.91 (+, C-1), 67.10 (−, CH_2OCH_2), 119.91 (+, C-7), 124.75 (C_{quat}), 136.82 (C_{quat}), 146.69 (C_{quat}), 165.78 (C_{quat}, C=O), 168.46 (C_{quat}, C=O); MS (70 eV, EI), *m/z* (%): 335 (41) [M^+], 334 (100) [M^+ −H], 320 (12), 276 (16), 216 (13), 189 (17), 157 (11), 114 (26), 100 (34); elemental analysis calcd (%) for $C_{18}H_{25}NO_5$ (335.4): C 64.46, H 7.51; found: C 64.19, H 7.76.

4.3.27. 2-Methyl-8-*tert*-butoxycarbonylspiro[cyclopropane-1′,10-(3-oxabicyclo[4.4.0]dec-1(6)-ene)] (55). According to GP-B, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), K_2CO_3 (556 mg, 4.00 mmol), Et_4NCl (332 mg, 2.00 mmol), 3-iodobut-3-en-1-ol (**53**, 396 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous MeCN (4 mL) at 80 °C for 24 h. After cooling the mixture to

room temperature, *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and then the mixture was heated with stirring at 80 °C for an additional 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate, 4:1) to yield **55** (140 mg, 25%, yellowish oil) as a mixture of two diastereomers (ratio 1.3:1 according to NMR).

*Major and minor diastereomers**. R_f=0.56 (light petroleum/ethyl acetate, 4:1); IR (film): $\tilde{\nu}$=3081, 2977, 2932, 1726, 1452, 1392, 1367, 1318, 1259, 1153, 1107, 1036, 984, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.34–0.72 (m, 6H, *c*Pr-H), 0.76–0.89 (m, 2H, *c*Pr-H), 1.11 (d, J=6.5 Hz, 3H, CH_3), 1.15–1.23 (m, 2H), 1.28 (d, J=6.4 Hz, 3H, CH_3), 1.44 [s, 18H, 2×$C(CH_3)_3$], 1.69–2.27 (m, 10H), 2.68–2.82 (m, 2H), 3.58–3.78 (m, 3H), 3.80–3.99 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=10.23 (−, *c*Pr-C), 11.87 (−, *c*Pr-C), 13.08 (−, *c*Pr-C), 13.43 (−, *c*Pr-C), 18.37 (C_{quat}, *c*Pr-C), 19.03 (C_{quat}, *c*Pr-C), 19.80 (+, CH_3), 20.58 (+, CH_3), 28.02 [+, 2×$C(CH_3)_3$], 29.09 (−), 30.08 (−), 32.69 (−), 33.54 (−), 38.06 (−), 39.32 (−), 40.13 (+), 40.43 (+), 57.45 (−), 54.49 (−), 66.13 (+), 68.77 (+), 79.99 [C_{quat}, 2×$C(CH_3)_3$], 124.40 (C_{quat}), 127.22 (C_{quat}), 132.29 (C_{quat}), 133.58 (C_{quat}), 174.68 (C_{quat}, C=O), 174.79 (C_{quat}, C=O); MS (DCI), *m*/*z* (%): 296 (100) [$M+NH_4^+$], 279 (2) [$M+H^+$], 240 (73), 232 (20); elemental analysis calcd (%) for $C_{17}H_{26}O_3$ (278.4): C 73.35, H 9.41; found: C 73.59, H 9.41. *Proton and carbon chemical shifts are given in one series for both diastereomers together because ^1H NMR and ^{13}C NMR spectra were not appropriate to classify all of the peaks for major and minor diastereomers. IR, DCI mass and elemental analysis were carried out for the mixture of diastereomers.

4.3.28. 2-Methyl-3-(toluene-4-sulfonyl)-8-*tert*-butoxycarbonylspiro[cyclopropane-1′,10-(3-azabicyclo[4.4.0]dec-1(6)-ene)](56) and 2,2-dimethylpropionic acid 8-[1-methylene-3-toluene-4-sulfonylamino)propyl]spiro[2.5]oct-7-en-5-yl ester (57). According to GP-A, $Pd(OAc)_2$ (22.4 mg, 100 μmol), tri-2-furylphosphine (46.4 mg, 200 μmol), Et_3N (202 mg, 2.00 mmol), *N*-(3-iodobut-3-enyl)-4-methylbenzenesulfonamide (**54**, 702.4 mg, 2.00 mmol) and bicyclopropylidene (**1**, 320 mg, 4.00 mmol) were stirred in anhydrous DMF (2 mL), at 80 °C for 3 h. After cooling the mixture to room temperature *tert*-butyl acrylate (**15**, 512 mg, 4.00 mmol) was added, and the mixture stirred at 80 °C for 48 h. After work-up and drying ($MgSO_4$), the solvent was removed in a rotatory evaporator. The residue was subjected to column chromatography on silica gel (100 g, 3×30 cm, light petroleum/ethyl acetate 4:1) to yield **56** (328 mg, 38%, colorless solid) and **57** (311 mg, 36%, yellowish oil), **56**: mp 110 °C, R_f=0.35 (light petroleum/ethyl acetate 4:1); IR (KBr): $\tilde{\nu}$=3097, 3072, 3002, 2978, 2909, 2869, 2829, 1716, 1597, 1448, 1433, 1372, 1367, 1338, 1263, 1158, 1089, 1033, 942, 815, 694 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.36–0.44 (m, 1H, *c*Pr-H), 0.49–0.67 (m, 2H, *c*Pr-H), 0.80–0.89 (m, 1H, *c*Pr-H), 1.05–1.11 (m, 1H), 1.18 (d, J=6.5 Hz, 3H, CH_3), 1.42 [s, 9H, $C(CH_3)_3$], 1.63–1.98 (m, 4H), 2.03–2.18 (m, 1H), 2.41 (s, 1H, CH_3), 2.47–2.59 (m, 1H), 3.26–3.38 (m, 1H), 3.63–3.79 (m, 2H), 7.25 (d, J=7.8 Hz, 2H, Ph), 7.65 (d, J=8.3 Hz, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=11.91 (−, *c*Pr-C), 13.17 (−, *c*Pr-C), 18.75 (C_{quat}, *c*Pr-C), 20.21 (+, CH_3), 21.10 (+, CH_3), 28.01 [+, $C(CH_3)_3$], 28.25 (−), 33.09 (−), 37.42 (−), 38.15 (−), 40.47 (+), 46.93 (+), 79.52 [C_{quat}, $C(CH_3)_3$], 125.59 (C_{quat}), 127.45 (+, Ph-C), 129.42 (+, Ph-C), 132.62 (C_{quat}), 139.07 (C_{quat}), 142.67 (C_{quat}), 174.13 (C_{quat}, C=O); MS (70 eV, EI), *m*/*z* (%): 431 (4) [M^+], 416 (4) [M^+-CH_3], 375 (6), 361 (17), 360 (100), 220 (26), 204 (10), 174 (18), 133 (11), 105 (15), 91 (66), 57 (52), 41 (24); elemental analysis calcd (%) for $C_{24}H_{33}NO_4S$ (431.6): C 66.79, H 7.71; found: C 66.68, H 7.50. **57**: R_f=0.31 (light petroleum/ethyl acetate 4:1); IR (film): $\tilde{\nu}$=3275 (N–H), 3080, 3003, 2976, 2924, 2872, 1728 (C=O), 1599, 1457, 1421, 1392, 1367, 1337, 1257, 1167, 1095, 985, 903, 847, 814, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=0.20–0.28 (m, 1H, *c*Pr-H), 0.37–0.44 (m, 2H, *c*Pr-H), 0.46–0.57 (m, 1H, *c*Pr-H), 1.14–1.20 (m, 1H), 1.35 [s, 9H, $C(CH_3)_3$], 1.80 (t, J=12.1 Hz, 1H), 2.02–2.09 (m, 2H), 2.11–2.18 (m, 2H), 2.34 (s, 3H, CH_3), 2.48–2.58 (m, 1H, 5-H), 2.77–2.99 (m, 2H), 4.27 (t, J=5.9 Hz, 1H), 4.53 (d, J=2.7 Hz, 1H, vinyl), 4.66 (br s, 1H, vinyl), 5.00–5.03 (m, 1H, 7-H), 7.23 (d, J=8.0 Hz, 2H, Ph), 7.68 (d, J=8.0 Hz, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=11.71 (−, *c*Pr-C), 13.12 (−, *c*Pr-C), 18.43 (C_{quat}, *c*Pr-C), 21.26 (+, CH_3), 27.81 (−)*, 27.81 [+, $C(CH_3)_3$], 36.50 (−), 36.81 (−), 39.94 (+, C-5), 40.82 (−), 79.78 [C_{quat}, $C(CH_3)_3$], 115.14 (−, vinyl), 122.46 (+, C-7), 126.91 (+, Ph-C), 129.44 (+, Ph-C), 136.56 (C_{quat}), 141.52 (C_{quat}), 143.08 (C_{quat}), 144.14 (C_{quat}), 174.50 (C_{quat}, C=O). *The peak of this carbon sits under the broad singlet of the *tert*-butyl group. This carbon peak correlates clearly with the multiplet between 2.11–2.18 ppm in the HMQC spectrum. MS (ESI, MeOH) *m*/*z* (%): 885 (100) $[2M+Na]^+$, 454 (63) $[M+Na]^+$; HRMS (ESI) calcd for $C_{24}H_{33}NO_4S$ $[M+H]^+$432.22031; found 432.22036

4.3.29. 5-(1-Iodovinyl)benzo[1,3]dioxole (32). To an ice-cold solution of 5-[(1-diethoxyphosphinyl)oxo-vinyl]-benzo[1,3]dioxole* (2 g, 6.66 mmol) in anhydrous CH_2Cl_2 (20 mL) was added Me_3SiI (2.85 mL, 20.0 mmol) dropwise with a syringe. After stirring 15 min at 0 °C, the reaction mixture was quenched by addition of saturated $NaHCO_3$ (20 mL) and saturated Na_2SO_3 (20 mL) solutions. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The vinyl iodide was purified by column chromatography using *n*-pentane as an eluent. **36** was isolated as a very sensitive pink oil (1.092 g, 60%) and immediately used after isolation. *This precursor was prepared according to a known procedure from the corresponding ketone and directly used for the preparation of **32** without further purification.[24]

^1H NMR (250 MHz, $CDCl_3$) δ=5.98 (s, 2H, OCH_2O), 6.35 (d, J=1.4 Hz, 1H, vinyl), 6.71–6.75 (m, 1H, vinyl), 7.01–7.05 (m, 3H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=101.36 (−), 106.68 (C_{quat}), 107.49 (+, Ph), 108.16 (+, Ph-C), 122.13 (+, Ph-C), 126.13 (−), 135.84 (C_{quat}), 147.16 (C_{quat}), 147.93 (C_{quat}).

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Multiple component Fischer indole reactions

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Abstract—New 3-component variations of the Fischer synthesis of substituted indoles have been developed based on the reaction of organometallic reagents with nitriles or carboxylic acids. The new variations expand the scope and synthetic utility of the method.

1. Introduction

Multiple component condensation (MCC) reactions, defined as processes 'in which three or more reactants come together in a single reaction to form a new product that contains portions of all the components,'[1] play a central role in diversity-oriented synthesis. Despite their utility, such reactions remain a small subset of known organic reactions. Recent discoveries by our group[2] and others[3] have expanded the repertoire of useful MCC reactions. However, significant advances in this area might also be achieved by modifying known MCC reactions, either by broadening input types or increasing reaction dimensionality (i.e., >3-component Mannich or >4-component Ugi condensations). Here, we use a combination of those approaches to demonstrate that the well-known 2-component Fischer indole synthesis can be re-engineered into a higher-order, more broadly based 3-component process.

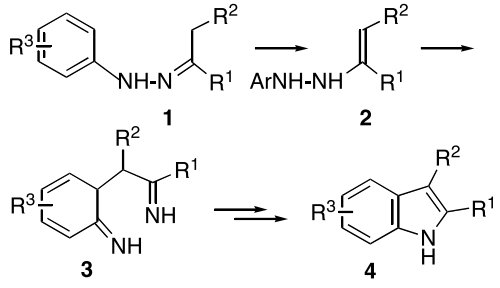
2. Background

Over a century ago Emil Fischer discovered that hydrazones **1**, prepared from arylhydrazines and enolizable ketones, rearranged upon heating in acid with loss of ammonia to afford indoles **4** (Scheme 1).[4] The process involved initial tautomerization to an ene-hydrazine **2** that underwent a [3,3]-sigmatropic rearrangement to **3** followed by ring closure and aromatization. We reasoned that identifying other reactant combinations leading to intermediates in Scheme 1 might increase the dimensionality of the Fisher indole synthesis, thus widening its scope.

With three contiguous bonds involving two well-differentiated heteroatoms, arylhydrazone **1** presented a particularly attractive target. Such arylhydrazones have previously been formed by Pd-catalyzed cross-coupling of benzophenone hydrazones with aryl bromides, leading to indoles in excellent yield.[5] Substituted indoles have also been prepared by alkyne hydroamination with hydrazines[6] and by the tandem hydroformylation/hydrazination of alkenes.[7] However, each of these methods uses only two variable components.

By contrast, metallated ketimines **5** (Scheme 2), generated by the reaction of nitriles with Grignard[8] or organolithium[9] compounds, should react in situ (after protonation) with arylhydrazines to form arylhydrazones **1**. Rearrangement to the corresponding indoles would thus incorporate structural diversity from three different inputs. Moreover, species like **5** could in most cases be formed from two complementary reactant combinations as shown, thus making the overall synthesis plan even more flexible.

Here, we report this 3-component condensation can be successfully implemented as a one pot process. By using anhydrous ether as solvent in the addition of organometallic reagents, byproducts arising from competing deprotonation



Scheme 1.

Keywords: Deprotonation; Fisher cyclization; Tandem hydroformylation.
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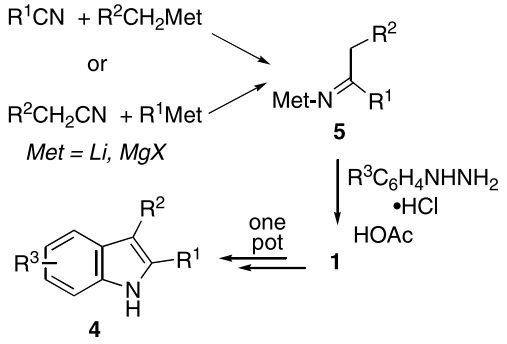


Scheme 2.

reactions of α-acidic nitriles[10] could be suppressed so as to obtain metallated ketimines **5** in good yield.[11]

3. Results and discussion

Protonation of **5** and conversion of the corresponding arylhydrazones **1** to indoles **4** was achieved by brief heating (90 °C, 3 h) in glacial acetic acid containing 2.1 equiv of the appropriate arylhydrazine hydrochloride.[12] This method, first reported by Dave, avoids the use of toxic, air- and light-sensitive $PhNHNH_2$ as well as the customary higher temperatures and more corrosive Lewis acids. Representative examples of the reaction, shown in Table 1, illustrate the scope and generality of the method.

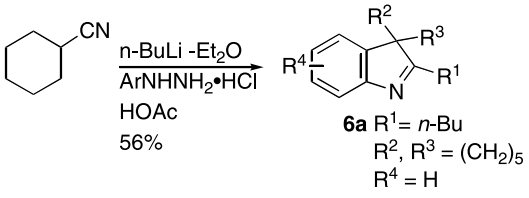
The new 3-component route afforded indoles in yields similar to the classical 2-component Fischer synthesis. In most cases, a small amount (ca. 15% yield based on phenylhydrazine) of $PhNHNHCOCH_3$ was also obtained as a byproduct.[13] Condensation of propionitrile with BuLi or BuMgCl led to the same 2:1 mixture of indoles **4h** and **4i**, in agreement with earlier observations on the rearrangement of α,α′-unbranched arylhydrazones.

The Dave conditions for Fischer cyclization, originally applied only to $PhNHNH_2 \cdot HCl$, could be extended to ring-substituted arylhydrazine hydrochloride salts leading to 4, 5, 6, and 7-substituted indoles (e.g., **4b**, **4c**, **4f**, **4j**), albeit in slightly lower yields. Cyclizations leading to 2-arylindoles required somewhat longer heating (15–19 h).

Table 1 also showed that the scope of the method could be extended beyond commercially available organometallic reagents. For example, the synthesis of indoles **4e**, **4f** and **4k** demonstrated the successful use of organolithium reagents prepared by halogen–metal exchange methods, which significantly expanded the utility of the 3CC indole synthesis.

One limitation of the method was encountered in efforts to transform halo-substituted nitriles (e.g., 3-bromopropionitrile, 4-chlorobutyronitrile) into the correspondingly functionalized indoles. All attempts to trap metallated imine **5**, the corresponding ketone or hydrazone **1** failed, suggesting that **5** might be susceptible to inter- or intramolecular decomposition.

The method was successful in preparing indolenines by way of α-branched arylhydrazones. Reaction of cyclohexylcarbonitrile with BuLi followed by $PhNHNH_2 \cdot HCl$ afforded **6a** (Eq. 1) in 56% yield, in accordance with literature precedent.[14]



(1)

An alternative 3-component route to indoles has also been devised from the well-known reaction of a carboxylic acid with 2 equiv of an organolithium reagent in ether.[15] The method affords a useful synthetic approach to ketones, by hydrolysis of the intermediate dialkoxides **7** (Scheme 3).

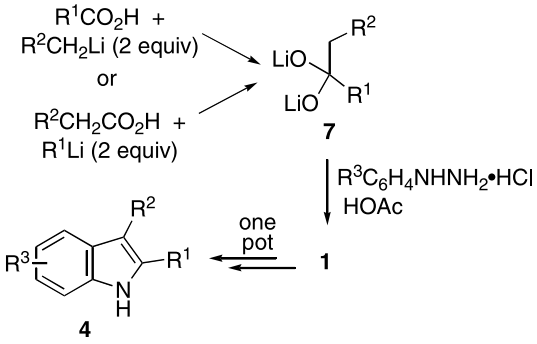
In the present variation, stepwise reaction of a carboxylic acid with RLi was followed by the addition of a sufficient quantity of arylhydrazine hydrochloride. By using 3.1 equiv of $ArNHNH_2 \cdot HCl$ in HOAc, it proved possible to protonate dianion **7** and generate the corresponding ketone. Arylhydrazone formation in situ and Fischer cyclization catalyzed by the residual hydrochloride salt in glacial HOAc at 90 °C afforded indoles **4**. Table 2 presents representative examples of indoles that could be prepared in this fashion.

The higher-order variants of the Fischer synthesis reported

Table 1. 3-Component condensations of nitriles, RMet and $ArNHNH_2$ leading to indoles **4**[a]

Nitrile	RMet	$ArNHNH_2Ar=$	Product (% yield)
PhCN	BuLi	Ph[b]	**4a** 2-Phenyl-3-propylindole (60)
PhCN	BuLi	*m*-Cl-Ph[b]	**4b** 4-Chloro-2-phenyl-3-propylindole (19), **4c** 6-Chloro-2-phenyl-3-propylindole (19)
PhCN	BuMgCl	Ph	**4a** (42)
n-$C_5H_{11}CN$	PhLi	Ph	**4d** 3-Butyl-2-phenylindole (49)
n-$C_5H_{11}CN$	PhMgCl	Ph	**4d** (45)
n-$C_5H_{11}CN$	*p*-OMe-C_6H_4Li	Ph[a]	**4e** 3-Butyl-2-(*p*-CH_3OPh)-indole (64)
n-$C_5H_{11}CN$	*p*-OMe-C_6H_4Li	*o*-Cl-Ph[b]	**4f** 3-Butyl-7-chloro-2-(*p*-CH_3OPh)-indole (34)
n-$C_5H_{11}CN$	CH_3Li	Ph	**4g** 3-Butyl-2-methylindole (54)
CH_3CH_2CN	BuLi	Ph	**4h** R^1=2-butyl-3-methylindole (46), **4i** 2-Ethyl-3-propylindole (23)
CH_3CH_2CN	BuMgCl	Ph	**4h** (40); **4i** (20)
CH_3CH_2CN[c]	PhMgBr	*p*-OMe-Ph	**4j** 5-Methoxy-3-methyl-2-phenylindole (32)
CH_3CH_2CN	3,5-Dibromo-PhLi	Ph[b]	**4k** 2-(3′,5′-Dibromophenyl)-3-methylindole (57)

[a] The nitrile was combined with RMet in ether, followed by the addition of $ArNHNH_2 \cdot HCl$. The ether was removed in vacuo and HOAc added. The reaction mixture was then heated at 90 °C.
[b] $ArNHNH_2 \cdot HCl$ (2.6 equiv) added.
[c] Nitrile added in C_6H_6.



Scheme 3.

Table 2. 3-Component condensations of carboxylic acids, RLi and $ArNHNH_2$ leading to indoles **4** and indolenines[a]

Acid	RLi	$ArNHNH_2Ar=$	Product (% yield)
Benzoic	BuLi	Ph	**4a** 2-Phenyl-3-propylindole (72)
Nonanoic	CH_3Li	Ph	**4l** 3-Heptyl-2-methylindole (55)
Isobutyric	BuLi	Ph	**6b** 2-Butyl-3,3-dimethylindolenine (66)
Isobutyric	BuLi	*o*-Cl-Ph	**6c** 2-Butyl-7-chloro-3,3-dimethylindolenine (48)
4-Pentenoic	PhLi	Ph	**4m** 3-Allyl-2-phenylindole (52)
4-Pentenoic	PhLi	*p*-OMe-Ph	**4n** 3-Allyl-5-methoxy-2-phenylindole (54)
4-pentenoic	3,5-Dibromo-PhLi	*p*-OMe-Ph	**4o** 3-Allyl-2-(3′,5′-dibromophenyl)-5-methoxyindole (29)

[a] The acid was combined with R-Met in ether at 0 °C, followed by heating at 45–90 °C. After addition of $ArNHNH_2 \cdot HCl$ at 0 °C, the ether was removed in vacuo and HOAc added. The reaction mixture was then heated at 90 °C.

here, should prove useful in the convergent assembly of indoles from a more diverse array of available reactants. Indeed, many simple substituted indole alkaloids have significant therapeutic potential, including antibacterial, antiphosphatase, antipeptidase, anticancer and insecticidal activity.[16]

4. Experimental

4.1. Representative procedure for the synthesis of 2-arylindoles from nitriles and organolithiums

4.1.1. Procedure A: synthesis of 2-phenyl-3-propylindole (4a).[17] To *n*-butyllithium (hexane solution, 0.18 mL, 0.25 mmol) in anhydrous ether (0.25 mL) at 0 °C, under argon, was added a solution of benzonitrile (22 μL, 0.21 mmol) in ether (0.25 mL) by syringe over a 2 min period. The reaction mixture was stirred for 30 min under argon at 0 °C. Phenylhydrazine·HCl (73 mg, 0.55 mmol) was then added with stirring for 5 min at 0 °C, then 5 min at rt. The heterogeneous mixture was concentrated to remove ether. Glacial acetic acid (0.9 mL) was added and the reaction heated to 90 °C in an oil bath for 15 h.

The reaction mixture was diluted with ether (10 mL) and water (2 mL). The aqueous phase was extracted with ether (3×1 mL) and the combined organic layers were washed with NaOH (1 N) until basic, then with saturated NaCl (1 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to furnish an oil that was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f=0.3$), to afford an off-white solid (30 mg, 60%): mp 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.64 (d, 1H, $J=7.6$ Hz), 7.56 (d, 2H, $J=7.1$ Hz), 7.48 (t, 2H, $J=7.4$ Hz), 7.37 (m, 2H), 7.20 (t, 1H, $J=6.8$ Hz), 7.13 (t, 1H, $J=6.8$ Hz), 2.86 (t, 2H, $J=7.8$ Hz), 1.76 (sextet, 2H, $J=7.6$ Hz), 1.00 (t, 3H, $J=7.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.07, 134.30, 133.69, 129.54, 129.02, 128.14, 127.67, 122.36, 119.63, 119.57, 114.19, 110.92, 26.92, 24.47, 14.67; IR (neat) 3408 (s), 3054 (m), 2954 (s), 1610 (w), 1465 (s), 1311 (m), 739 (s), 694 (s); CIMS (methane) *m/z*: 236 (M+H), 206.

4.1.2. 4-Chloro-2-phenyl-3-propylindole (4b). The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f=0.19$), to afford an off-white solid (10 mg, 19%): mp 110–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.52 (d, 2H, $J=7.0$ Hz), 7.48 (t, 2H, $J=7.5$ Hz), 7.39 (t, 1H, $J=7.2$ Hz), 7.25 (d, 1H, $J=7.5$ Hz), 7.07 (m, 2H), 2.96 (t, 2H, $J=8.0$ Hz), 1.78 (sextet, 2H, $J=8.0$ Hz), 0.97 (t, 3H, $J=7.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.49, 135.73, 133.12, 129.03, 128.64, 128.15, 126.71, 125.75, 122.68, 121.06, 114.69, 109.64, 27.27, 26.70, 14.42; IR (neat) 3418 (s), 2959 (s), 1600 (m), 1485 (s), 1446 (s), 1336 (s), 1197 (s), 764 (s), 739 (s), 699 (s); CIMS (methane) *m/z*: 270 (M+H), 240, 205.

4.1.3. 6-Chloro-2-phenyl-3-propylindole (4c). The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f=0.31$), to afford an off-white solid (10 mg, 19%): mp 60–61 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.51 (d, 3H, $J=8.2$ Hz), 7.46 (t, 2H, $J=7.6$ Hz), 7.36 (t, 1H, $J=7.3$ Hz), 7.31 (s, 1H), 7.08 (d, 1H, $J=7.1$ Hz), 2.80 (t, 2H, $J=7.8$ Hz), 1.71 (sextet, 2H, $J=7.8$ Hz), 0.96 (t, 3H, $J=7.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.36, 134.95, 133.18, 129.08, 128.17, 128.07, 127.92, 120.39, 120.33, 114.20, 110.84, 26.76, 24.39, 14.58; IR (neat) 3418 (s), 3064 (w), 2964 (s), 1595 (s), 1466 (s), 774 (s), 704 (s); CIMS (methane) *m/z*: 270 (M+H), 240, 234.

4.1.4. 3-Butyl-2-phenylindole (4d).[18] The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, $R_f=0.29$) to furnish a light orange powder (26 mg, 49%): mp 57–59 °C, lit. mp 60–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.66 (d, 1H, $J=7.6$ Hz), 7.57 (d, 2H, $J=8.1$ Hz), 7.49 (t, 2H, $J=7.3$ Hz), 7.3 (t, 2H, $J=8.1$ Hz), 7.22 (t, 1H, $J=7.0$ Hz), 7.15 (t, 1H, $J=7.4$ Hz), 2.90 (t, 2H, $J=7.8$ Hz), 1.73 (p, 2H, $J=7.5$ Hz), 1.43 (sextet, 2H, $J=7.6$ Hz), 0.94 (t, 3H, $J=7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.08, 134.18, 133.65, 129.49, 128.99, 128.11, 127.64, 122.35, 119.61, 119.52, 114.31, 110.94, 33.47, 24.52, 23.19, 14.21; IR (neat) 3407 (s), 3064 (m), 2925 (s), 1605 (m), 1461 (s), 1341

(m), 1311 (m), 1241 (m), 749 (s), 694 (s); CIMS (methane) *m/z*: 250 (M+H), 206.

4.1.5. 2-(3′,5′-Dibromophenyl)-3-methylindole (4k). 3,5-Dibromophenyllithium was prepared from 1,3,5-tribromobenzene following a literature procedure.[19] The product was purified by silica gel flash column chromatography (16:1 hexanes/ether, then 8:1 hexanes/ether), to afford a yellow powder upon cooling in the freezer overnight (29 mg, 57%): mp 100–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.62 (m, 4H), 7.36 (d, 1H, J=8.2 Hz), 7.24 (t, 1H, J=8.1 Hz), 7.16 (t, 1H, J=8.1 Hz), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.95, 136.29, 132.68, 131.05, 129.90, 129.31, 123.54, 123.49, 120.15, 119.57, 111.08, 110.95, 9.91; IR (neat) 3412 (m), 3059 (w), 2919 (w), 1595 (s), 1540 (s), 1461 (m), 863 (m), 744 (s); CIMS (methane) *m/z*: 366 (M+H), 286, 79.

4.1.6. 3-Butyl-2-(*p*-methoxyphenyl)indole (4e). To a solution of *p*-bromoanisole (25 μL, 0.2 mmol) in ether (0.25 mL) at 0 °C under argon was added *n*-BuLi (hexane solution, 0.12 mL, 0.2 mmol) via syringe over 1 min. The reaction mixture was warmed to rt and stirred for 1 h.[20] After cooling to 0 °C, a solution of hexanenitrile (22 μL, 0.18 mmol) in ether (0.10 mL) was added via syringe over 1 min, then stirred for 30 min. Following Method A afforded an oily solid that was purified by silica gel flash column chromatography (8:1 hexanes/ether, then 4:1 hexanes/ether), to afford a clear oil (32 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.62 (d, 1H, J=7.8 Hz), 7.48 (d, 2H, J=8.0 Hz), 7.36 (d, 1H, J=8.0 Hz), 7.18 (t, 1H, J=7.9 Hz), 7.12 (t, 1H, J=7.8 Hz), 7.01 (d, 2H, J=8.1 Hz), 3.87 (s, 3H), 2.85 (t, 2H, J=7.8 Hz), 1.70 (p, 2H, J=7.7 Hz), 1.41 (sextet, 2H, J=7.5 Hz), 0.92 (t, 3H, J=7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.25, 135.92, 134.16, 129.55, 129.38, 126.21, 122.02, 119.53, 119.31, 114.44, 113.48, 110.81, 55.56, 33.48, 24.52, 23.20, 14.23; IR (neat) 3412 (m), 2959 (s), 2940 (s), 1615 (w), 1510 (s), 1460 (s), 1251 (s), 833 (m), 744 (m); CIMS (methane) *m/z*: 280 (M+H), 265, 236, 188.

4.1.7. 3-Butyl-7-chloro-2-(4′-methoxyphenyl)indole (4f). Following the procedure for **4e**, the product was purified by silica gel flash column chromatography (8:1 hexanes/ether, R_f=0.29), to afford a clear oil (17 mg, 34%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.51 (m, 3H), 7.17 (d, 1H, J=7.9 Hz), 7.05 (t, 1H, J=7.7 Hz), 7.02 (m, 2H), 3.88 (s, 3H), 2.83 (t, 2H, J=7.8 Hz), 1.68 (p, 2H, J=7.6 Hz), 1.40 (sextet, 2H, J=7.5 Hz), 0.92 (t, 3H, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.56, 135.01, 133.11, 130.96, 129.53, 125.55, 121.28, 120.32, 117.89, 116.35, 114.53, 114.45, 55.59, 33.40, 24.63, 23.12, 14.20; IR (neat) 3427 (m), 2959 (s), 2934 (s), 1610 (w), 1510 (s), 1461 (s), 1252 (s), 834 (m); CIMS (methane) *m/z*: 314 (M+H), 270.

4.2. Representative procedure for the synthesis of aliphatic substituted indoles and indolenines from nitriles and organolithiums

4.2.1. Procedure B: synthesis of 3-butyl-2-methylindole (4g).[21] Methyllithium in ether (0.20 mL, 0.32 mmol) was added to a 0 °C solution of ether (0.30 mL) under argon. A solution of hexanenitrile (35 μL, 0.29 mmol) and ether (0.30 mL) was added by syringe over a 2 min period. The reaction mixture was stirred 30 min under argon at 0 °C. Phenylhydrazine·HCl (88 mg, 0.61 mmol) was added quickly and the reaction stirred 5 min at 0 °C, then 5 min at rt. The heterogeneous mixture was concentrated to remove ether. Glacial acetic acid (0.9 mL) was added and the reaction mixture was heated to 90 °C for 3 h. After following the extractive workup of procedure A, the product was purified by silica gel flash column chromatography (4:1 hexanes/ether, R_f=0.27), to afford a yellow oil (27 mg, 54%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.51 (d, 1H, J=7.1 Hz), 7.26 (m, 1H), 7.13–7.03 (m, 2H), 2.68 (t, 2H, J=7.4 Hz), 2.36 (s, 3H), 1.60 (p, 2H, J=7.7 Hz), 1.37 (sextet, 2H, J=7.2 Hz), 0.92 (t, 3H, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.40, 130.75, 129.02, 120.92, 119.09, 118.35, 112.65, 110.27, 33.20, 24.04, 22.86, 14.28, 11.87; IR (neat) 3407 (s), 3064 (w), 2959 (m), 2924 (s), 1461 (s), 1301 (w), 739 (s); CIMS (methane) *m/z*: 188 (M+H), 144.

4.2.2. 2′-Butylspiro[cyclohexane-1,3′-3′H-indole] (6a):. The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, R_f=0.3), to afford an off-white powder (28 mg, 56%): mp 69–71 °C; ^{1}H (500 MHz, $CDCl_3$) δ 7.71 (d, 1H, J=7.4 Hz), 7.60 (d, 1H, J=7.7 Hz), 7.33 (t, 1H, J=7.6 Hz), 7.15 (t, 1H, J=7.5 Hz), 2.52 (t, 2H, J=7.6 Hz), 1.99–1.77 (m, 10H), 1.46 (sextet, 2H, J=7.8 Hz), 1.26 (m, 2H), 0.97 (t, 3H, J=7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.14, 154.72, 144.70, 127.63, 124.47, 124.25, 120.41, 58.32, 31.09, 29.24, 29.16, 25.53, 23.17, 21.82, 14.20; IR (neat) 2930 (s), 2869 (m), 1580 (m), 1456 (s), 749 (s); CIMS (methane) *m/z*: 242 (M+H), 199, 144.

4.3. Representative procedures for the synthesis of indoles and indolenines from nitriles and Grignard reagents

4.3.1. Procedure C: synthesis of 2-butyl-3-methylindole (4h). A solution of butylmagnesium chloride in ether (0.15 mL, 0.29 mmol) in ether (0.25 mL) was brought to reflux under argon. A solution of propionitrile (19 μL, 0.27 mmol) in ether (0.25 mL) was added over 1 min via syringe. The reaction was heated at reflux for 4 h under argon. The reaction was then cooled to 0 °C and phenylhydrazine·HCl (81 mg, 0.56 mmol) was added. The resulting heterogeneous mixture was stirred 5 min at 0 °C, 5 min at rt, then concentrated to remove ether. Glacial acetic acid (1.0 mL) was added and the reaction was heated to 90 °C in an oil bath for 3 h before performing the extractive workup of procedure A.

4.3.2. Procedure D:[22] synthesis of 2-butyl-3-methylindole (4h).[23] To a solution of butylmagnesium chloride in ether, (0.15 mL, 0.29 mmol) in benzene (0.25 mL) at rt under argon was added a solution of propionitrile (19 μL, 0.27 mmol) in benzene (0.25 mL) over 1 min. The reaction was stirred at rt for 1 h. Phenylhydrazine·HCl (81 mg, 0.56 mmol) added and the mixture stirred 5 min at 0 °C, 5 min at rt, then concentrated to remove ether. Glacial acetic acid (1.0 mL) added and the reaction mixture was heated to 90 °C for 3 h. The extractive workup of procedure A was followed to afford an orange oil, which was purified by

silica gel flash column chromatography (8:1 hexanes/ether, R_f=0.34), to afford an orange solid upon cooling in the freezer overnight (20 mg, 40%); mp 41–43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.5 (d, 1H, J=7.5 Hz), 7.27 (d, 1H, J=7.0 Hz), 7.11 (m, 2H), 2.73 (t, 2H, J=7.5 Hz), 2.25 (s, 3H), 1.64 (p, 2H, J=7.5 Hz), 1.39 (sextet, 2H, J=7.6 Hz), 0.95 (t, 3H, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.49, 135.29, 129.56, 121.04, 119.11, 118.21, 110.28, 106.98, 32.05, 26.04, 22.60, 14.11, 8.69; IR (neat) 3403 (s), 2969 (s), 2924 (s), 1470 (s), 1336 (m), 1306 (m), 744 (s); CIMS (methane) *m/z*: 188 (M+H), 144.

4.3.3. 2-Ethyl-3-propylindole (4i). Synthesized following either procedure C or D. The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, R_f=0.26), to afford a waxy orange solid after standing (10 mg, 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.52 (d, 1H, J=6.8 Hz), 7.28 (d, 1H, J=7.3 Hz), 7.09 (m, 2H), 2.76 (q, 2H, J=7.6 Hz), 2.67 (t, 2H, J=7.6 Hz), 1.65 (sextet, 2H, J=7.5 Hz), 1.28 (t, 3H, J=7.6 Hz), 0.95 (t, 3H, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.75, 135.40, 129.02, 120.98, 119.10, 118.57, 111.60, 110.39, 26.35, 24.31, 19.54, 14.56, 14.42; IR (neat) 3402 (s), 2959 (s), 2929 (s), 1461 (s), 1321 (m), 744 (s); CIMS (methane) *m/z*: 188 (M+H), 158.

4.3.4. 5-Methoxy-3-methyl-2-phenylindole (4j).[24] Synthesized following procedure D. The product was purified by silica gel flash column chromatography (4:1 hexanes/ether, R_f=0.3), to afford a white powder (16 mg, 32%): mp 116–117 °C, lit. mp[25] 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.57 (d, 2H, J=8.3 Hz), 7.47 (t, 2H, J=8.9 Hz), 7.35 (t, 1H, J=7.4 Hz), 7.27 (d, 1H, J=8.3 Hz), 7.04 (d, 1H, J=2.4 Hz), 6.87 (dd, 1H, J=2.4, 8.7 Hz), 3.90 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.32, 135.16, 133.58, 131.18, 130.60, 129.00, 127.85, 127.47, 112.62, 111.65, 108.69, 101.00, 56.16, 9.97; IR (neat) 3412 (m), 2929 (w), 1620 (m), 1585 (m), 1486 (s), 1461 (s), 1291 (m), 1217 (s), 774 (m), 699 (m); CIMS (methane) *m/z*: 238 (M+H), 223.

4.4. Representative procedure for the synthesis of indoles and indolenines from carboxylic acids and organolithiums

4.4.1. Procedure E:[26] synthesis of 3-heptyl-2-methylindole (4l) Methyllithium in ether (0.28 mL, 0.45 mmol) was added to a stirring ether (1.0 mL) solution at 0 °C, under argon. A solution of nonanoic acid (38 μL, 0.22 mmol) in ether (0.1 mL) was added over 3 min. The reaction mixture was stirred at 0 °C for 5 min, then at rt 10 min. The reaction mixture was then heated at 45 °C for 30 min. The resulting heterogeneous mixture was cooled to 0 °C and phenylhydrazine·HCl (96 mg, 0.67 mmol) quickly added. The reaction mixture was stirred 5 min at 0 °C, 5 min at rt, then concentrated to remove ether. Glacial acetic acid (0.9 mL) added and the reaction mixture was heated to 90 °C for 3 h. Following the extractive workup of procedure A, the product was purified by silica gel flash column chromatography (8:1 hexanes/ether, R_f=0.3), to afford a yellow oil (28 mg, 55%); 1H NMR (300 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.53 (m, 1H), 7.26 (m, 1H), 7.11 (m, 2H), 2.69 (t, 2H, J=7.4 Hz), 2.37 (s, 3H), 1.62 (p, 2H, J=7.4 Hz), 1.30 (m, 8H), 0.90 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.40, 130.73, 129.00, 120.90, 119.09, 118.35, 112.69, 110.27, 32.15, 31.01, 29.82, 29.50, 24.33, 22.92, 14.35, 11.86; IR (neat) 3407 (s), 2930 (s), 2860 (s), 1466 (s), 1306 (m), 739 (s); CIMS (methane) *m/z*: 230 (M+H), 144.

4.4.2. 3-Allyl-2-phenylindole (4m).[27] Synthesized following procedure E, except the reaction was heated at 90 °C for 19 h. The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, R_f=0.3), to afford a yellow/white powder (26 mg, 52%): mp 98–99 °C, lit. mp[28] 72–73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.56 (m, 3H), 7.44 (t, 2H, J=7.3 Hz), 7.34 (m, 2H), 7.19 (t, 1H, J=8.1 Hz), 7.11 (t, 1H, J=7.9 Hz), 6.12 (m, 1H), 5.08 (m, 2H), 3.61 (dt, 2H, J=1.8, 5.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.57, 136.10, 135.01, 133.16, 129.55, 129.04, 128.02, 127.86, 122.53, 119.84, 119.59, 115.38, 110.96, 110.66, 29.15; IR (neat) 3402 (s), 3078 (w), 3014 (w), 1610 (w), 1455 (s), 1306 (m), 992 (m), 928 (m), 759 (s), 700 (m); CIMS (methane) *m/z*: 234 (M+H), 206.

4.4.3. 3-Allyl-5-methoxy-2-phenylindole (4n). Synthesized following procedure E, except the reaction was heated at 90 °C for 15 h. The product was purified by silica gel flash column chromatography (45 mL of 8:1 hexanes/ether, then 4:1 hexanes/ether), to afford a white powder (27 mg, 54%): mp 102–104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.55 (d, 2H, J=8.1 Hz), 7.46 (t, 2H, J=7.9 Hz), 7.36 (t, 1H, J=7.4 Hz), 7.28 (d, 1H, J=8.7 Hz), 7.04 (sd, 1H, J=2.4 Hz), 6.87 (dd, 1H, J=2.4, 8.8 Hz), 6.13 (m, 1H), 5.11 (m, 2H), 3.87 (s, 3H), 3.60 (dt, 2H, J=1.8, 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.32, 137.44, 135.97, 133.26, 131.33, 130.06, 129.02, 127.95, 127.80, 115.37, 112.53, 111.71, 110.44, 101.52, 56.14, 29.20; IR (neat) 3402 (m), 2939 (w), 1625 (m), 1486 (s), 1456 (s), 1222 (s), 1037 (w), 763 (m), 699 (m); CIMS (methane) *m/z*: 264 (M+H), 249.

4.4.4. 3-Allyl-2-(3′,5′-dibromophenyl)-5-methoxyindole (4o). Synthesized following procedure E, except the reaction was heated at 90 °C for 15 h. The product was purified by silica gel flash column chromatography (4:1 hexanes/ether, R_f=0.3), to afford a pale yellow powder (15 mg, 29%): mp 111–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.60 (s, 3H), 7.25 (d, 1H, J=8.8 Hz), 6.99 (sd, 1H, J=2.4 Hz), 6.88 (dd, 1H, J=2.4, 8.8 Hz), 6.07 (m, 1H), 5.08 (m, 2H), 3.84 (s, 3H), 3.55 (dt, 2H, J=1.8, 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.56, 136.77, 136.60, 132.93, 132.71, 131.55, 129.76, 129.35, 123.51, 115.91, 113.74, 112.34, 112.01, 101.37, 56.07, 29.08; IR (neat) 3408 (m), 2929 (m), 1585 (s), 1540 (m), 1490 (m), 1216 (s), 749 (s); CIMS (methane) *m/z*: 422 (M+H), 342, 264.

4.4.5. 2-Butyl-3,3-dimethylindolenine (6b). The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, R_f=0.3), to afford a yellow oil (33 mg, 66%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, 1H, J=7.6 Hz), 7.28 (m, 2H), 7.17 (t, 1H, J=7.3 Hz), 2.52 (t, 2H, J=8.2 Hz), 1.83 (p, 2H, J=8.0 Hz) 1.45 (sextet, 2H, J=7.6 Hz), 1.28 (s, 6H), 0.97 (t, 3H, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.36, 154.02, 145.81, 127.72, 125.16, 121.35, 120.19, 53.97, 28.89, 28.76, 23.40, 23.11,

14.17; IR (neat) 2964 (s), 2934 (s), 2869 (m), 1580 (s), 1461 (s), 1207 (w), 754 (s); CIMS (methane) *m/z*: 216 (M+CH_3), 202 (M+H), 146, 71.

4.4.6. 2-Butyl-7-chloro-3,3-dimethylindolenine (6c). The product was purified by silica gel flash column chromatography (8:1 hexanes/ether, R_f=0.3), to afford an off-white powder (24 mg, 48%): mp 43–45 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, 1H, J=1.4, 7.7 Hz), 7.12 (m, 2H), 2.56 (t, 2H, J=7.9 Hz), 1.84 (p, 2H, J=7.8 Hz), 1.46 (sextet, 2H, J=7.5 Hz), 1.30 (s, 6H), 0.97 (t, 3H, J=7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.84, 150.66, 147.78, 128.23, 126.32, 125.20, 119.72, 55.47, 29.43, 29.29, 23.22, 23.23, 14.11; IR (neat) 2964 (s), 2930 (s), 2865 (m), 1575 (s), 1461 (s), 1431 (s), 1201 (w), 963 (m), 754 (s); CIMS (methane) *m/z*: 236 (M+H), 193, 180, 157.

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Four-component Pd-catalysed cascade/ring closing metathesis. Synthesis of heterocyclic enones☆

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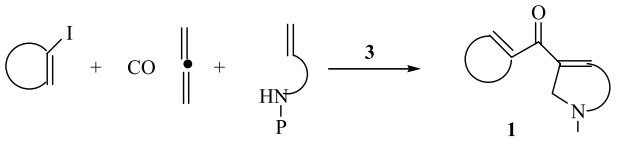
Abstract—A palladium-catalysed four-component process is described involving carbon monoxide, allene and aryl/heteroaryl iodides generating (π-allyl) palladium species, which are intercepted by alkene tethered nitrogen nucleophiles to afford 1,6- and 1,7-dienones. Subsequent ring closing metathesis affords five- and six-membered *N*-heterocyclic enones. The *N*-heterocyclic enones are active dipolarophiles in 1,3-dipolar cycloaddition reactions as exemplified by azomethine ylide and nitrone cycloadditions.

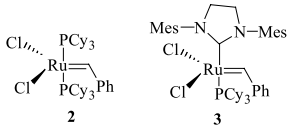
1. Introduction

Previously, we reported the devlopment of a Pd-catalysed three-component cascade/ring closing metathesis (RCM) route for five- and six-membered *N*-heterocycles.[2] In this system the muti-component cascade created the diversity, which is relayed into the final heterocycle by a RCM. Success of this methodology prompted us into investigate a more challenging four-component cascade (4CC)/RCM process accessing versatile heterocylic enones **1** (Scheme 1).

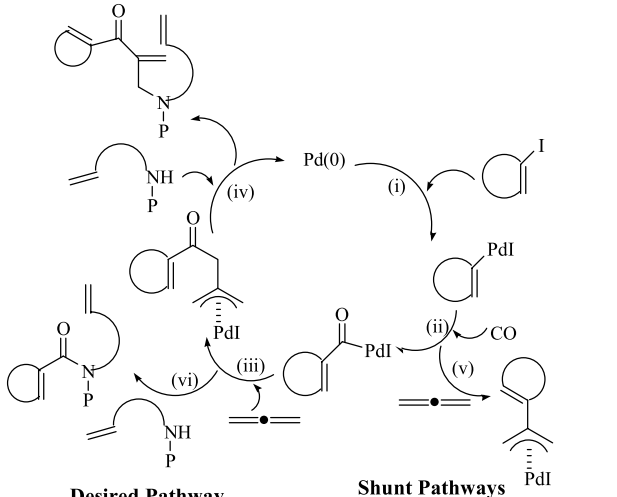


Scheme 1.

The development of new improved metathesis catalysts continues to increase the popularity of this reaction.[3] Whilst RCM reports of acrylates catalysed by **2** can be found in the literature they are not general and often require Lewis acids to achieve synthetically useful yields.[4,5]



Amongst the extended substrate scope second generation Ru catalyst 2 tolerates electron deficient alkenes particularly well. Access via RCM to various cyclic α,β-unsaturated



Scheme 2.

☆ See Ref. 1.

Keywords: Ring closing metathesis; Catalytic cascades; Heterocyclic enones; 1,3-Dipolar cycloadditions.
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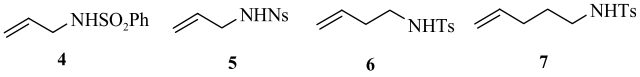
esters, amides and ketones employing **3** is being exploited by a growing number of groups.[6]

In the studies reported herein, we have explored interfacing a 4CC with RCM and RCM with cycloadditions. For the 4CC to be successful carbonylation must occur before allene insertion and allene insertion must in turn be faster than nucleophilic substitution (Scheme 2). An incorrect reactivity order would lead inter alia to shunt pathways (v) and (vi) (Scheme 2). The desired 'molecular queuing' in these 4CC has been reported by the Grigg group for certain nucleophiles[7] and examples employing solid phase combinatorial chemistry reported.[8]

2. Results and discussion

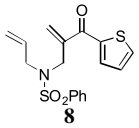
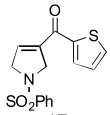
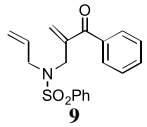
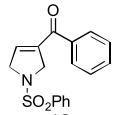
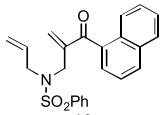
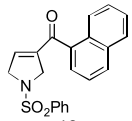
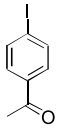
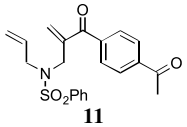
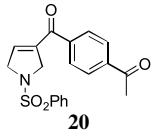
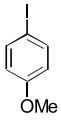
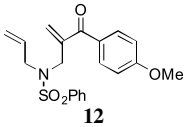
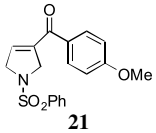
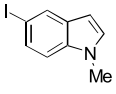
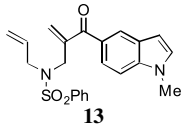
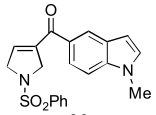
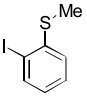
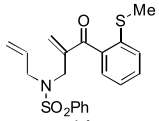
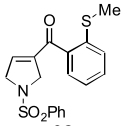
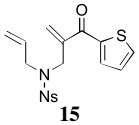
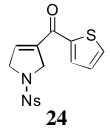
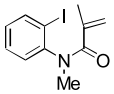
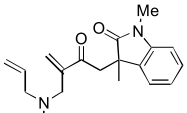
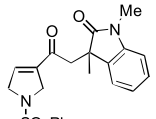
2.1. Four-component cascades employing pronucleophiles 4 and 5



4 **5** **6** **7**

Nitrogen protected alkenyl tethered amine pronucleophiles **4–7** were prepared by literature procedures.[2,8,9] Initial studies employed **4** along with iodothiophene, palladium acetate, triphenylphosphine and potassium carbonate as

Table 1. Sequential four-component cascade-RCM employing nucleophiles **4** and **5**

Entry	Aryl/heteroaryl iodide	Pd-cascade product[a]	Yield (%)[b]	RCM product[c]	Yield (%)[b]
1		 **8**	75	 **17**	94
2		 **9**	75	 **18**	88
3		 **10**	70	 **19**	90
4		 **11**	70	 **20**	93
5		 **12**	55	 **21**	92
6		 **13**	70	 **22**	87
7		 **14**	68	 **23**	25[d]
8		 **15**	65	 **24**	56
9	 **26**	 **16**	65	 **25**	93

[a] $Pd(OAc)_2$ 10 mol%, PPh_3 20 mol%, K_2CO_3 2 mol equiv, toluene, 70 °C, 22–44 h.
[b] Isolated yields.
[c] Compound **3** (5 mol%), toluene 80 °C, 1–14 h.
[d] Compound **3** (12 mol%) employed.

base. The reaction was conducted in toluene at 70 °C under 1 atm of allene and 1 atm of carbon monoxide in a Schlenk tube. To our delight, complete chemoselective conversion to the dienone, **8** was achieved within 38 h (Table 1, entry 1).

Subjecting dienone **8** to **3** (5 mol%) in toluene at 80 °C produced complete conversion to heterocyclic enone **17** (Table 1, entry 1). The scope of the reaction was then explored through variation of the aryl/heteroaryl iodide (Table 1). Electron deficient, electron rich and heteroaryl iodides worked equally well in the tetramolecular cascade, furnishing the dienones **8–15** inside 44 h and with complete conversion in all cases. In each case the ^{1}H NMR spectrum of the crude reaction mixture was devoid of by-products confirming the cascade is chemo- and regioselective. Nucleophile **4** could also be interfaced with the cyclisation-anion capture methodology developed by Grigg et al.,[10] affording dienone **16** from the 'zipper' starting species **26**. Three new carbon–carbon and one carbon–nitrogen bonds are thus formed in this cascade (Table 1, entry 9).

2.2. RCM affording 3-pyrrolines

Catalyst **3** effected complete RCM of **8–16** to the heterocyclic enones, **17–25** within 1–8 h in all cases with the exception of **23**. In this latter case a maximum 40% conversion was achieved with a total catalyst loading of 12 mol%, added in three separate portions of 5, 5 and 2 mol% after 2 and 13 h with a total reaction time of 14 h (Table 1, entry 7). Catalyst poisoning by the nucleophilic sulphur of **14** may be a reason for this. Another possibility could be the formation of an unfavourable and stable chelate. Chelation has been shown in many cases to be detrimental to the ring closing reaction.[11]

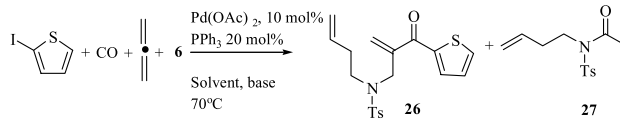
Table 2. Effect of solvent/base on Scheme 3

Entry	Solvent	Base	Yield (%)[a]
1	Toluene	K_2CO_3	33 (20)
2	Toluene	Cs_2CO_3	100 (71)[b]
3	Toluene	NaO^{t}Bu	13
4	CH_3CN	K_2CO_3	60 (41)
5[c]	CH_3CN	K_2CO_3	20
6[d]	CH_3CN	K_2CO_3	57
7	DMF	K_2CO_3	50
8	Toluene	Rb_2CO_3	100 (74)

[a] Conversion calculated from ^{1}H NMR. Isolated yield in parenthesis.
[b] 1:1 mixture of **26** and **27**.
[c] NEt_4Cl (1 mol equiv) added.
[d] $Pd(PPh_3)_4$ used as catalyst.

2.3. Four-component cascades employing nucleophile 6

Initial attempts to employ **6** in the 4CC with iodothiophene resulted in poor conversion to the desired product (Scheme 3, Table 2, entry 1). Optimisation of the reaction conditions was thus investigated. Using cesium carbonate as base



Scheme 3.

resulted in a 1:1 mixture of **26** and **27** (Table 2, entry 2) whilst sodium tertiary butoxide gave poor conversion (Table 2, entry 3). Polar solvents gave greater conversion to product (Table 2, entries 4 and 7) when employing potassium carbonate as the base. However, addition of tetraethylammonium chloride suppressed the reaction (Table 2, entry 5). Preformed Pd(0) catalyst tetrakis triphenylphosphinepalladium did not improve the conversion (Table 2, entry 6). However, rubidium carbonate as base resulted in complete chemoselective conversion to **26** (Table 1, entry 8).

Possible explanations for the unique effect of Rb_2CO_3 include an increased concentration of deprotonated pronucleophile, that is, a low concentration of deprotonated pronucleophile results in poor product conversion (Table 1, entry 1). However, an excess of pronucleophile **6** leads to trapping of the acyl-palladium intermediate (Scheme 2) and the formation of amide **27** (Table 2, entry 2). On moving down group 1 of the periodic table, metal carbonate bonding becomes less covalent in character resulting in a higher concentration of the basic carbonate anion. The concentration of anion follows the trend $K_2CO_3 < Rb_2CO_3 < Cs_2CO_3$. Perhaps rubidium carbonate serendipitously forms the optimum concentration of deprotonated pronucleophile required for total chemoselectivity and conversion to **26** (Table 1, entry 8). Alternatively or additionally it may produce a more active Pd(0) species as a polycarbonate[12] $[Pd(0)(CO_3)_n]^{2n-}$ analogous to the effect of Cl^- ions from $R_4N^+Cl^-$.[13] To our knowledge there is only one other report[14] describing the superiority of Rb_2CO_3 over the more usual K_2CO_3 and Cs_2CO_3.

A comparison of the predicted pK_a's for the protected allylamine, **4** (10.0) and homoallylamine **6** (11.6),[15] shows a difference of over 1.5 units. This suggests, to achieve complete product conversion the necessary concentration of anion is formed from **4** with potassium carbonate (Table 1, entry 1). However, due to its less acidic proton, **6** is only partially deprotonated and poor conversion results (Table 2, entry 1).

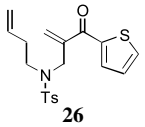
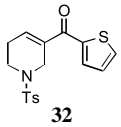
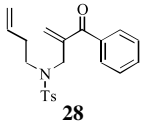
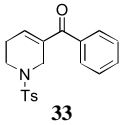
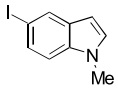
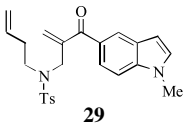
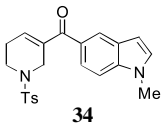
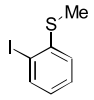
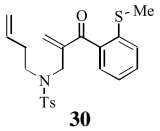
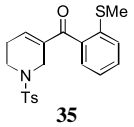
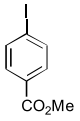
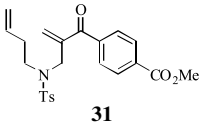
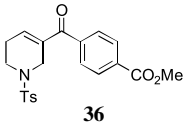
2.4. RCM affording 3-piperideines

With the reaction conditions optimised for **6** the scope of the reaction with respect to the aryl iodide was evaluated (Table 3). The process worked well for a series of iodides yielding acylic dienones **26–31** in 68–75% yield. Subjecting dienones **26–31** to **3** (5 mol%) afforded the six-membered heterocylic enones **32–36** in 73–92% yield (Table 3). Interestingly RCM of thioether analogue **30** afforded 92% conversion and 73% isolated yield of heterocylic enone **35** with 7 mol% of **3** added in two separate portions (Table 3, entry 4). Comparisons with the synthesis of **23** in the analogous five-membered series indicates the formation of a six-membered ring by RCM is more favourable.

2.5. Four-component cascades employing pronucleophile 7

Results achieved from using alkenyl tethered amine **7** in the four-component Pd-cascade parallel those obtained employing **6**. Potassium carbonate was found to give poor

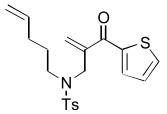
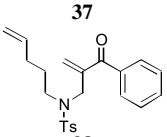
Table 3. Sequential four-component cascade-RCM employing nucleophile **6**

Entry	Aryl/heteroaryl iodide	Pd-cascade product[a]	Yield (%)[b]	RCM product[c]	Yield (%)[b]
1		 **26**	74	 **32**	92
2		 **28**	72	 **33**	90
3		 **29**	68	 **34**	91
4		 **30**	75	 **35**	73[d]
5		 **31**	70	 **36**	86

[a] $Pd(OAc)_2$ 10 mol%, PPh_3 20 mol%, Rb_2CO_3 2 mol equiv, toluene, 70 °C, 18–25 h.
[b] Isolated yields.
[c] Compound **3** (5 mol%), toluene 80 °C, 2–7 h.
[d] Compound **3** (5 mol%) added time zero followed by 2 mol% of **3** after 4 h.

conversions, cesium carbonate gave product mixtures, whilst rubidium carbonate gave near complete conversion to dienone **37**, in 56% isolated yield when using 2-iodothiophene (Table 4, entry 1). This was expected, considering the essential equivalence of the pK_a's of **6** (11.6) and **7** (11.74).[14] Dienone **38** was also formed with complete conversion from iodobenzene in 68% isolated yield employing the same conditions (Table 4, entry 2). Unfortunately subjecting **37** and **38** to RCM using **3** failed to afford any of the seven-membered ring analogues. The acyclic dienone was recovered unchanged after 24 h in both cases.

Table 4. Sequential four-component cascade-RCM employing nucleophile **7**

Entry	Aryl/heteroaryl iodide	Pd-cascade product[a]	Yield (%)[b]
1		 **37**	56
2		 **38**	68

[a] $Pd(OAc)_2$ 10 mol%, PPh_3 20 mol%, Rb_2CO_3 2 mol equiv, toluene, 70 °C, 25 h.
[b] Isolated yields.

2.6. Microwave-accelerated RCM[1]

Microwave irradiation is reported to dramatically accelerate a number of metal catalysed reactions.[16] This encouraged us to evaluate the technique for RCM processes of our acyclic enones. Initially, we studied the microwave-accelerated RCM of **8** using the Smith Creator microwave. DCM was the solvent of choice owing to its microwave transparency[17] allowing the maximum uptake of microwave energy by the substrate and catalyst. A target temperature of 100 °C was set and the catalyst loading and concentration of **8** varied to find the optimum reaction conditions. The results are summarised in Table 5. The best set of conditions (Table 5, entry 3) furnished **17** in 86% yield. Increasing the concentration was found to impede the reaction (Table 5, entries 3 and 4). The temperature profile of the reaction mixture shows rapid heating, which could be ascribed to energy absorption by the ruthenium catalyst **3** or the diene substrate. However, a recent report by Lavastre et al. rules out the former.[18] The pressure of the sealed reaction vessel was monitored and found to stay below 5 bar. Next, we studied the formation of a range of 3-substituted five- and six-membered heterocyclic enones via microwave induced RCM by varying the aryl/heteroaryl group (Table 6).

Table 5. Optimisation of microwave RCM reaction conditions[a]

Entry	Time (min)	Concn (mM)	Catalyst loading (mol%)	Conversion (%)
1	5	1.5	5	100
2	1	1.5	5	100
3	**1**	**1.5**	**2.5**	**100**
4	1	3.0	2.5	90
5	2	3.0	1	88
6	1	3.0	1	88

[a] All reactions performed in CH_2Cl_2. The temperature was set to reach a maximum of 100 °C in all cases.

Table 6. Microwave acclerated RCM[a]

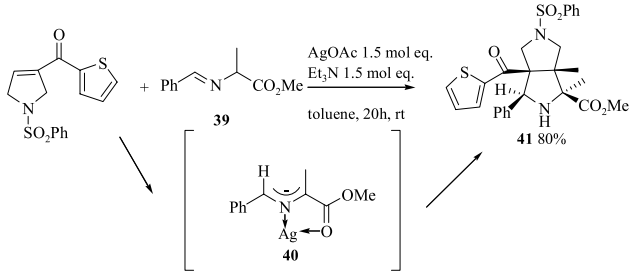
Entry	Starting material	Catalyst loading (mol%)	Product	Conversion (%)[b]	Yield (%)[c]
1	**13**	2.5	**22**	93	80
2	**11**	2.5	**20**	100	87
3	**16**	1	**25**	100	90
4	**8**	2.5	**17**	100	86
5	**29**	5	**34**	92	77
6	**30**	2.5	**35**	92	78

[a] As for Table 6 with a 1 min reaction time and a substrate concentration of 1.5–3.0 mM.
[b] Conversion calculated by ^{1}H NMR.
[c] Isolated yield.

Microwave heating results in shorter reaction times and lower catalyst loadings. Wilson et al. have reported a closely related process.[19]

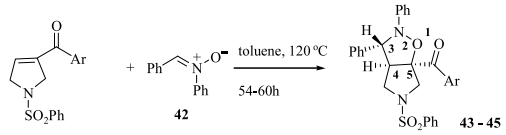
2.7. 1,3-Dipolar cycloaddition reactions

The heterocyclic enones described above were shown to be active dipolarophiles in cycloadditions with azomethine ylides and nitrones. Thus, stiring imine **39** with silver acetate, triethylamine and enone **17** in toluene at room temperature for 20 h afforded a single cycloadduct **41** in 80% isolated yield arising via an *endo*-transition state of the *syn*-metallodipole **40** (Scheme 4). The regio- and stereochemistry of the cycloadduct **41** were established by NOE studies and conform to that expected for Grigg's metal catalysed proline synthesis.[20]



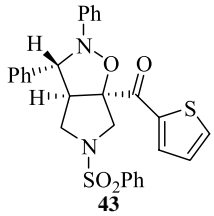
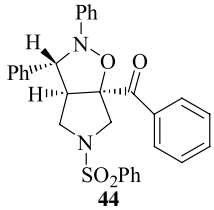
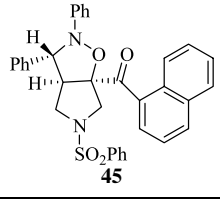
Scheme 4.

Heating the five-membered heterocylic enones **17–19** with diphenyl nitrone **42** in toluene at 120 °C (Schlenk tube) afforded the bicyclic isoxazolidines **43–45** in 58–80% yield as single regio- and diastereoisomers (Scheme 5, Table 7). The nitrone cycloadditions proved to be extremely sensitive towards variation in reaction temperature. Employing enone **17** and decreasing the reaction temperature to 80 °C causes a change in the regioselectivity of the reaction affording a 3.5:1 mixture of diastereoisomers **46** and **47**, respectively, in 70% yield (Scheme 6). Only trace amounts of the thermodynamic regioisomer **43** are formed at this temperature as shown by ^{1}H NMR. Subjecting **46** to reflux in toluene affords the thermodynamic isomer **43** via a retro-cycloaddition/1,3-dipolar cycloaddition along with trace

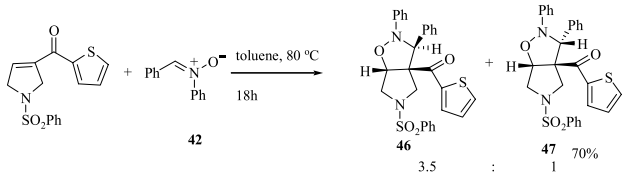


Scheme 5.

Table 7. Cycloadditions of enones **17–19** and nitrone **42**[a]

Entry	Enone	Product	Yield (%)[b]
1	**17**	 **43**	80[c]
2	**18**	 **44**	70
3	**19**	 **45**	58

[a] Toluene 120 °C, sealed tube, 54–60 h.
[b] Isolated yield.
[c] Trace amounts of isomer **45** formed.



Scheme 6.

amounts of enone **17** and diphenyl nitrone **42**. Regioisomer **43** is thought to be favoured under thermodynamic control due to the minimization of steric interactions between the 3-phenyl group of the nitrone and the aryl ketone of the enone.

2.8. Cascade RCM-1,3-dipolar cycloaddition

Finally, a cascade RCM-nitrone cycloaddition was shown to be possible. The ability to create a dipolarophile (dienophile) in situ and interface it with a cycloaddition in a cascade provides valuable synthetic flexibility. Additionally, in this case it results in the formation of three-new bonds and four stereocentres. Heating a mixture of dienone **8**, diphenyl nitrone **42** and catalyst **3** in toluene at 70 °C for

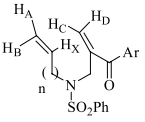
1 h followed by further heating at 90 °C for 17 h afforded a 3:1 mixture of **46** and **47** in 59% isolated yield. Heating to higher temperatures afforded complex mixtures. We have previously reported numerous examples of palladium catalysed multi-component cascades directly interfaced with cycloadditions.[21]

In summary, a novel and diverse route accessing 3-aryl/heteroaryl-acyl substituted heterocyles has been developed via the sequential application of a chemoselective four-component Pd-cascade/RCM sequences. The heterocyclic enones produced via this method can be further elaborated via cycloaddition chemistry. Investigation into the compatibility of other alkene-tethered nucleophiles and substituted allenes in this process is currently underway.

3. Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec instrument operating at 70 eV (EI and FAB) or ZD 2000 electrospray instrument (ES). Accurate molecular masses were obtained from the EPSRC Swansea Mass Spectroscopy service using perfluorotributylamine or polyethylenimine as an internal standard. Microanalyses were obtained using a Carbo Erba MOD11016 instrument. IR spectra were determined on a Nicolet Magna FT-IR 560 spectrometer. The IR samples were prepared as thin films by evaporation of a solution of the compound in DCM onto a germanium plate. Nuclear magnetic resonance spectra were recorded on Bruker DPX250, DPX300 and DPX500 instruments operating at 250, 300 and 500 MHz, respectively. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; q_i, quintet; m, multiplet; dd, doublet of doublets; ddd, double doublet of doublets; ddt, double doublet of triplets; b, broad. Solvents were dried according to established methods, unless purchased dry from Aldrich in sure-seal bottles. Palladium acetate was supplied by Johnson Matthey and ruthenium alkylidene catalysts were were purchased from Strem and Aldrich and used as received. The term ether refers to diethyl ether and the term petrol refers to the 40–60 °C boiling point fraction of petroleum ether. All the compounds are named according to the IUPAC system and names were obtained using the ACD/*i*-Lab software version 4.5.

3.1. ^{1}H NMR proton labels:



3.1.1. *N*-Allyl-*N*-[2-(thien-2-ylcarbonyl)prop-2-enyl]benzenesulfonamide (8). Prepared by the general cascade procedure (below) on a 5 mmol scale, using 5.5 mmol of aryl iodide and a reaction time of 38 h. Purification by flash chromatography eluting with 1:20 v/v ether/petrol afforded the product (1.29 g, 75%) as a viscous pale yellow oil; R_f 0.05; (Found: C, 58.80; H, 4.90; N, 4.10. $C_{17}H_{17}NO_3S_2$ requires C, 58.75; H, 4.95; N, 4.05%) υ_{max}/cm^{-1} (film) 1637 (C=O), 1621, 1413, 1342 (S=O_{as}), 1159 (S=O_s), 1091; δ_H (500 MHz, $CDCl_3$) 7.84–7.82 (2H, m, SO_2PhH), 7.68 (1H, dd, $J=5.0$, 1.1 Hz, ArH), 7.63 (1H, dd, $J=3.8$, 1.1 Hz, ArH), 7.58–7.55 (1H, m, SO_2PhH), 7.51–7.48 (2H, m, SO_2PhH), 7.12 (1H, dd, $J=5.0$, 3.8 Hz, ArH), 6.10 (1H, t, $J=1.5$ Hz, =C$H_C$$H_D$), 6.05 (1H, t, $J=1.0$ Hz, =C$H_C$$H_D$), 5.60 (1H, ddt, $J=16.7$, 10.0, 6.6 Hz, CH_X=C$H_A$$H_B$), 5.14 (1H, ddd, $J=16.7$, 2.7, 1.3 Hz, CH_X=CH_A-H_B), 5.11 (1H, ddd, $J=10.0$, 2.3, 1.7 Hz, CH_X=C$H_A$$H_B$), 4.14 (2H, s, NCH_2), 3.86 (2H, d, $J=6.6$ Hz, NCH_2); δ_C (125 MHz, $CDCl_3$) 187.9 (C=O), 143.4, 142.9, 139.8, 134.3, 134.2, 132.7, 132.1, 129.1, 128.0, 127.2, 125.8, 119.9, 51.5 (NCH_2), 47.7 (NCH_2); *m/z* (CI) 365 (60%, M+NH_4^+), 215 (100%).

3.2. General tetramolecular cascade procedure

3.2.1. *N*-Allyl-*N*-(2-benzoylprop-2-enyl)benzenesulfonamide (9). Palladium acetate (112 mg, 0.5 mmol), triphenyl phosphine (262 mg, 1 mmol), potassium carbonate (1.381 g, 10 mmol) and toluene (10 ml) were added to a Schlenk tube, containing a magnetic stirrer bar. A solution of the sulfonamide **4** (985 mg, 5 mmol), and iodobenzene (1.224 g, 6 mmol) in toluene (4 ml) was then added. The tube was sealed and the mixture frozen in liquid nitrogen, and degassed by vacuum pump. The mixture was then allowed to reach room temperature, followed by refreezing and degassing for a second time. Allene (1 bar) was then added to the Schlenk tube and the mixture frozen in a liquid nitrogen bath. Following this CO (1 bar) was added, the tube sealed and the mixture allowed to reach room temperature, before heating in an oil bath at 65–70 °C for 44 h. On completion of the reaction the mixture was allowed to cool to room temperature, the excess gas released and the mixture filtered. Concentration of the filtrate in vacuo gave an orange oil, which was purified by flash chromatography, eluting with 1:4 v/v ether/petrol to afford the product (1.275 mg, 75%) as a viscous, colourless oil; R_f 0.2; (Found: C, 66.55; H, 5.85; N, 4.15. $C_{19}H_{19}NO_3S$ requires C, 66.85; H, 5.60; N, 4.10%); υ_{max}/cm^{-1} (film) 1653 (C=O), 1447, 1344 (S=O_{as}), 1160 (S=O_s), 1092, 983, 932; δ_H (250 MHz, $CDCl_3$) 7.88–7.84 (2H, m, ArH), 7.72–7.60 (2H, m, ArH), 7.60–7.53 (6H, m, ArH), 6.27 (1H, t, $J=1.3$ Hz, =C$H_C$$H_D$), 5.89 (1H, s, =C$H_C$$H_D$), 5.62 (1H, ddt, $J=16.6$, 10.0, 6.6 Hz, CH_X=C$H_A$$H_B$), 5.19–5.10 (2H, m, C$H_X$=C$H_A$$H_B$), 4.15 (2H, t, $J=1.3$ Hz, NCH_2), 3.89 (2H, d, $J=6.6$ Hz, NCH_2); δ_C (63 MHz, $CDCl_3$) 197.3 (C=O), 143.4, 140.0, 137.6, 133.1, 132.9, 132.7, 129.9, 129.6, 129.2, 128.7, 127.6, 120.3, 52.2 (NCH_2), 47.9 (NCH_2); *m/z* (ES) 364 (M^++Na).

3.2.2. *N*-Allyl-*N*-[2-(1-naphthoyl)prop-2-enyl]benzenesulfonamide (10). Prepared by the general cascade procedure on a 5 mmol scale, using 5.5 mmol of aryl iodide and a reaction time of 42 h. Purification by flash chromatography eluting with DCM afforded the product (1.350 g, 70%) as a viscous colourless oil; R_f 0.32; (Found: C, 70.30; H, 5.35; N, 3.60. $C_{23}H_{21}NO_3S$ requires C, 70.55; H, 5.40; N, 3.60%); υ_{max}/cm^{-1} (film) 1652 (C=O), 1446, 1342 (S=O_{as}), 1160 (S=O_s), 1090; δ_H (250 MHz, $CDCl_3$) 8.05–7.87 (5H, m, ArH), 7.62–7.43 (7H, m, ArH), 6.63 (1H, t, $J=1.5$ Hz, =C$H_C$$H_D$), 5.91 (1H, s, =C$H_C$$H_D$), 5.66 (1H, ddt, $J=16.9$, 9.9, 6.8 Hz, CH_X=C$H_A$$H_B$), 5.21 (1H, ddd, $J=16.9$, 2.6, 1.3 Hz, CH_X=C$H_A$$H_B$), 5.18 (1H, dd, $J=9.9$, 1.1 Hz, CH_X=C$H_A$$H_B$), 4.27 (2H, s, NCH_2), 3.93 (2H, d, $J=6.8$ Hz, NCH_2); δ_C (63 MHz, $CDCl_3$), 199.1 (C=O),

145.3, 140.0, 136.1, 134.1, 133.2, 132.9, 132.1, 131.8, 131.1, 129.7, 128.9, 128.1, 127.7, 127.6, 126.9, 125.7, 124.7, 120.03, 52.5 (NCH_2), 47.3 (NCH_2); *m/z* (%) (FAB) 364 (37, $M^+ + H$), 250 (31, $M - SO_2Ph$), 210 (100), 195 (32), 141 (28, SO_2Ph).

3.2.3. *N*-[2-(4-Acetobenzoyl)prop-2-enyl]-*N*-allylbenzenesulfonamide (11). Prepared by the general cascade procedure on a 3 mmol scale, using 3.1 mmol of aryl iodide and a reaction time of 40 h. Purification by flash chromatography eluting with 3:2 v/v ether/petrol afforded the product (800 mg, 70%) as a pale yellow oil; R_f 0.2; (Found: C, 66.05; H, 5.65; N, 3.40. $C_{21}H_{21}NO_4S$ requires C, 65.80; H, 5.50; N, 3.60%); υ_{max}/cm^{-1} (film) 1686 (C=O), 1652 (C=O), 1446, 1343 (S=O_{as}), 1264, 1160 (S=O_s), 1091; δ_H (250 MHz, $CDCl_3$) 8.01 (2H, d, $J=8.3$ Hz, ArH), 7.87–7.84 (2H, m, SO_2PhH), 7.77 (2H, d, $J=8.3$ Hz, ArH), 7.60–7.51 (3H, m, SO_2PhH), 6.35 (H, s, $=CH_CH_D$), 5.90 (1H, s, $=CH_CH_D$), 5.61 (1H, ddt, $J=16.9$, 9.7, 6.5 Hz, $CH_X=CH_AH_B$), 5.15 (1H, d, $J=16.9$ Hz, $CH_X=CH_AH_B$), 5.14 (1H, d, $J=9.7$ Hz, $CH_X=CH_AH_B$), 4.14 (2H, s, NCH_2), 3.89 (2H, d, $J=6.5$ Hz, NCH_2), 2.66 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 197.9 (C=O), 198.6 (C=O), 143.5, 141.3, 140.0, 139.8, 133.2, 132.7, 130.2, 130.0 (=CH_2), 129.7, 128.6, 127.7, 120.4 (=CH_2), 52.4 (NCH_2), 47.7 (NCH_2), 27.3 (CH_3); *m/z* (%) (FAB) 384 (33, $M^+ + H$), 242 (40, $M - SO_2Ph$), 210 (77), 147 (100), 141 (28, SO_2Ph), 115 (47).

3.2.4. *N*-Allyl-*N*-[2-(4-methoxybenzoyl)prop-2-enyl]benzenesulfonamide (12). Prepared by the general cascade procedure on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 44 h. Purification by flash chromatography eluting with 3:7 v/v ethyl acetate/petrol afforded the product (204 mg, 55%) as a colourless oil; R_f 0.25; (Found: C, 64.40; H, 5.75; N, 3.95. $C_{20}H_{21}NO_4S$ requires C, 64.65; H, 5.70; N, 3.75%); υ_{max}/cm^{-1} (film) 1647 (C=O), 1599, 1333 (S=O_{as}), 1308, 1258 (OCH_3), 1160 (S=O_s), 1091; δ_H (250 MHz, $CDCl_3$), 7.87–7.83 (2H, m, SO_2PhH), 7.26 (2H, d, $J=8.9$ Hz, ArH), 7.59–7.47 (3H, m, SO_2PhH), 6.92 (2H, d, $J=8.9$ Hz, ArH), 6.14 (1H, s, $=CH_CH_D$), 5.79 (1H, s, $=CH_CH_D$), 5.61 (1H, ddt, $J=16.6$, 10.0, 6.6 Hz, $CH_X=CH_AH_B$), 5.20–5.06 (2H, m, $CH_X=CH_AH_B$), 4.14 (2H, s, NCH_2), 3.88 (2H, d, $J=6.5$ Hz, NCH_2), 3.87 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$), 195.9 (C=O), 163.8, 143.5, 140.1, 133.1, 132.7, 132.4, 130.0, 129.6, 127.6, 126.9, 120.2, 114.0, 55.9 (OMe), 52.0 (NCH_2), 48.3 (NCH_2); *m/z* (ES) 394 ($M^+ + Na$).

3.2.5. *N*-Allyl-*N*-{2-[(1-methyl-1*H*-indol-5-yl)carbonyl]prop-2-en-1-yl}benzenesulfonamide (13). Prepared by the general cascade procedure on a 5 mmol scale, using 5.5 mmol of aryl iodide and a reaction time of 44 h. Purification by flash chromatography eluting with DCM afforded the product (1.320 g, 70%) as a viscous pale yellow oil; R_f 0.15; (Found: C, 67.05; H, 5.65; N, 7.10. $C_{22}H_{22}N_2O_3S$ requires C, 67.00; H, 5.60; N, 7.10%); υ_{max}/cm^{-1} (film) 1652 (C=O), 1605, 1340 (S=O_{as}), 1159 (S=O_s), 1091; δ_H (250 MHz, $CDCl_3$) 8.06 (1H, d, $J=1.6$ Hz, ArH), 7.89–7.84 (2H, m, SO_2PhH), 7.71 (1H, dd, $J=8.7$, 1.6 Hz, ArH), 7.61–7.47 (3H, m, SO_2PhH), 7.34 (d, 1H, $J=8.7$ Hz, ArH) 7.13 (d, 1H, $J=3.2$ Hz, ArH), 6.60 (dd, 1H, $J=3.2$, 0.5 Hz, ArH), 6.15 (1H, s, $=CH_CH_D$), 5.83 (1H, s, $=CH_CH_D$), 5.64 (1H, ddt, $J=16.7$, 10.0, 6.6 Hz, $CH_X=CH_AH_B$), 5.18 (1H, dd, $J=16.7$, 1.3 Hz, $CH_X=CH_AH_B$), 5.13 (1H, dd, $J=10.0$, 1.3 Hz, $CH_X=CH_AH_B$) 4.20 (2H, s, NCH_2), 3.91 (2H, d, $J=6.6$ Hz, NCH_2), 3.84 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$), 197.0 (C=O), 143.4, 139.9, 132.6, 132.3, 130.4, 129.1, 128.7, 127.6, 127.3, 126.3, 124.8, 123.2, 119.8, 109.1, 103.0, 51.5 (NCH_2), 48.0 (NCH_2); 33.0 (CH_3); *m/z* (%) (EI) 394 (4, M^+), 253 (100, M^+), 198, (28), 144, (75), 77 (57).

3.2.6. *N*-Allyl-*N*-{2-[2-(methylthio)benzoyl]prop-2-en-1-yl}benzenesulfonamide(14). Prepared by the general cascade procedure on a 5 mmol scale, using 6 mmol of aryl iodide and a reaction time of 22 h. Purification by flash chromatography eluting with DCM afforded the product (1.320 g, 68%) as a viscous pale yellow oil, which solidified on standing, mp 44–46 °C; R_f 0.15; (Found: C, 61.70; H, 5.50; N, 3.75. $C_{20}H_{21}NO_3S_2$ requires C, 62.00; H, 5.45; N, 3.60%); υ_{max}/cm^{-1} (film) 1655 (C=O), 1446, 1434, 1344 (S=O_{as}), 1161 (S=O_s), 1092; δ_H (250 MHz, $CDCl_3$) 7.88–7.85 (2H, m, SO_2PhH), 7.60–7.53 (3H, m, SO_2PhH), 7.44–7.19 (4H, m, ArH), 6.27 (1H, s, $=CH_CH_D$) 5.80 (1H, s, $=CH_CH_D$), 5.59 (1H, ddt, $J=16.7$, 10.0, 6.6 Hz, $CH_X=CH_AH_B$), 5.15 (1H, d, $J=16.7$ Hz, $CH_X=CH_AH_B$), 5.13 (1H, d, $J=10$ Hz, $CH_X=CH_AH_B$), 4.18 (2H, s, NCH_2), 3.89 (2H, d, $J=6.6$ Hz, NCH_2), 2.42 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$), 197.9 (C=O), 144.3, 140.2, 138.8, 138.1, 133.1, 132.5, 131.5, 130.7, 129.7, 129.6, 127.9, 127.6, 125.0, 120.4, 52.1 (NCH_2), 47.0 (NCH_2), 17.4 (CH_3); *m/z* (ES) 388 ($M^+ + H$).

3.2.7. *N*-Allyl-4-nitro-*N*-[2-(2-thienylcarbonyl)prop-2-en-1-yl]benzenesulfonamide (15). Prepared by the general cascade procedure on a 5 mmol scale, using 5.5 mmol of aryl iodide and a reaction time of 38 h. Purification by flash chromatography eluting with DCM afforded the product (1.260 g, 65%) as colourless viscous oil; R_f 0.18; (Found: C, 52.25; H, 4.15; N, 7.15. $C_{17}H_{16}N_2O_5S_2$ requires C, 52.05; H, 4.10; N, 7.15%); υ_{max}/cm^{-1} (film) 1633 (C=O), 1615, 1527 (NO_2), 1345 (S=O_{as}), 1153 (S=O_s), 1093; δ_H (250 MHz, $CDCl_3$) 8.29 (2H, d, $J=9.0$ Hz, ArH), 7.98 (2H, d, $J=9.0$ Hz, ArH), 7.69 (1H, dd, $J=4.8$, 1.1 Hz, ArH), 7.57 (1H, dd, $J=3.8$, 1.1 Hz, ArH), 7.11 (1H, dd, $J=5.0$, 3.8 Hz, ArH), 6.06 (1H, s, $=CH_CH_D$), 6.05 (1H, s, $=CH_CH_D$), 5.64 (1H, ddt, $J=16.4$, 9.9, 6.5 Hz, $CH_X=H_AH_B$), 5.21 (1H, dd, $J=16.4$, 1.1 Hz, $CH_X=H_AH_B$), 5.20 (1H, dd, $J=9.9$, 1.3 Hz, $CH_X=CH_AH_B$), 4.21 (2H, s, NCH_2), 3.95 (2H, d, $J=6.5$ Hz, NCH_2); δ_C (75 MHz, $CDCl_3$) 187.9 (C=O), 150.3, 146.3, 143.0, 142.9, 135.2, 134.6, 131.9, 128.8, 128.5, 126.8, 124.7, 120.9, 51.6 (NCH_2), 48.2 (NCH_2); *m/z* (%) (EI) 206 (100, $M - SO_2PhNO_2$), 111 (69).

3.2.8. *N*-Allyl-*N*-{[2-[1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetyl]prop-2-enyl}benzenesulfonamide (16). Prepared by the general cascade procedure on a 1 mmol scale, using 1 mmol of aryl iodide and a reaction time of 28 h. Purification by flash column chromatography eluting with 4:1 v/v ether/petrol afforded the product (282 mg, 65%) as a viscous colourless oil; R_f 0.17; (Found: C, 65.50; H, 6.15; N, 6.50. $C_{24}H_{26}N_2O_4S$ requires C, 65.75; H, 6.00; N, 6.80%); υ_{max}/cm^{-1} (film) 1711 (C=O), 1679 (N–C=O), 1614, 1348 (S=O_{as}), 1159 (S=O_s), 1092; δ_H

(250 MHz, $CDCl_3$) 7.74–7.71 (2H, m, SO_2PhH), 7.56–7.46 (3H, m, SO_2PhH), 7.24 (1H, td, $J=7.7$, 1.3 Hz, ArH), 7.09 (1H, dd, $J=7.5$, 1.0 Hz, ArH), 7.02 (1H, td, $J=7.5$, 0.9 Hz, ArH), 6.88 (1H, d, $J=7.5$ Hz, ArH), 6.25 (1H, s, $=CH_CH_D$), 6.14 (1H, s, $=CH_CH_D$), 5.39 (1H, ddt, $J=$ 16.8, 10.1, 6.6 Hz, $CH_X=CH_AH_B$), 4.97 (1H, d, $J=$ 10.1 Hz, $CH_X=CH_AH_B$), 4.93 (1H, d, $J=16.8$ Hz, $CH_X=CH_AH_B$), 3.73 (2H, d, $J=1.3$ Hz, NCH_2), 3.66 (2H, d, $J=6.6$ Hz, $=CHCH_2$), 3.49 (1H, d, $J=17.8$ Hz, O=CCHH), 3.37 (1H, d, $J=17.8$ Hz, COCHH), 3.27 (3H, s, NCH_3), 1.36 (3H, s, CCH_3); δ_C (63 MHz, $CDCl_3$) 197.3 (C=O), 180.4 (C=O), 143.7, 142.9, 139.5, 133.4, 132.6, 131.8, 129.1, 127.9, 127.1, 126.5 ($=CH_2$), 122.2, 121.8, 119.7 ($=CH_2$), 108.1, 51.5 (CH_2), 46.4 (CH_2), 45.3 (CH_2), 45.1 (CCH_3), 26.4 (CH_3), 24.9 (CH_3); *m/z* (ES) 461 ($M^+ + Na$).

3.3. General RCM procedure

Grubb's second generation catalyst **3** (5.5 mg, 6.5 μmol) was added to a magnetically stirred solution of acyclic enone (0.13 mmol), in anhydrous toluene (50 ml) and the mixture stirred under argon atmosphere at 80 °C for 1–14 h. Concentration in vacuo yielded the crude product, which was purified by flash chromatography.

3.3.1. [1-(Phenysulfonyl)-2,5-dihydro-1*H*-pyrrol-3-yl] (thien-2-yl)methanone (17). Prepared by the general RCM procedure on a 0.33 mmol scale and a reaction time of 3 h. Purification by flash chromatography eluting with DCM afforded the product (99 mg, 94%), which crystallised from petrol/DCM as colourless needles, mp 152–154 °C; R_f 0.1; (Found: C, 56.15; H, 4.20; N, 4.50; $C_{15}H_{13}NO_3S_2$ requires C, 56.40; H, 4.10; N, 4.30%); υ_{max}/cm^{-1} (film); δ_H (500 MHz, $CDCl_3$) 7.90–7.86 (2H, m, SO_2PhH), 7.67 (1H, dd, $J=4.9$, 1.1 Hz, ArH), 7.65 (1H, dd, $J=3.8$, 1.1 Hz, ArH) 7.63–7.60 (1H, m, SO_2PhH), 7.57–7.54 (2H, m, SO_2PhH), 7.12 (1H, dd, $J=4.9$, 3.8 Hz, ArH), 6.58 (1H, q_i, $J=2.1$ Hz, =CH), 4.48 (2H, 2×ddd, $J=4.9$, 2.1, 1.0 Hz, NCH_2), 4.44 (2H, 2×ddd, $J=4.9$, 2.1, 1.0 Hz, NCH_2); δ_C (125 MHz, $CDCl_3$) 181.2 (C=O), 142.3, 138.9, 136.8, 134.8, 134.2, 133.1, 133.0, 129.4, 128.1, 127.5, 57.0 (NCH_2), 54.5 (NCH_2); *m/z* (%) (FAB) 320 (100, $M^+ + H$), 178 (23, $M-SO_2Ph$), 111 (60).

3.3.2. Phenyl[1-(phenylsulfonyl)-2,5-dihydro-1*H*-pyrrol-3-yl]methanone (18). Prepared by the general RCM procedure on a 0.12 mmol scale and a reaction time of 3 h. Purification by flash chromatography eluting with 7:3 v/v petrol/ethyl acetate afforded the product (34 mg, 88%), which crystallised from petrol/ether as colourless needles, mp 102–104 °C; R_f 0.19; (Found: C, 65.05; H, 4.90; N, 4.60. $C_{17}H_{15}NO_3S$ requires C, 65.15; H, 4.80; N, 4.45%); υ_{max}/cm^{-1} (film) 1644 (C=O), 1446, 1346 ($S=O_{as}$), 1291, 1165 ($S=O_s$), 1103; δ_H (500 MHz, $CDCl_3$) 7.90–7.88 (2H, m, ArH), 7.68–7.61 (3H, m, ArH), 7.59–7.54 (3H, m, ArH), 7.46–7.42 (m, 2H, ArH), 6.36 (1H, q, $J=2.1$ Hz, =CH), 4.48 (2H, 2×ddd, $J=4.7$, 2.1, 1.0 Hz, NCH_2), 4.43 (2H, 2×ddd, $J=4.7$, 2.1, 1.0 Hz, NCH_2); δ_C (125 MHz, $CDCl_3$) 190.6 (C=O), 138.9, 137.2, 137.1, 136.9, 133.0, 132.8, 129.4, 128.8, 128.6, 127.5, 56.1 (NCH_2), 54.4 (NCH_2); *m/z* (%) (CI), 331 (100, $M+NH_4^+$), 172 (100, $M-SO_2Ph$).

3.3.3. 1-Naphthyl[1-(phenylsulfonyl)-2,5-dihydro-1*H*-pyrrol-3-yl]methanone (19). Prepared by the general RCM procedure on a 0.2 mmol scale and a reaction time of 5 h. Purification by flash chromatography eluting with DCM afforded the product (63 mg, 90%) as an off white amorphous solid, mp 61–63 °C; R_f 0.05; (Found: C, 68.85; H, 4.85; N, 4.00. $C_{21}H_{17}NO_3S$ requires C, 69.40; H, 4.70; N, 3.85%); υ_{max}/cm^{-1} (film) 1644 (C=O), 1446, 1347 ($S=O_{as}$), 1290, 1166 ($S=O_s$), 1102; δ_H ($CDCl_3$, 250 MHz) 8.00–7.90 (5H, m, ArH), 7.62–7.45 (7H, m, ArH), 6.26 (1H, q, $J=2.1$ Hz, =CH), 4.56 (2H, 2×dd, $J=$ 4.2, 2.1 Hz, NCH_2), 4.39 (2H, 2×dd, $J=4.4$, 2.1 Hz, NCH_2); δ_C ($CDCl_3$, 63 MHz), 199.5 (C=O), 145.3, 139.9, 136.1, 134.1, 133.2, 132.9, 132.1, 131.8, 131.1, 129.7, 128.1, 127.7, 127.6, 126.9, 125.7, 124.7, 120.3, 52.4 (NCH_2), 47.3 (NCH_2); *m/z* (%) (EI) 363 (11, M^+), 155 (55), 127 (72), 77 (100); HRMS found 364.1000. $C_{21}H_{18}NO_3S$ requires 364.1007.

3.3.4. 1-{(4-[(1-Phenylsulfonyl)-2,5-dihydro-1*H*-pyrrol-3-yl]carbonyl)phenyl}ethanone (20). Prepared by the general RCM procedure on a 0.15 mmol scale and a reaction time of 2 h. Purification by flash chromatography eluting with ether afforded the product (50 mg, 93%) as colourless needles, mp 167–169 °C; R_f 0.27; (Found: C, 64.30; H, 4.75; N, 3.90. $C_{17}H_{19}NO_4S$ requires C, 64.20; H, 4.80; N, 3.95%); υ_{max}/cm^{-1} (film) 1685 (C=O), 1652 (C=O), 1350 ($S=O_{as}$), 1167 ($S=O_s$), 1092; δ_H (250 MHz, $CDCl_3$) 8.01 (2H, d, $J=8.6$ Hz, ArH), 7.91–7.88 (2H, m, SO_2PhH), 7.73 (2H, d, $J=8.6$ Hz, ArH), 7.65–7.53 (3H, m, SO_2PhH), 6.40–6.39 (1H, br m, =CH), 4.49–4.34 (4H, m, 2×NCH_2), 2.64 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 197.3 (C=O), 189.9 (C=O), 141.1, 140.3, 139.3, 138.8, 136.6, 133.6, 129.8, 129.3, 128.8, 127.9, 56.6 (NCH_2), 54.6 (NCH_2), 27.3 (CH_3); *m/z* (%) (EI) 355 (6, M^+), 214 (67, $M-SO_2Ph$), 147 (100), 77 (78).

3.3.5. (4-Methoxyphenyl)[1-(phenylsulfonyl)-2, 5-dihydro-1*H*-pyrrol-3-yl]methanone (21). Prepared by the general RCM procedure on a 0.3 mmol scale and a reaction time of 4 h. Purification by flash chromatography eluting with 3:2 v/v ether/petrol afforded the product (89 mg, 92%) as colourless needles, mp 162–164 °C; R_f 0.17; (Found: C, 62.70; H, 5.00; N, 4.05. $C_{18}H_{17}NO_4S$ requires C, 62.95; H, 5.00; N, 4.10%); υ_{max}/cm^{-1} (film) 1633 (C=O), 1568, 1334 ($S=O_{as}$), 1153 ($S=O_s$), 1099, 1023; δ_H (250 MHz, $CDCl_3$) 7.91–7.87 (2H, m, SO_2PhH), 7.71 (2H, d, $J=$ 9.0 Hz, ArH), 7.63–7.57 (3H, m, SO_2PhH), 6.92 (2H, d, $J=$ 9.0 Hz, ArH), 6.30 (1H, q, $J=2.0$ Hz, =CH), 3.87 (3H, s, CH_3) 4.50–4.39 (4H, m, 2×NCH_2); δ_C (63 MHz, $CDCl_3$) 189.5 (C=O), 163.9, 139.3, 137.1, 135.9, 133.4, 131.6, 130.1, 129.8, 127.9, 114.2, 56.4, 55.9, 55.0; *m/z* (ES) 344 ($M+H^+$).

3.3.6. (1-Methyl-1*H*-indol-5-yl)[1-(phenylsulfonyl)-2,5-dihydro-1*H*-pyrrol-3-yl]methanone (22). Prepared by the general RCM procedure on a 0.4 mmol scale and a reaction time of 2 h. Purification by flash chromatography eluting with 3:2 v/v ether/petrol afforded the product (129 mg, 87%) as colourless needles, mp 139–141 °C; R_f 0.2; (Found: C, 65.45; H, 5.15; N, 7.60. $C_{20}H_{18}N_2O_3S$ requires C, 65.55; H, 4.95; N, 7.65%); υ_{max}/cm^{-1} (film) 1652 (C=O), 1344 ($S=O_{as}$), 1166 ($S=O_s$); δ_H (250 MHz,

$CDCl_3$) 8.03 (s, 1H, ArH), 7.92–7.90 (2H, m, SO_2PhH), 7.70–7.54 (4H, m, SO_2PhH and ArH), 7.34 (1H, d, J= 8.8 Hz, ArH), 7.13 (1H, d, J=3.1 Hz, ArH), 6.58 (1H, d, J=3.1 Hz, ArH), 6.32 (1H, br s, =CH), 4.53–4.51 (2H, br m, NCH_2), 4.45–4.44 (2H, br m, NCH_2); δ_C (63 MHz, $CDCl_3$) 190.8 (C=O), 139.3, 139.1, 136.9, 135.0, 133.0, 130.6, 129.3, 128.8, 127.7, 127.5, 123.8, 122.5, 109.4, 103.0, 56.0 (NCH_2), 54.8 (NCH_2), 33.1 (CH_3); *m/z* (ES) 344 ($M^+ + Na$).

3.3.7. [2-(Methylthio)phenyl][1-(phenylsulfonyl)-2,5-dihydro-1*H*-pyrrol-3-yl]methanone (23). Prepared by the general RCM procedure on a 0.18 mmol scale and a reaction time of 14 h. Purification by flash chromatography eluting with DCM afforded the product (16 mg, 25%), which crystallised from DCM/hexane as colourless needles, mp 135–137 °C; R_f 0.1; (Found: C, 59.95; H, 4.50; N, 3.70. $C_{18}H_{17}NO_3S_2$ requires C, 60.15; H, 4.75; N, 3.90%); υ_{max}/cm^{-1} 1625 (C=O), 1460, 1332 ($S=O_{as}$), 1159 ($S=O_s$), 1073; δ_H (300 MHz, $CDCl_3$) 7.88 (2H, m, SO_2PhH), 7.66–7.54 (3H, m, SO_2PhH), 7.43 (1H, t, J=7.5 Hz, ArH), 7.33 (2H, d, J=7.5 Hz, ArH), 7.16 (1H, t, J=7.5 Hz, ArH), 6.20 (1H, br s, =CH), 4.48–4.47 (2H, br m, NCH_2), 4.38–4.37 (2H, br m, NCH_2), 2.40 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 191.5 (C=O), 140.4, 139.5, 138.6, 137.1, 137.0, 133.4, 131.9, 129.7, 129.4, 127.9, 127.5, 124.8, 56.4 (NCH_2), 54.18 (NCH_2), 17.0 (CH_3); *m/z* (ES) 360 ($M+H^+$).

3.3.8. {1-[(4-Nitrophenyl)sulfonyl]-2, 5-dihydro-1*H*-pyrrol-3-yl}(2-thienyl)methanone (24). Prepared by the general RCM procedure on a 1.45 mmol scale and a reaction time of 6 h. The product precipitated as an off white solid (295 mg, 56%), mp 216–218 °C; R_f 0.1; (Found: C, 49.50; H, 3.50; N, 7.90. $C_{15}H_{12}N_2O_5S_2$ requires C, 49.45; H, 3.30; N, 7.7%); υ_{max}/cm^{-1} 1633 (C=O), 1596, 1527 (NO_2), 1345 ($S=O_{as}$), 1157 ($S=O_s$), 1108, 1062; δ_H (250 MHz, $CDCl_3$) 8.41 (2H, d, J=8.9 Hz, ArH), 8.07 (2H, d, J=8.9 Hz, ArH), 7.71–7.68 (2H, m, ArH and ArH), 7.14 (1H, dd, J=4.8, 3.9 Hz, ArH), 6.60 (1H, q_i, J=1.9 Hz, =CH), 4.52–4.46 (br m, 1H, 2×NCH_2); *m/z* (%) (EI) 178 (49, $M-SO_2PhNO_2$), 111 (100).

3.3.9. 1,3-Dimethyl-3-{2-oxo-2-[(1-phenylsulfonyl)-2,5-dihydro-1*H*-pyrrol-3-yl]ethyl}-1,3-dihydro-2*H*-indol-2-one (25). Prepared by the general RCM procedure on a 0.08 mmol scale and a reaction time of 1 h. Purification by flash chromatography eluting with ether yielded the product (33 mg, 93%) as a colourless solid, mp 69–71 °C; R_f 0.1; (Found: C, 64.30; H, 5.45; N, 6.55. $C_{22}H_{22}N_2O_4S$ requires C, 64.35; H, 5.40; N, 6.80%); υ_{max}/cm^{-1} (film) 1709 (C=O), 1677 (N–C=O), 1614, 1348 ($S=O_{as}$), 1167 ($S=O_s$), 1104; δ_H (250 MHz, $CDCl_3$) 7.79 (2H, m, SO_2PhH), 7.61–7.48 (3H, m, SO_2PhH), 7.25 (1H, td, J= 7.5, 1.4 Hz, ArH), 7.06 (1H, dd, J=7.5, 1.4 Hz, ArH), 6.98 (1H, td, J=7.5, 0.9 Hz, ArH), 6.86 (1H, d, J=7.5 Hz, ArH), 6.50 (1H, q_i, J=2.0 Hz, =CH), 4.43–4.29 (2H, m, NCH_2), 4.09–4.05 (2H, m, NCH_2), 3.26 (2H, s, CCH_2), 3.24 (3H, s, CH_3), 1.33 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 192.5 (C=O), 180.5 (C=O), 143.9, 139.8, 136.9, 135.1, 133.5, 133.4, 129.8, 128.5, 127.8, 122.7, 122.2, 108.7, 56.2, 53.6, 46.3, 45.4, 26.8, 25.0; *m/z* (FAB) 411 (28%, $M^+ + H$), 215 (48%, $M-SO_2Ph$), 174 (49%), 160 (100%), 108 (90%).

3.3.10. *N*-But-3-en-1-yl-4-methyl-*N*-[2-(2-thienylcarbonyl)prop-2-en-1-yl]benzenesulfonamide (26). Prepared by the general cascade procedure employing rubidium carbonate base on a 2 mmol scale, using 2.4 mmol of aryl iodide and a reaction time of 18 h. Purification by flash chromatography eluting with petrol/ether 7:3 v/v afforded the product (540 mg, 72%) as a pale yellow oil; R_f 0.2; (Found: C, 60.55; H, 5.65; N, 3.65. $C_{19}H_{21}NO_3S_2$ requires C, 60.75; H, 5.65; N, 3.75%); υ_{max}/cm^{-1} (film) 1641 (C=O), 1432, 1342 ($S=O_{as}$), 1298, 1166 ($S=O_s$), 1093; δ_H (250 MHz, $CDCl_3$) 7.71 (2H, d, J=8.2 Hz, ArH), 7.79 (1H, dd, J=4.9, 1.1 Hz, ArH), 7.64 (1H, dd, J=3.8, 1.1 Hz, ArH), 7.29 (2H, d, J=8.2 Hz, ArH), 7.13 (1H, dd, J=4.9, 3.8 Hz, ArH), 6.15 (1H, t, J=1.5 Hz, =C$H_C$$H_D$), 6.07 (1H, s, =C$H_C$$H_D$), 5.66 (1H, ddt, J=17.0, 10.5, 6.7 Hz, CH_X=C$H_A$$H_B$), 5.06–4.97 (2H, m, C$H_X$=C$H_A$$H_B$), 4.14 (2H, s, NCH_2), 3.25 (2H, t, J=7.5 Hz, NCH_2), 2.43 (3H, s, CH_3), 2.26 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 188.4 (C=O), 143.8, 143.2, 136.9, 134.9, 134.8, 134.8, 130.2, 128.4, 127.6, 126.5, 117.7, 49.4 (NCH_2), 49.3 (NCH_2), 33.1 (=CHCH_2), 21.9 (CH_3); *m/z* (ES) 348 ($M+H^+$).

3.3.11. *N*-(2-Benzoylprop-2-en-1-yl)-*N*-but-3-en-1-yl-4-methylbenzenesulfonamide (28). Prepared by the general cascade procedure employing rubidium carbonate base on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 19 h. Purification by flash chromatography eluting with petrol/ether 4:1 v/v afforded the product (265 mg, 72%) as a viscous colourless oil; R_f 0.12; υ_{max}/cm^{-1} (film) 1652 (C=O), 1340 ($S=O_{as}$), 1157 ($S=O_s$), 1091; δ_H (250 MHz, $CDCl_3$) 7.74–7.70 (3H, m, ArH), 7.73 (2H, d, J=8.0 Hz, ArH) 7.61–7.53 (1H, m, ArH), 7.48–7.41 (2H, m, ArH), 7.32 (2H, d, J=8.0 Hz, ArH), 6.31 (1H, t, J= 1.5 Hz, =C$H_C$$H_D$), 5.91 (1H, s, =C$H_C$$H_D$), 5.68 (1H, ddt, J=17, 10.4, 6.7 Hz, CH_X=C$H_A$$H_B$), 5.07–4.99 (2H, m, C$H_X$=C$H_A$$H_B$), 4.16 (2H, s, NCH_2), 3.29–3.23 (2H, m, NCH_2), 2.44 (3H, s, CH_3), 2.31–2.22 (2H, m, CH_2); δ_C (63 MHz, $CDCl_3$) 197.3 (C=O), 143.9, 143.6, 137.6, 136.9, 134.8, 133.0, 130.2, 130.0, 129.3, 128.7, 127.7, 117.7, 49.5 (NCH_2), 49.2 (NCH_2), 33.1 (=CHCH_2), 21.9 (CH_3); *m/z* (EI) 370 ($M+H^+$); HRMS found 370.1472, $C_{21}H_{24}NO_3S$ requires 370.1471.

3.3.12. *N*-But-3-en-1-yl-4-methyl-*N*-{2-[(1-methyl-1*H*-indol-5-yl)carbonyl]prop-2-en-1-yl}benzenesulfonamide (29). Prepared by the general cascade procedure employing rubidium carbonate on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 25 h. Purification by flash chromatography eluting with DCM afforded the product (282 mg, 68%), which crystallised from DCM/petrol as colourless prisms, mp 103–105 °C; R_f 0.26; (Found: C, 67.90; H, 6.10; N, 6.60. $C_{24}H_{26}N_2O_3S$ requires C, 68.20; H, 6.20; N, 6.65%); υ_{max}/cm^{-1} (film) 1645 (C=O), 1339 ($S=O_{as}$), 1157 ($S=O_s$), 1091; δ_H (250 MHz, $CDCl_3$) 8.09 (1H, d, J=1.5 Hz, ArH), 7.73 (2H, d, J=8.2 Hz, ArH), 7.72 (1H, dd, J=8.7, 1.5 Hz, ArH), 7.33 (1H, d, J=8.7 Hz, ArH), 7.28 (2H, d, J=8.2 Hz, ArH), 7.12 (1H, d, J=3.2 Hz, ArH), 6.58 (1H, d, J=3.2 Hz, ArH), 6.17 (1H, s, =C$H_C$$H_D$), 5.83 (1H, s, =CH$H_D$), 5.69 (1H, ddt, J= 17.0, 10.2, 6.7 Hz, CH_X=C$H_A$$H_B$), 5.07–4.99 (2H, m, C$H_X$=C$H_A$$H_B$), 4.22 (2H, s, NCH_2), 3.81 (3H, s, CH_3), 3.32–3.26 (2H, m, NCH_2), 2.40 (3H, s, CH_3), 2.40–2.26 (2H, m, CH_2); δ_C (63 MHz, $CDCl_3$) 198.5 (C=O), 144.1,

143.8, 139.5, 137.1, 135.0, 131.0, 130.1, 129.0, 128.0, 127.7, 126.9 (=CH_2), 125.2, 123.6, 117.6 (=CH_2), 109.6, 103.4, 49.7 (NCH_2), 49.3 (NCH_2), 33.5 (=$CHCH_2$), 33.1 (NCH_3), 21.9 (CH_3); *m/z* (%) (EI) 422 (1, M^+), 267 (43, M−Ts), 144 (51), 91 (49).

3.3.13. *N*-But-3-en-1-yl-4-methyl-*N*-{2-[2(methylthio) benzoyl]prop-2-en-1-yl}benzenesulfonamide (30). Prepared by the general cascade procedure employing rubidium carbonate on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 22 h. Purification by flash chromatography eluting with petrol/ether 4:1 v/v afforded the product (310 mg, 75%), which crystallised from DCM/petrol as pale yellow needles, mp 97–99 °C; R_f 0.1; (Found: C, 63.30; H, 5.95; N, 3.60. $C_{22}H_{25}NO_3S_2$ requires C, 63.60; H, 6.05; N, 3.35%); υ_{max}/cm^{-1} (film) 1653 (C=O), 1340 (S=O_{as}), 1157 (S=O_s), 1091; δ_H (250 MHz, $CDCl_3$) 7.74 (2H, d, J=8.0 Hz, ArH), 7.47–7.16 (4H, m, ArH), 7.33 (2H, d, J=8.0 Hz, ArH), 6.32 (1H, s, =C$H_C$$H_D$), 5.81 (1H, s, =C$H_C$$H_D$), 5.67 (1H, ddt, J=17.0, 10.4, 6.8 Hz, CH_X=C$H_A$$H_B$), 5.07–4.99 (2H, m, C$H_X$=C$H_A$$H_B$), 4.18 (2H, s, NCH_2), 3.27 (2H, m, NCH_2), 2.44 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.33–2.22 (2H, m, CH_2); δ_C (63 MHz, $CDCl_3$) 198.5 (C=O), 144.6, 143.9, 138.7, 138.2, 136.9, 134.9, 131.5, 130.9, 130.2, 129.6, 128.0, 127.6, 125.1, 117.7, 49.5 (NCH_2), 48.3 (NCH_2), 33.1 (=CCH_2), 21.9 (CH_3), 17.5 (CH_3); *m/z* (%) (EI) 260 (22, M−Ts), 191 (75), 137 (63), 91 (100).

3.3.14. Methyl 4-[2-({but-3-en-1-yl[(4-methylphenyl)sulfonyl]amino}methyl)acryloyl]benzenesulfonamide (31). Prepared by the general cascade procedure employing rubidium carbonate on a 1 mmol scale, using 1.2 mmol of aryl iodide and a reaction time of 21 h. Purification by flash chromatography eluting with petrol/ether 1:1 v/v afforded the product (300 mg, 70%), which crystallised from ether/hexane as colourless needles, mp 79–80 °C; R_f 0.2; (Found: C, 64.60; H, 6.00; N, 3.25. $C_{23}H_{25}NO_5S$ requires C, 64.60; H, 5.90; N, 3.30%); υ_{max}/cm^{-1} (film) 1723 (MeOC=O), 1653 (C=O), 1340 (S=O_{as}), 1158 (S=O_s), 1109, 1092; δ_H (250 MHz, $CDCl_3$) 8.11 (2H, d, J=8.2 Hz, ArH), 7.75 (2H, d, J=8.2 Hz, ArH), 7.72 (2H, d, J=8.2 Hz, ArH), 7.32 (2H, d, J=8.2 Hz, ArH), 6.38 (1H, s, =C$H_C$$H_D$), 5.91 (1H, s, =C$H_C$$H_D$), 5.68 (1H, ddt, J=17.3, 10.7, 6.7 Hz, CH_X=C$H_A$$H_B$), 5.07–5.00 (2H, m, C$H_X$=C$H_A$$H_B$), 4.15 (2H, s, NCH_2), 3.96 (3H, s, CH_3), 3.30–3.29 (2H, m, NCH_2), 2.44 (3H, s, CH_3), 2.31–2.22 (2H, m, CH_2); δ_C (63 MHz, $CDCl_3$) 196.7 (C=O), 166.6 (C=O), 144.0, 143.6, 141.3, 136.8, 134.8, 133.7, 130.4, 130.2, 129.9, 129.7, 127.7, 117.7, 52.9 (OCH_3), 49.7 (NCH_2), 49.1 (NCH_2), 33.2 (=CHCH_2), 21.9 (CH_3); *m/z* (ES) 428 ($M+H^+$).

3.3.15. {1-[(4-Methylphenyl)sulfonyl]-1,2,5,6-tetrahydropyridin-3-yl}(2-thienyl)methanone (32). Prepared by the general RCM procedure on a 0.26 mmol scale and a reaction time of 3 h. Purification by flash chromatography eluting with 3:2 v/v petrol/ether afforded the product (83 mg, 92%) as colourless needles, mp 119–120 °C; R_f 0.06; (Found: C, 58.65; H, 5.20; N, 4.30. $C_{17}H_{17}NO_3S_2$ requires C, 58.75; H, 4.95; N, 4.05%); υ_{max}/cm^{-1} (film) 1642 (C=O), 1343 (S=O_{as}), 1273, 1166 (S=O_s), 1093; δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, J=8.1 Hz, ArH), 7.65 (1H, d, J=4.9 Hz, ArH), 7.56 (1H, d, J=3.7 Hz, ArH), 7.34 (2H, d, J=8.1 Hz, ArH), 7.11 (1H, dd, J=4.9, 3.7 Hz, ArH), 6.83 (1H, br s, =CH), 3.95 (2H, s, NCH_2), 3.26 (2H, t, J=5.6 Hz, NCH_2), 2.51–2.50 (2H, br m, CH_2), 2.43 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 186.2 (C=O), 143.8, 142.2, 137.3, 135.3, 133.6, 133.4, 133.2, 129.8, 127.8, 44.5 (NCH_2), 42.0 (NCH_2), 25.9 (=CHCH_2), 21.5 (CH_3); *m/z* (%) (EI) 347 (3, M^+), 192 (80, M−Ts), 124.1 (49), 111 (92), 91 (100).

3.3.16. {1-[(4-Methylphenyl)sulfonyl]-1,2,5,6-tetrahydropyridin-3-yl}(phenyl)methanone (33). Prepared by the general RCM procedure on a 0.2 mmol scale and a reaction time of 2 h. Purification by flash chromatography eluting with 7:3 v/v petrol/ether afforded the product (60 mg, 90%) as colourless needles, mp 134–135 °C; R_f 0.05; (Found: C, 67.05; H, 5.65; N, 4.10. $C_{19}H_{19}NO_3S$ requires C, 66.85; H, 5.60; N, 4.15%); υ_{max}/cm^{-1} (film) 1642 (C=O), 1343 (S=O_{as}), 1166 (S=O_s), 1092; δ_H (250 MHz, $CDCl_3$) 7.74 (2H, d, J=8.2 Hz, ArH), 7.59–7.50 (3H, m, ArH), 7.44–7.27 (2H, m, ArH), 7.34 (2H, d, J=8.2 Hz, ArH), 6.2 (1H, q, J=2.1 Hz, =CH), 3.96 (2H, br d, J=2.1 Hz, NCH_2), 3.23 (2H, t, J=5.7 Hz, NCH_2), 2.53–2.46 (2H, m, CH_2), 2.44 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 198.0 (C=O), 144.3, 141.4, 137.7, 135.4, 133.4, 132.4, 130.2, 129.5, 128.7, 128.2, 44.7 (NCH_2), 42.4 (NCH_2), 26.5 (=CHCH_2), 22.0 (CH_3); *m/z* (ES) 342 (M^++H).

3.3.17. (1-Methyl-2,3-dihydro-1*H*-indol-5-yl){1-[(4-methylphenyl)sulfonyl]-1,2,5,6-tetrahydropyridin-3-yl}methanone (34). Prepared by the general RCM procedure on a 0.15 mmol scale and a reaction time of 5 h. Purification by flash chromatography eluting with 2:3 v/v petrol/ether afforded the product (54 mg, 91%) as colourless needles, mp 116–118 °C; R_f 0.16; υ_{max}/cm^{-1} (film) 1635 (C=O), 1340 (S=O_{as}), 1164 (S=O_s), 1098; δ_H (250 MHz, $CDCl_3$) 7.95 (1H, d, J=1.5 Hz, ArH), 7.74 (2H, d, J=8.2 Hz, ArH), 7.59 (1H, dd, J=8.6, 1.5 Hz, ArH), 7.34 (2H, d, J=8.2 Hz, ArH) 7.33 (1H, d, J=8.6 Hz, ArH), 7.13 (1H, d, J=3.5 Hz, ArH), 6.57 (1H, d, J=3.5 Hz, ArH), 6.57–6.54 (H, m, =CH), 4.01 (2H, br d, J=2.1 Hz, NCH_2), 3.82 (3H, s, CH_3), 3.26 (2H, t, J=5.7 Hz, NCH_2), 2.52–2.47 (2H, m, CH_2), 2.44 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 198.0 (C=O), 144.1, 139.2, 138.6, 135.7, 133.6, 130.9, 130.2, 129.1, 128.2, 128.0, 124.5, 123.4, 109.6, 103.1, 45.2 (NCH_2), 42.6 (NCH_2), 33.5, 26.2, 22.0; *m/z* (%) (CI) 395 (100, M^++H), 241 (90) 189 (31); HRMS found 395.1426, $C_{22}H_{23}N_2O_3S$ requires 384.1424.

3.3.18. {1-[(4-Methylphenyl)sulfonyl]-1,2,5,6-tetrahydropyridin-3-yl}[2-(methylthio)phenyl]methanone (35). Prepared by the general RCM procedure employing 5 mol% of **3**, followed by an extra 2 mol% of **3** after 4 h on a 0.32 mmol scale and a reaction time of 7 h. Purification by flash chromatography eluting with 3:2 v/v petrol/ether afforded the product (90 mg, 73%), which crystallised from DCM/petrol as colourless needles, mp 139–141 °C; R_f 0.11; (Found: C, 62.00; H, 5.50; N, 3.60. $C_{20}H_{21}NO_3S_2$ requires C, 62.00; H, 5.45; N, 3.60%); υ_{max}/cm^{-1} (film) 1644 (C=O), 1340 (S=O_{as}), 1162 (S=O_s), 1091; δ_H (250 MHz, $CDCl_3$) 7.74 (2H, d, J=8.1 Hz, ArH), 7.43–7.32 (2H, m, ArH), 7.36 (2H, d, J=8.1 Hz, ArH), 7.19–7.17 (2H, m, ArH), 6.49 (1H, br s, =CH), 3.97 (2H, br d, J=1.8 Hz, NCH_2), 3.21 (2H, t, J=5.7 Hz, NCH_2), 2.44 (5H, s, CH_3

and CH_2), 2.40 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 195.9 (C=O), 144.2, 142.9, 138.3, 138.0, 136.4, 133.4, 131.1, 130.2, 128.8, 128.2, 128.0, 125.1, 44.2 (NCH_2), 42.3 (NCH_2), 26.7, 22.0, 17.4; *m/z* (ES) 388 ($M^+ + H$).

3.3.19. Methyl 4-({1-[(4-methylphenyl)sulfonyl]-1,2,5,6-tetrahydropyridin-3-yl}carbonyl)benzoate (36). Prepared by the general ring closing metathesis procedure on a 0.12 mmol scale and a reaction time of 3 h. Purification by flash chromatography eluting with 7:3 v/v petrol/ether afforded the product (41 mg, 86%) as colourless needles, mp 157–159 °C; R_f 0.15; (Found: C, 62.70; H, 5.50; N, 3.20. $C_{21}H_{21}NO_5S$ requires C, 63.15; H, 5.30; N, 3.50%); υ_{max}/cm^{-1} (film) 1723 (MeOC=O) 1645 (C=O), 1344 ($S{=}O_{as}$), 1280, 1166 ($S{=}O_s$), 1093; δ_H (250 MHz, $CDCl_3$) 8.09 (2H, d, $J=8.3$ Hz, ArH), 7.74 (2H, d, $J=8.2$ Hz, ArH), 7.61 (2H, d, $J=8.3$ Hz, ArH), 7.36 (2H, d, $J=8.2$ Hz, ArH), 6.62 (1H, q, $J=2.0$ Hz, =CH), 3.96–3.94 (2H, m, NCH_2), 3.94 (3H, s, OCH_3), 3.25 (2H, t, $J=5.7$ Hz, NCH_2), 2.52–2.50 (2H, m, CH_2), 2.45 (3H, s, CH_3); δ_C (63 MHz, $CDCl_3$) 197.7 (C=O), 166.6 (C=O), 144.3, 142.5, 141.6, 135.5, 133.4, 133.3, 130.2, 129.9, 129.2, 128.2, 52.9 (OCH_3), 44.5 (NCH_2), 42.3 (NCH_2), 26.6 (=CH*C*H_2), 22.0 (CH_3); *m/z* (ES) 400 ($M^+ + H$); HRMS found 417.1476, $C_{21}H_{25}N_2O_5S$ requires 417.1479.

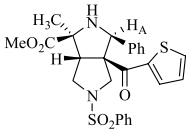
3.3.20. *N*-Pent-4-en-1-yl-*N*-[2-(2-(thienyl)prop-2-en-1-yl (37). Prepared by the general cascade procedure on a 2 mmol scale, using 2.5 mmol of aryl iodide and a reaction time of 25 h. Purification by flash chromatography eluting with 4:1 v/v petrol/ether afforded the product (440 mg, 56%) as a viscous pale yellow oil; R_f 0.12; υ_{max}/cm^{-1} (film) 1636 (C=O), 1622, 1413, 1340 ($S{=}O_{as}$), 1158 ($S{=}O_s$), 1091; δ_H (250 MHz, $CDCl_3$) 7.70 (2H, d, $J=8.2$ Hz, ArH), 7.69 (1H, d, $J=5.1$ Hz, ArH), 7.64 (1H, d, $J=3.6$ Hz, ArH) 7.33 (2H, d, $J=8.2$ Hz, ArH), 7.12 (1H, dd, $J=5.1$, 3.6 Hz, ArH), 6.16 (1H, s, =CH_CH$_D$), 6.06 (1H, s, =CH$_C$$H_D$), 5.71 (1H, ddt, $J=16.9$, 10.3, 6.6 Hz, CH_X=CH$_A$H$_B$), 4.99 (1H, d, $J=10.3$ Hz, CHX=CH_AH$_B$), 4.97 (1H, d, $J=16.9$ Hz, CH$_X$=CH$_A$$H_B$), 4.11 (2H, s, NCH_2), 3.17 (2H, t, $J=7.7$ Hz, NCH_2), 2.43 (3H, s, CH_3), 2.04–1.96 (2H, m, =CHCH_2), 1.59 (2H, q_i, $J=7.7$ Hz, CH_2); δ_C (63 MHz, $CDCl_3$) 188.5 (C=O), 144.1, 143.8, 143.3, 137.7, 136.9, 134.9, 134.8, 130.1, 128.4, 127.6, 126.4 (=CH_2), 115.8 (=CH_2), 49.6 (NCH_2), 49.4 (NCH_2), 31.2 (=CH*C*H_2), 27.7 (CH_2), 21.9 (CH_3); *m/z* (%) (CI) 390 (5, $M^+ + H$), 170 (48), 99 (100), 86 (100); HRMS found 390.1192, $C_{20}H_{24}NO_3S_2$ requires 390.1192.

3.3.21. *N*-Pent-4-en-1-yl-*N*-(2-phenyl)prop-2-en-1-yl] benzenesulfonamide (38). Prepared by the general cascade procedure on a 2 mmol scale, using 2.5 mmol of aryl iodide and a reaction time of 25 h. Purification by flash chromatography eluting with DCM afforded the product (520 mg, 68%) as a viscous pale yellow oil; R_f 0.27; υ_{max}/cm^{-1} (film) 1654 (C=O), 1448, 1339 ($S{=}O_{as}$), 1159 ($S{=}O_s$), 1091; δ_H (250 MHz, $CDCl_3$) 7.72 (2H, d, $J=8.2$ Hz, ArH), 7.71 (2H, d, $J=7.5$ Hz, ArH), 7.57 (1H, t, $J=7.5$ Hz, ArH), 7.44 (2H, t, $J=7.5$ Hz, ArH), 7.31 (2H, d, $J=8.2$ Hz, ArH), 6.31 (1H, s, =CH_CH$_D$), 5.90 (1H, s, =CH$_C$$H_D$), 5.73 (1H, ddt, $J=16.9$, 10.2, 6.6 Hz, CH_X=CH$_A$H$_B$), 5.00 (1H, d, $J=10.2$ Hz, CH$_X$=CH_AH$_B$), 4.97 (1H, d, $J=16.9$ Hz, CH$_X$=CH$_A$$H_B$), 4.13 (2H, s, NCH_2), 3.18 (2H, t, $J=7.7$ Hz, NCH_2), 2.44 (3H, s, CH_3), 2.06–1.97 (2H, m, =CHCH_2), 1.60 (2H, q_i, $J=7.7$ Hz, CH_2); δ_C (63 MHz, $CDCl_3$) 197.1 (C=O), 143.8, 143.7, 137.7, 137.6, 136.9, 133.0, 130.2, 130.0, 129.2, 128.7, 127.7, 115.8, 49.8 (NCH_2), 49.2 (NCH_2), 31.2 (=CH*C*H_2), 27.8 (CH_2), 21.9 (CH_3); *m/z* (%) (CI) 384 (10, $M^+ + H$), 164 (90), 86 (100); HRMS found 384.1632, $C_{22}H_{26}NO_3S$ requires 384.1628.

3.4. General procedure for microwave RCM

Substrate and CH_2Cl_2 (4 ml) were combined in a microwave pressure vial, containing a small magnetic stirrer bar, to afford solutions of either 1.5 or 3.0 mM. Catalyst **3** (1–5 mol%) was then added to this solution and the pressure vial immediately sealed and subjected to microwave irradiation (Smith Creator model). The solvent was then removed and the product conversion measured by 500 MHz NMR analysis. Passing the crude product through a small pad of silica, eluting with ether/petrol, afforded the product.

3.4.1. Methyl 1-methyl-2,3-diphenyl-5-(phenylsulfonyl)-3a-(thien-2-yl carbonyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (41). Triethylamine (57 µl, 0.4 mmol), and silver acetate (66 mg, 0.4 mmol) were added to a stirred solution of enone **17** (84 mg, 0.26 mmol) in toluene (10 ml). A solution of imine (60 mg, 0.29 mmol) in toluene (1 ml) was then added and reaction mixture stirred at room temperature for 20 h. Filtration and concentration in vacuo afforded the crude product as a single isomer. Purification by flash column chromatography eluting with 1:2 v/v ethyl acetate/petrol afforded the product as a colourless amorphous solid, mp 75–77 °C; R_f 0.15; υ_{max} /cm^{-1} (film) 3334 (NH), 1733 (C=O), 1637 (MeOC=O), 1412, 1350 (S=Oas), 1246, 1169 (S=Os), δ_H (500 MHz, CDCl3) 7.83–7.81 (2H, m, SO_2PhH), 7.62–7.60 (1H, m, SO_2PhH), 7.55–7.52 (2H, m, SO_2PhH), 7.37 (1H, dd, $J=5.0$, 1.0 Hz, ArH), 7.14–7.12 (2H, m, ArH), 7.09–7.07 (3H, m, ArH), 6.84 (1H, dd, $J=4.0$, 1.0 Hz, ArH), 6.75 (1H, dd, $J=5.0$, 4.0 Hz, ArH), 4.48 (1H, s, NCH_APh), 4.03 (1H, d, $J=10.0$ Hz, NCHH), 3.82 (3H, s, OCH3), 3.77–3.71 (2H, m, NCH_2), 3.27 (1H, d, $J=10.0$ Hz, NCHH), 3.14 (1H, br s, NH), 2.93 (1H, dd, $J=10.2$, 8.1 Hz, CH), 1.61 (3H, s, CH3); *m/z* (ES) 533 ($M^+ + Na$); HRMS found 533.6284, $C_{26}H_{26}N_2O_5S_2 + Na$ requires 533.6280.



NOE data:

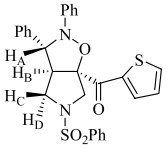
Signal irradiated	Enhancement (%)
	H_A
CH_3	2.1

3.5. General thermodynamic controlled nitrone cycloaddition procedure (A)

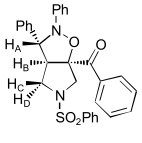
Diphenyl nitrone (183 mg, 0.93 mmol) was added to a solution of **17** (145 mg, 0.46 mmol) in toluene (20 ml) in

a Schlenk tube. The reaction mixture was immersed in a pre-heated oil bath at 120 °C and stirred under a nitrogen atmosphere for 54 h. Concentration in vacuo afforded the crude product comprising of a 9:1 mixture of **43** and **46**. Flash chromatograph eluting with DCM afforded the pure isomers in a 80% combined yield.

3.5.1. 2,3-Diphenyl-5-(phenylsulfonyl)hexahydro-6a*H*-pyrrolo[3,4-*a*]isoxazol-6a-yl(thien-2-yl)methanone (43). Crystallisation from DCM/petrol afforded colourless needles; mp 157–159 °C; R_f 0.3; (Found: C, 65.25; H, 4.80; N, 5.60. $C_{28}H_{24}N_2O_4S_2$ requires C, 65.10; H, 4.70; N, 5.40%); υ_{max}/cm^{-1} (film) 1657 (C=O), 1490, 1446, 1353 (S=O_{as}), 1170 (S=O_s), 1091; δ_H (500 MHz, $CDCl_3$) 8.22 (1H, dd, J=3.2, 1.2 Hz, ArH), 7.80–7.88 (2H, m, SO_2PhH), 7.71 (1H, dd, J=3.2, 1.2 Hz, ArH), 7.61 (1H, tt, J=6.7, 1.2 Hz, SO_2PhH), 7.54–7.50 (2H, m, SO_2PhH), 7.36–7.28 (4H, m, ArH), 7.18–7.15 (3H, m, ArH) 7.06 (1H, tt, J=6.7, 1.2 Hz, ArH), 7.00–6.96 (3H, m, ArH), 4.11 (1H, d, J=11 Hz, NCH), 4.10 (1H, d, J=8.0 Hz, NCH_A), 3.78 (1H, td, J=8.0, 1.3 Hz, CH_B), 3.73 (1H, br d, J=10.4 Hz, NCH_D), 3.03 (1H, dd, J=10.4, 8 Hz, NCH_C), 3.02 (1H, d, J=11 Hz, NCH); δ_C (125 MHz, $CDCl_3$) 191.7 (C=O), 147.8, 139.4, 137.5, 136.0, 135.8, 135.0, 133.3, 129.3, 129.0, 128.6, 128.5, 128.3, 128.0, 127.9, 125.1, 119.9, 94.1, 77.9, 61.1, 57.0, 51.7; *m/z* (ES) 517 (M^++H).



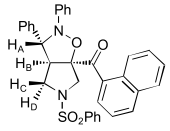
3.5.2. 2,3-Diphenyl-5-(phenylsulfonyl)hexahydro-6a*H*-pyrrolo[3,4-*a*]isoxazol-6a-yl(phenyl)methanone (44). Following procedure A (0.47 mmol scale, 60 h) using enone **18** a single isomer was obtained. Purification by flash column chromatography eluting with DCM afforded the product (140 mg, 70%), which crystallised from DCM/petrol as colourless needles, mp 161–163 °C; R_f 0.4; (Found: C, 70.40; H, 5.05; N, 5.50. $C_{30}H_{26}N_2O_4S$ requires C, 70.55; H, 5.15; N, 5.50%); υ_{max}/cm^{-1} (film) 1681 (C=O), 1490, 1446, 1351 (S=O_{as}), 1170 (S=O_s), 1091; δ_H (500 MHz, $CDCl_3$) 8.18 (2H, d, J=7.9 Hz, ArH), 7.79 (2H, d, J=7.9 Hz, ArH), 7.63–7.57 (2H, m, ArH), 7.51–7.48 (4H, m, ArH), 7.31–7.30 (5H, m, ArH), 7.12 (2H, t, J=7.9 Hz, ArH), 6.99 (1H, t, J=7.2 Hz, ArH), 6.84 (2H, d, J=7.9 Hz, ArH), 4.19 (1H, d, J=11.2 Hz, NCH), 4.10 (1H, d, J=7.3 Hz, NCH_APh), 3.96 (1H, dd, J=7.3, 7.2 Hz, CH_B), 3.72 (1H, d, J=10.3 Hz, NCH_D), 3.04 (1H, dd, J=10.3, 7.2 Hz, NCH_C), 3.02 (1H, d, J=11.2 Hz, NCH); δ_C (125 MHz, $CDCl_3$) 198.2 (C=O), 147.6, 137.9, 135.0, 134.2, 133.8, 133.3, 130.0, 129.9, 129.1, 128.6, 128.5 128.4, 127.9, 127.7, 124.7, 119.6, 94.2, 76.7, 60.8, 56.6, 51.3; *m/z* (ES) 511 (M^++H).



NOE data:

Signal irradiated	Enhancement (%)		
	H_A	H_B	H_C
H_A		0	4.8
H_C	11.2		

3.5.3. 2,3-Diphenyl-5-(phenylsulfonyl)hexahydro-6a*H*-pyrrolo [3,4-*a*]isoxazol-6a-yl(1-napththyl)methanone (45). Following proceedure A (0.43 mmol scale, 58 h) using enone **19** a single isomer was obtained. Purification by flash column chromatograph eluting with DCM afforded the product (140 mg, 58%), which crystallised from DCM/petrol as colourless needles, mp 165–167 °C; R_f 0.35; (Found: C, 72.60; H, 5.05; N, 5.15. $C_{34}H_{28}N_2O_4S$ requires C, 72.85; H, 5.05; N, 5.00%); υ_{max}/cm^{-1} (film) 1641 (C=O), 1490, 1446, 1350 (S=O_{as}), 1170 (S=O_s), 1091; δ_H (500 MHz, $CDCl_3$) 8.21 (1H, d, J=8.2 Hz, ArH), 8.07 (1H, d, J=7.3 Hz, ArH), 8.02 (1H, d, J=8.3 Hz, ArH), 7.90 (1H, d, J=7.3 Hz, ArH), 7.84 (2H, d, J=7.3 Hz, ArH), 7.60–7.50 (6H, m, ArH), 7.29–7.23 (5H, m, ArH), 7.02 (2H, t, J=7.5 Hz, ArH), 6.92 (1H, t, J=7.5 Hz, ArH), 6.60 (2H, d, J=7.5 Hz, ArH), 4.20 (1H, d, J=11.0 Hz, NCH), 4.09 (1H, d, J=7.3 Hz, NCH_A), 3.80 (1H, d, J=10.3 Hz, NCH_D), 3.81–3.76 (1H, m, CH_B), 3.32 (1H, d, J=11.0 Hz, NCH), 3.20 (1H, dd, J=10.3, 7.3 Hz, NCH_C); δ_C (125 MHz, $CDCl_3$) 205.05 (C=O), 147.1, 138.1, 135.3, 133.9, 133.3, 133.0, 132.6, 130.7, 129.3, 129.2, 128.7, 28.4, 128.3, 128.1, 127.9, 127.8, 127.2, 126.4, 125.2, 124.5, 124.1, 119.5, 94.7, 75.6, 63.5, 56.9, 51.7; *m/z* (%) (EI) 560 (16, M^+), 155 (100), 127 (68), 77 (78).



NOE data:

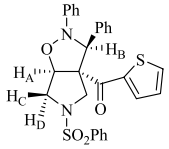
Signal irradiated	Enhancement (%)		
	H_A	H_B	H_C
H_A		0	11.1
H_C	5.1		

3.6. General kinetic controlled nitrone cycloaddition procedure (B)

Diphenyl nitrone (125 mg, 0.63 mmol) was added to a solution of **17** (180 mg, 0.57 mmol) in toluene (20 ml). The reaction mixture was immersed in a pre-heated oil bath at 80 °C and stirred under a nitrogen atmosphere for 32 h. Concentration in vacuo afforded the crude product comprising of a 3.5:1 mixture of **45** and **46**, respectively. Flash chromatography eluting with DCM afforded the pure isomers in a 70% combined yield. The data for **45** is collected above.

3.6.1. *exo*-[2,3-Diphenyl-(5-(phenylsulfonyl)hexahydro-3a*H*-pyrrolo[3,4-*a*]isoxazol-3a-yl]thien-2-yl)methanone (46). Crystallisation from DCM/petrol afforded colourless needles, mp 149–151 °C; R_f 0.2; (Found: C, 65.30; H, 4.95; N, 5.55. $C_{28}H_{24}N_2O_4S_2$ requires C, 65.10; H, 4.70; N, 5.40%); υ_{max}/cm^{-1} (film) 1652 (C=O), 1352 (S=O_{as}),

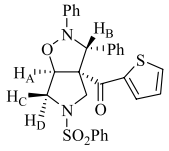
1167 (S=O_s), δ_H (500 MHz, $CDCl_3$) 7.81–7.79 (2H, m, SO_2PhH), 7.66 (1H, dd, $J=3.7$, 0.8 Hz, ArH_C), 7.61–7.57 (1H, m, SO_2PhH), 7.53 (1H, dd, $J=4.9$, 0.8 Hz, ArH), 7.50–7.48 (2H, m, SO_2PhH), 7.18–6.88 (11H, m, 10×ArH), 5.57 (1H, dd, $J=5.1$, 1.2 Hz, OCH_A), 4.74 (1H, s, $PhCH_B$), 3.94 (1H, d, $J=10.5$ Hz, NCH), 3.82 (1H, d, $J=10.5$ Hz, NCH), 3.76 (1H, dd, $J=11.3$, 1.2 Hz, NCH_C), 3.38 (1H, dd, $J=11.3$, 5.1 Hz, NCH_D); δ_C (125 MHz, $CDCl_3$) 188.0 (C=O), 147.5, 143.6, 135.0, 134.6, 134.5, 133.3, 133.2, 129.3, 128.7, 128.6, 128.5, 128.3, 127.9, 127.8, 123.9, 118.3, 81.8, 77.6, 74.9, 56.1, 53.4; *m/z* (ES) 539 ($M^+ + Na$).



NOE data:

Signal irradiated	Enhancement (%)
	H_C
H_A	5.9
H_B	4.0

3.6.2. [*endo*-2,3-Diphenyl-(5-(phenylsulfonyl)hexahydro-3a*H*-pyrrolo[3,4-*a*]isoxazol-3a-yl]thien-2-yl)methanone (47). The product is isolated as a pale yellow froth. R_f 0.15; (Found: C, 64.95; H, 4.70; N, 5.40. $C_{28}H_{24}N_2O_4S_2$ requires C, 65.10; H, 4.70; N, 5.40%); υ_{max}/cm^{-1} (film) 1644 (C=O), 1490, 1353 (S=O_{as}), 1169 (S=O_s), δ_H (250 MHz, $CDCl_3$) 7.84 (1H, dd, $J=3.92$, 0.9 Hz, ArH), 7.76–7.53 (5H, m, ArH), 7.67 (1H, dd, $J=4.9$, 0.9 Hz, ArH) 7.08 1H, dd, $J=4.9$, 3.9 Hz, ArH) 7.34–6.99 (10H, m, ArH), 5.35 (1H, dd, $J=6.8$, 3.0 Hz, OCH_A), 5.07 (1H, s, NCH_B), 3.79 (1H, dd, $J=10.0$, 3.0 Hz, NCH_C), 3.47 (1H, dd, $J=10.6$, 6.8 Hz, NCH_D), 3.25 (1H, d, $J=11.2$ Hz, NCH), 3.19 (1H, d, $J=11.2$ Hz, NCH); *m/z* (ES) 539 ($M^+ + Na$).



Acknowledgements

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The stereoselective synthesis of α-substituted β-amino secondary alcohols based on the proline-mediated, asymmetric, three-component Mannich reaction and its application to the formal total synthesis of nikkomycins B and B_x

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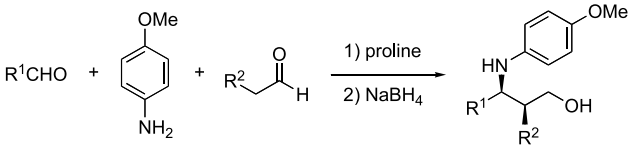
Abstract—A general method for the asymmetric synthesis of α-substituted β-amino secondary alcohols is described, which comprises the four-reaction sequence (1) the proline-mediated, asymmetric, three-component Mannich reaction of two different aldehydes, (2) nucleophilic carbon addition to aldehyde, (3) oxidation of the resulting alcohol to the corresponding ketone, and (4) diastereoselective reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ or catecholborane. The former reductant afforded the 1,2-*syn* isomer, while the latter gave the 1,2-*anti* isomer stereoselectively. The present method was successfully applied to the efficient asymmetric synthesis of the N-terminal amino acid moiety of nikkomycin B and B_X.

1. Introduction

β-Amino alcohols are not only found in many natural products[1] and potent drugs,[2] but are also used as a component of ligands in asymmetric catalysts.[3] In spite of this synthetic utility, there are few methods for their asymmetric synthesis, which remains a considerable challenge.[4] Recently, Ellman and co-workers reported an asymmetric synthesis of both *syn* and *anti* β-amino alcohols based on the diastereoselective reactions of metallo-enamines derived from chiral *N*-sulfinyl imines, followed by the diastereoselective reduction, for which an equimolar amount of the chiral auxiliary is necessary.[4d] The development of a general and practical method for the synthesis of chiral β-amino alcohols based on catalytic asymmetric reactions is an important goal.

List reported a proline-mediated asymmetric Mannich reaction in 2000,[5] after which organocatalyst-mediated asymmetric Mannich reactions have been investigated by several research groups.[6] Our group have applied high-pressure induced by water freezing to the proline-mediated Mannich reaction, widening the generality of the reaction.[7] During the application of the high pressure to other proline-mediated reactions, we have discovered a proline-mediated, one-pot, three-component, cross-Mannich reaction involving two different aldehydes and *p*-anisidine proceeding at ambient pressure.[8] That is, in the presence of proline an aldehyde and anisidine react to give the corresponding imine, which reacts with a second, different aldehyde, affording an α-substituted β-amino aldehyde. As this β-aminoaldehyde is unstable, it is reduced immediately to give an α-substituted β-amino primary alcohol in good yield with excellent *syn* selectivity and enantioselectivity (Eq. 1). The similar Mannich reaction has been reported also by Barbas'[6i] and Cordova's[6k,u] groups, independently. The α-substituted β-amino aldehyde that was generated is a versatile synthetic intermediate, which can be further transformed to give the corresponding α-substituted β-amino secondary alcohols with a generation of a new chiral center by formation of a carbon–carbon bond. The utility of the present method is further demonstrated by an efficient formal asymmetric total synthesis of nikkomycin, which is also described in this full paper.



(1)

Keywords: Proline; Mannich reaction; Asymmetric synthesis; Nikkomycin; Three-component reaction.
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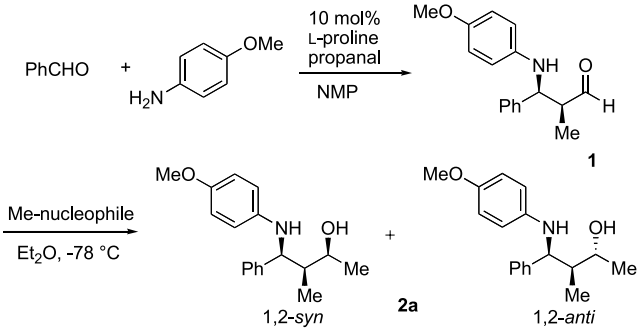
2. Results and discussion

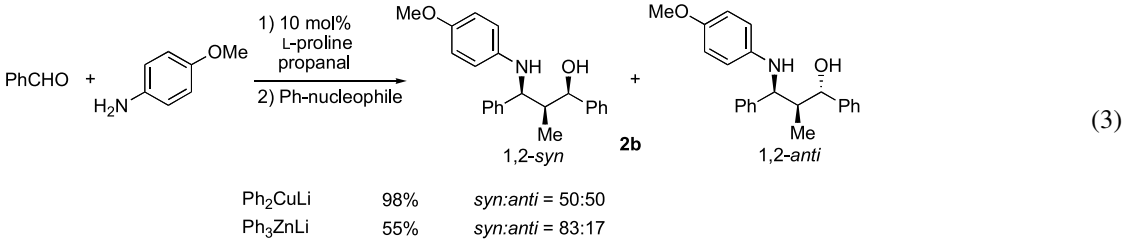
We have reported the proline-mediated, three component coupling Mannich reaction of benzaldehyde, propanal, and anisidine to afford an unstable, α-substituted β-amino aldehyde, which was reduced to an α-substituted β-amino primary alcohol with $NaBH_4$ in 90% yield with high *syn* selectivity and excellent enantioselectivity (Eq. 1, $R^1=Ph$, $R^2=Me$, *syn*/*anti* = >95:5, 98% ee).[8] This result indicates that the β-amino aldehyde is generated as intermediate in very high optical purity. By employing an organo-metallic nucleophile instead of $NaBH_4$, a β-amino secondary alcohol would be prepared, generating a new chiral center. With this scenario in mind, in a preliminary trial we examined the introduction of a methyl group, using MeMgI as nucleophile (Eq. 2). The reaction was performed as follows: the crude β-amino aldehyde generated as above was treated with MeMgI in Et_2O at −78 °C for 4 h, generating 4-amino-butan-2-ol derivative **2a** in 30% yield, as a 1:1 mixture of *syn* and *anti* isomers (Table 1, entry 1). As both the yield and diastereoselectivity of this reaction were insufficient, other organometallic reagents were examined, with the results summarized in Table 1.



(2)

Though the moderate yields were obtained in the cases of MeLi and $MeTi(O\text{-}i\text{-}Pr)_3$,[9] diastereoselectivity was low (entries 2 and 3). The *anti* isomer was obtained predominantly in good yield in the case of Me_2CuLi[10] (entry 4), while the *syn* isomer was generated predominantly in the reactions of $MeCeCl_2$[11] and Me_4AlLi[12] (entries 5 and 6). When Me_3ZnLi[13] was used, the *syn* isomer was generated selectively (83:17) in good yield (entry 7). Thus either *anti* or *syn* isomers could be selectively synthesized by the proper choice of metal. Namely, Me_2CuLi gave *anti* isomer, and Me_3ZnLi afforded *syn* isomer predominantly, though the selectivities were only moderate.

However, in spite of the successful results using methyl nucleophiles, aryl nucleophiles such as phenyl metal reagents gave disappointing results (Eq. 3). Though the *syn* isomer predominated with Ph_3ZnLi, the use of Ph_2CuLi gave equal amounts of *syn* and *anti* isomers. As *anti*-selective introduction of the aryl group had not proved successful, a new general method for the stereoselective formation of *syn* and *anti* β-amino secondary alcohol was investigated. Thus, the two-step protocol of oxidation followed by stereoselective reduction was investigated, for which phenyl-substituted β-amino alcohol **2b** was selected as a model.



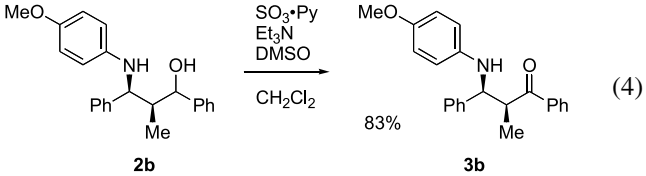
(3)

Table 1. The effect of reagent on diastereoselectivity[a]

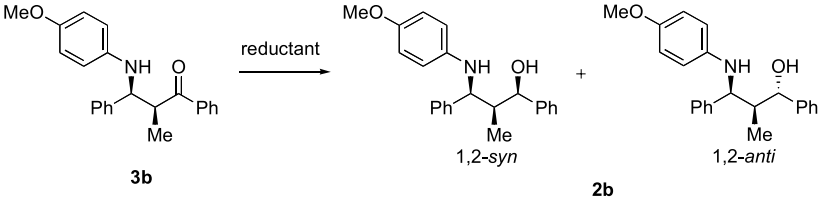
Entry	Reagent	Time (h)	Yield (%)[b]	*Syn*:*anti*[c]
1	MeMgI	4	30	50:50
2	MeLi	4	52	33:67
3[d]	$MeTi(O\text{-}i\text{-}Pr)_3$	18	60	33:67
4	Me_2CuLi	4	83	25:75
5[e]	$MeCeCl_2$	4	77	67:33
6	Me_4AlLi	4	71	67:33
7	Me_3ZnLi	4	82	83:17

[a] The reaction was performed at −78 °C in Et_2O, unless otherwise noted.
[b] Isolated yield.
[c] The diastereomeric ratio was determined by ^1H NMR.
[d] The reaction was performed at −20 °C.
[e] THF was used as solvent.

Oxidation of **2b** was successfully carried out using $SO_3\cdot$pyridine[14] to afford β-amino ketone **3b** in 83% yield (Eq. 4). Diastereoselective reduction of **3b** was investigated with a variety of reducing reagents (Eq. 5), the results of which are summarized in Table 2. When $NaBH_4$, $LiAlH_4$, and DIBAL were employed, the *anti* isomer was predominantly obtained (entries 1–3). In the presence of $LiAlH(O\text{-}t\text{-}Bu)_3$, the reaction took place with excellent *anti* selectivity and quantitative yield (entry 4). On the other hand, borane reagents afforded the *syn* isomer stereoselectively. In the case of catecholborane the *syn* isomer was obtained in good yield and excellent diastereoselectivity (98:2) (entry 6). As both *anti* and *syn* isomers had been synthesized in high stereoselective manner by the use of $LiAlH(O\text{-}t\text{-}Bu)_3$ and catecholborane, respectively, the generality of these conditions was then examined.



(4)



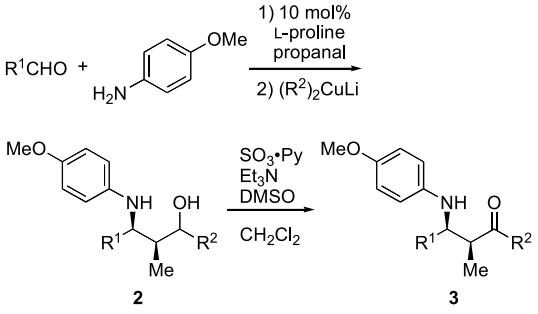
(5)

Table 2. The effect of reducing agent on the diastereoselectivity of **2b** formation

Entry	Reductant	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]	*syn*:*anti*[b]
1	$NaBH_4$	MeOH	−20	2	96	17:83
2	$LiAlH_4$	THF	−78	3	96	13:87
3	*i*-Bu_2AlH	CH_2Cl_2	−78	2	86	7:93
4	$LiAlH(O\text{-}t\text{-}Bu)_3$	THF	−78	0.5	Quant.	5:95
5	$BH_3\cdot THF$	THF	0	0.1	76	96:4
6	Catecholborane	THF	0	3	90	98:2

[a] Isolated yield.
[b] The diastereomeric ratio was determined by ^1H NMR.

First the synthesis of the starting β-amino ketone **3** was examined. The β-amino aldehyde was generated according to our asymmetric three-component Mannich reaction conditions, and then immediately treated with a lithium dialkyl- or diarylcuprate to afford β-amino alcohol **2**. The oxidation of **2** with $SO_3\cdot$pyridine gave β-amino ketone **3** (Eq. 6). The yields of **2** and **3** are summarized in Table 3, which shows that **3** was easily obtained in good yield from commercially available compounds.



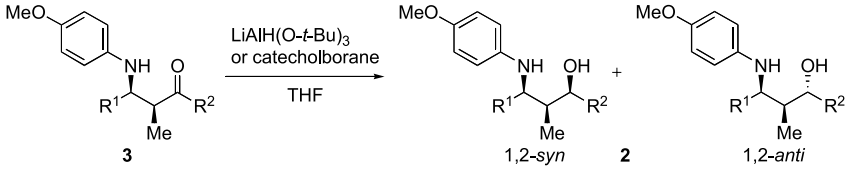
(6)

Table 3. Generality of the synthesis of β-amino alcohol **2** and β-amino ketone **3**

Entry	R^1	R^2	Yield of **2** (%)[a]	Yield of **3** (%)[b]
1	Ph	Me	83 (**2a**)	94 (**3a**)
2	Ph	Ph	98 (**2b**)	83 (**3b**)
3	Ph	Bu	78 (**2c**)	78 (**3c**)
4	4-BrC_6H_4–	Me	70 (**2d**)	86 (**3d**)
5	4-BrC_6H_4–	Bu	62 (**2e**)	93 (**3e**)
6	4-BrC_6H_4–	Ph	73 (**2f**)	77 (**3f**)

[a] Isolated yield over two steps.
[b] Isolated yield.

The stereoselective reduction of β-amino ketones was examined using $LiAlH(O\text{-}t\text{-}Bu)_3$ and catecholborane (Table 4). In the case of $LiAlH(O\text{-}t\text{-}Bu)_3$, the 1,2-*anti* isomer was obtained stereoselectively in quantitative yield. This *anti* selectivity can be rationalized by intramolecular hydride transfer, as shown in Figure 1. A similar model was proposed by Evans and co-workers for the *anti*-selective reduction of β-hydroxy ketones employing tetramethylammonium triacetoxyborohydride.[15] When catecholborane was employed as reducing reagent, the 1,2-*syn* isomer was generated, also with high to exellent diastereoselectivities and in good yield. The *syn*-selective reduction of β-hydroxy ketone with catecholborane[16] can be explained using six-membered chelation model (Fig. 2).



(7)

Table 4. Generality of the reduction of **3** with $LiAlH(O\text{-}t\text{-}Bu)_3$ or catecholborane

Entry	R^1	R^2	$LiAlH(O\text{-}t\text{-}Bu)_3$		Catecholborane	
			Yield (%)[a]	*Syn*:*anti*[b]	Yield (%)[a]	*Syn*:*anti*[b]
1	Ph	Me	Quant.	14:86	90	98:2
2	Ph	Bu	Quant.	11:89	67	75:25
3	Ph	Ph	Quant.	5:95	90	98:2
4	4-BrC_6H_4–	Me	Quant.	20:80	65	73:27
5	4-BrC_6H_4–	Bu	84	16:84	97	73:27
6	4-BrC_6H_4–	Ph	Quant.	6:94	86	99:1

[a] Isolated yield.
[b] The diastereomeric ratio was determined by ^1H NMR.

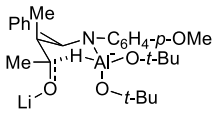


Figure 1. Transition state structure for the reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$.

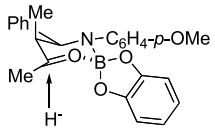


Figure 2. Transition state structure for the reduction with catecholborane.

2.1. The determination of the stereochemistry

As reported in our previous paper (Eq. 1),[8] the optical purity of the Mannich reaction of benzaldehyde, anisidine, and propanal, and that of *p*-bromobenzaldehyde, anisidine, and propanal were both excellent (98% ee). As the optical purity does not change during the oxidation and reduction processes, the α-alkyl β-amino secondary alcohols are also obtained in excellent enantiomeric purity, as was confirmed for compound **15** (vide infra).

The relative stereochemistry of the alkyl and hydroxy groups of **2a** was determined as following: the mixture of *syn* and *anti* isomers **2a** was treated with $ClCO_2Me$ and DMAP, affording **4a** as a mixture of diastereomers, which were separated by TLC. When **4a** was treated with NaH in THF, no reaction occurred with the more polar isomer. On the other hand, the less polar isomer gave a cyclic urethane **5a**, the stereochemistry of which was determined by NOESY spectra (Fig. 3). Thus, the configuration of the less polar isomer was determined to be 1,2-*syn*. The stereochemistry of phenyl-substituted **2b** was also determined using the same method.

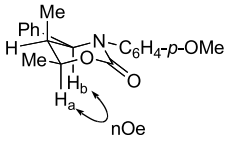
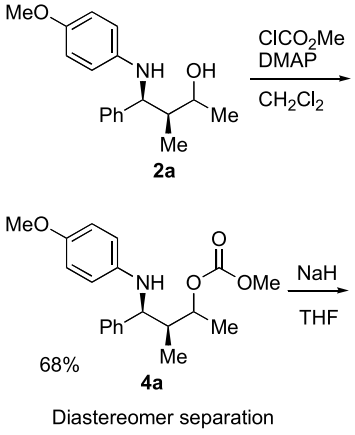


Figure 3. NOE observed in **5a**.



(8)

2.2. Formal total synthesis of nikkomycin

Nikkomycins B and B_X are nucleoside peptide antibiotics isolated from the culture broth of *Streptomyces tendae*.[17] They are potent chitin synthetase inhibitors, exhibiting fungicidal, insecticidal, and acaricidal activities.[18] Because of these important biological properties, nikkomycins are attractive synthetic targets. The Konig[19] and Barrett[20] groups have accomplished the total synthesis of nikkomycins B and B_X, respectively. The nikkomycins can be divided into two structural units, the C-terminal nucleoside amino acid and the N-terminal amino acid **8**. The N-terminal amino acid **8** and its synthetic equivalent **9** contain the three contiguous stereocenters of an α-methyl β-amino secondary alcohol moiety, the stereoselective synthesis of which is a synthetic challenge. Several methods to prepare this moiety in either racemic[21] or optically active form[22] have been reported. We have synthesized the N-terminal amino acid moiety **9** based on the method developed above, as will be described below (Fig. 4).

The synthesis starts with the Mannich reaction of 2-furylaldehyde. We had already found that the enantioselectivity of the Mannich reaction of 2-furylaldehyde was not satisfactory (84% ee).[8] In order to improve the enantioselectivity, we investigated this particular reaction in detail and found that addition of pyridine increased the enantioselectivity (Eq. 9). That is, while 84% ee was obtained under the standard reaction conditions, excellent enantioselectivity (92% ee) was realized in the presence of

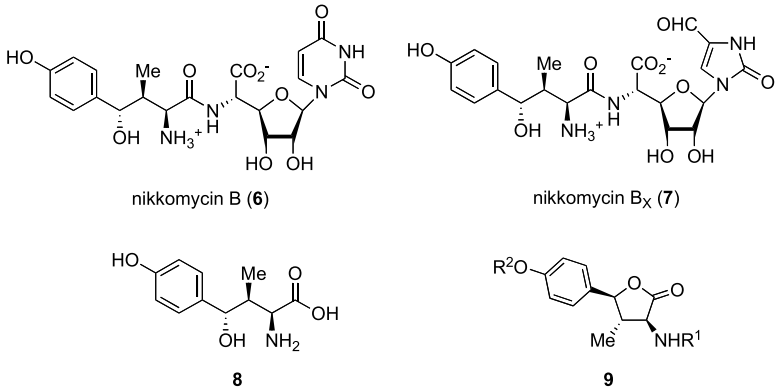
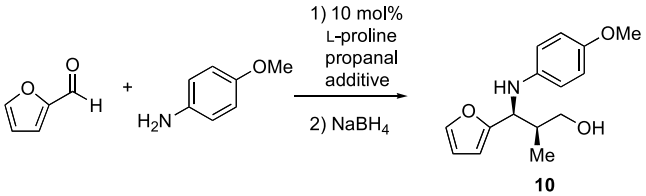


Figure 4. The structures of nikkomycin B and B_X, and of the N-terminal amino acid **8** and its synthetic equivalent **9**.

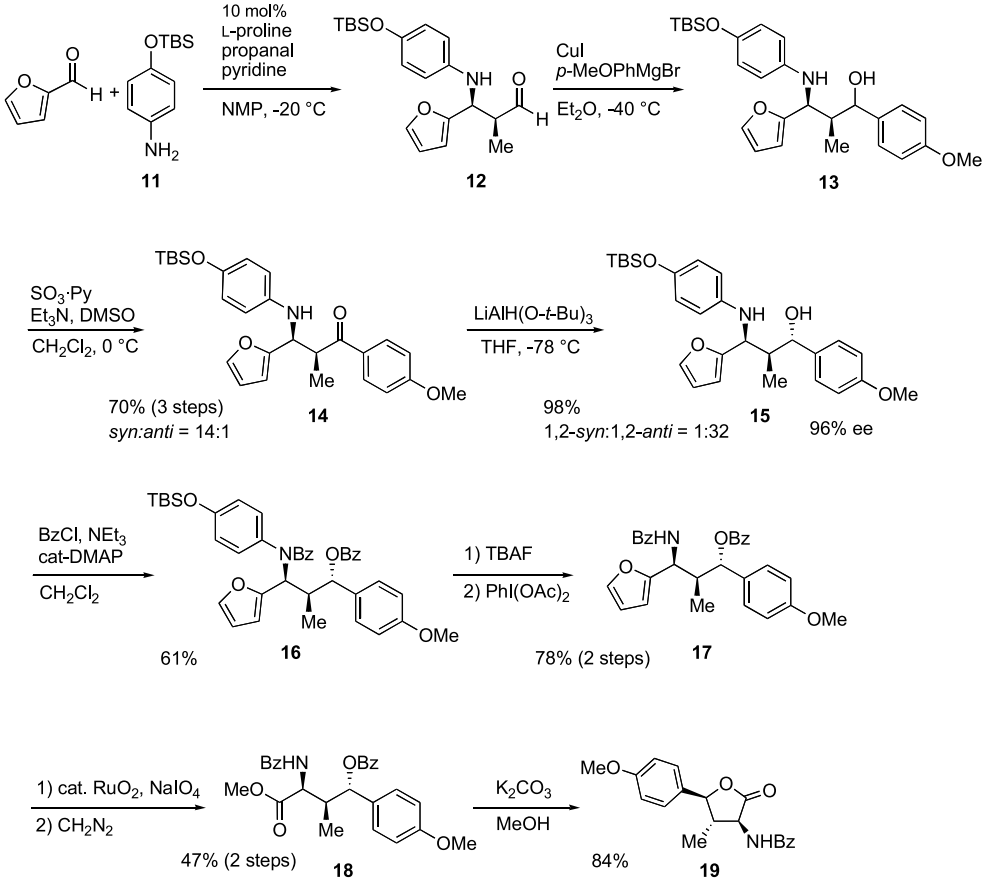
1.5 equiv of pyridine. It should be noted that this effect of pyridine was observed only in the reaction of 2-furylaldehyde, and no improvement in ee was seen for other aldehydes.



(9)

In the total synthesis of nikkomycin, we employed 4-*tert*-butyldimethylsiloxyaniline (**11**) instead of anisidine because the 4-*tert*-butyldimethylsiloxyphenyl moiety is easily cleaved from an amine under nearly neutral conditions (vide infra).[7] The Mannich reaction of 2-furylaldehyde, propanal, and 4-*tert*-butyldimethylsiloxyaniline proceeded with high diastereo- and enantioselectivities (96% ee, vide infra). Crude β-amino aldehyde **12** was immediately treated with $(p\text{-MeOC}_6H_4)_2CuMgBr$ in THF at −40 °C to give β-amino alcohol **13**. The crude mixture of *syn* and *anti* alcohols **13** was oxidized with $SO_3\cdot$pyridine to afford β-amino ketone **14** in 70% yield over three steps. These reactions could be easily scaled up because purification was performed only after the oxidation. Diastereoselective reduction of β-amino ketone **14** with $LiAlH(O\text{-}t\text{-}Bu)_3$ at −78 °C for 1 h proceeded smoothly, generating 1,2-*anti* alcohol **15** in excellent yield and diastereoselectivity (98%, 1,2-*syn*/1,2-*anti*=1:32). The optical purity of the alcohol **15** was determined by chiral HPLC analysis and shown to be 96% ee.[23] As the three continuous stereocenters had been established in a highly diastereo- and enantioselective manner, all that remained was oxidation of the furan to a carboxy group and transformations of the functional groups. However, the order of the reactions and the protecting groups used were found to be crucial for the successful transformation of **15** to **19**, because of the presence of three oxidatively-labile moieties, the furan, *p*-methoxyphenyl and *p*-*tert*-butyldimethylsilyloxyaniline groups.

First, the hydroxy and amino groups were protected with the electron-withdrawing benzoyl group by treatment with benzoyl chloride, Et_3N and a catalytic amount of DMAP, affording **16** in 61% yield. The *p*-*tert*-butyldimethylsiloxyphenyl substituent on nitrogen was successfully removed by successive treatment with TBAF and iodobenzene diacetate in 78% yield over two steps.[7] Iodobenzene diacetate is a mild oxidant, which afford the successful removal of the *p*-*tert*-butyldimethylsiloxyphenyl moiety without affecting the oxidatively-labile *p*-methoxyphenyl group and furan. In spite of several precedents for the conversion of furan into carboxy group, the oxidative modification of furan of **15** was found to be difficult. Though ozonolysis[24] gave the product in low yield, the reaction of **17** with sodium periodate and a catalytic amount of ruthenium dioxide[25] afforded the carboxylic acid, which was treated with diazomethane to



Scheme 1. Total synthesis of the N-terminal of amino acid equivalent **19** of nikkomycin B and B_X.

afford methyl ester **18** in 47% yield over two steps. Even under these conditions over-oxidation at the *p*-methoxyphenyl moiety proceeded to some extent. Treatment of **18** with K_2CO_3 in MeOH gave lactone **19** in 84% yield, which was identical to the literature [21d] (Scheme 1).

3. Conclusion

In summary, we have accomplished a general method for the synthesis of α-substituted β-amino secondary alcohols based on the following sequence of four reactions. (1) The proline-mediated, asymmetric, one-pot, three-component cross Mannich reaction of two different aldehydes to generate α-substituted β-amino aldehydes. (2) The nucleophilic addition reaction of R_2CuLi. (3) Oxidation of alcohol to ketone. (4) Diastereoselective reduction with LiAlH(O-*t*-Bu)$_3$ or catecholborane to generate the 1,2-*syn* or 1,2-*anti* isomer. This synthetic method was successfully applied to the formal total synthesis of the N-terminal amino acid moiety of nikkomycins B and B_X.

4. Experimental

4.1. Typical experimental procedures for the preparation of 2 (Table 3, entry 1)

To a solution of benzaldehyde (53 μL, 0.5 mmol) and *p*-anisidine (67.8 mg, 0.55 mmol) in NMP (0.5 mL) was added L-proline (5.8 mg, 0.05 mmol) and the reaction mixture was stirred for 2 h at room temperature. To this reaction mixture was added propanal (60.5 μL, 1.5 mmol) at −20 °C, which was further stirred for 20 h at this temperature. After addition of phosphate buffer, the organic materials were extracted with Et_2O three times and the combined organic phase was washed with brine three times, dried over $MgSO_4$. After filtration, the volatile materials were removed under reduced pressure to afford a crude β-amino aldehyde, which was used immediately in the next reaction.

To a suspension of CuI (238 mg, 1.25 mmol) in Et_2O (2.5 mL) was added MeLi (1.14 M in Et_2O, 2.19 mL, 2.5 mmol) at −20 °C over 5 min and the reaction mixture was stirred for 30 min at that temperature. To a Me_2CuLi solution was added a solution of crude β-amino aldehyde in Et_2O (1 mL) at −78 °C over 15 min and the reaction mixture was stirred for 3 h at this temperature. After addition of phosphate buffer and filtration of the insoluble materials via Celite pad, the organic materials were extracted with AcOEt three times and the combined organic phase was dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were obtained, which was purified by thin-layer chromatography (TLC) (AcOEt/hexane=1:3) to afford β-amino alcohol **2a** in 83% yield.

4.1.1. (2*S*,3*S*,4*S*)-4-(*p*-Anisidino)-3-methyl-4-phenylbutan-2-ol (*syn*-2a). Yellow solid; mp: 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, d, *J*=8.0 Hz), 1.20 (3H, d, *J*=6.4 Hz), 1.73–1.86 (1H, m), 3.66 (3H, s), 4.15 (1H, dq, *J*=1.8, 6.4 Hz) 4.54 (1H, d, *J*=3.6 Hz), 6.53 (2H, d, *J*=8.8 Hz), 6.66 (2H, d, *J*=8.8 Hz), 7.10–7.30 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 5.5, 21.7, 45.5, 55.6, 63.6, 71.6, 114.6, 116.0, 126.6, 126.8, 128.4, 140.8, 142.2, 152.6; IR (neat): ν 3367, 2927, 2918, 1512, 1450, 1234, 1039, 820, 702 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1721.

4.1.2. (2*R*,3*S*,4*S*)-4-(*p*-Anisidino)-3-methyl-4-phenylbutan-2-ol (*anti*-2a). Yellow solid; mp: 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, d, *J*=7.1 Hz), 1.26 (3H, d, *J*=6.3 Hz), 1.92 (1H, d of quintet, *J*=3.3, 7.1 Hz), 3.67 (3H, s), 3.77 (1H, quintet, *J*=6.3 Hz), 4.69 (1H, d, *J*=3.3 Hz), 6.52 (2H, br d, *J*=8.9 Hz), 6.67 (2H, br d, *J*=8.9 Hz), 7.15–7.25 (1H, m), 7.26–7.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 21.9, 45.9, 55.7, 59.5, 70.3, 114.8, 115.4, 126.7, 127.1, 128.3, 141.2, 142.0, 152.3; IR (neat): ν 3380, 2968, 2931, 2360, 1512, 1452, 1232, 1037, 820, 702 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1691; $[\alpha]_D^{20}$ −34.5 (*c* 0.10, $CHCl_3$).

4.1.3. (1*R*,2*S*,3*S*)-3-(*p*-Anisidino)-2-methyl-1,3-diphenylpropan-1-ol (*syn*-2b). Yellow solid; mp: 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, d, *J*=7.1 Hz), 2.13 (1H, tq, *J*=3.6, 7.1 Hz), 3.65 (3H, s), 4.56 (1H, d, *J*=3.6 Hz), 5.01 (1H, d, *J*=3.7 Hz), 6.49 (2H, br d, *J*=8.9 Hz), 6.66 (2H, br d, *J*=8.9 Hz), 7.13–7.37 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 6.2, 47.0, 55.6, 62.5, 77.4, 114.6, 115.9, 125.8, 126.6, 126.8, 127.1, 128.2, 128.4, 140.7, 142.2, 143.4, 152.5; IR (neat): ν 3379, 2933, 2908, 1512, 1452, 1234, 1036, 820, 740, 702 cm^{-1}; HRMS (FAB): calcd for $C_{23}H_{25}NO_2$ 347.1885, found 347.1862; $[\alpha]_D^{22}$ −5.4 (*c* 0.81, MeOH).

4.1.4. (1*S*,2*S*,3*S*)-3-(*p*-Anisidino)-2-methyl-1,3-diphenylpropan-1-ol (*anti*-2b). Yellow solid; mp: 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, d, *J*=7.2 Hz), 2.25–2.35 (1H, m), 3.68 (3H, s), 4.65–4.71 (2H, m), 6.53 (2H, br d, *J*=8.8 Hz), 6.67 (2H, br d, *J*=8.8 Hz), 7.14–7.23 (3H, m), 7.23–7.32 (3H, m), 7.32–7.40 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.7, 45.8, 55.6, 58.6, 77.6, 114.7, 115.9, 126.2, 126.7, 126.9, 127.5, 128.3, 128.5, 140.6, 141.6, 143.9, 152.5; IR (neat): ν 3419, 2912, 1612, 1512, 1448, 1234, 1030, 822, 746, 702 cm^{-1}; HRMS (FAB): calcd for $C_{23}H_{26}NO_2$ 348.1964, found 348.1992; $[\alpha]_D^{22}$ +0.5 (*c* 0.88, MeOH).

4.1.5. (1*S*,2*S*,3*S*)-1-(*p*-Anisidino)-2-methyl-1-phenylheptan-3-ol (*syn*-2c). Yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.83–0.95 (6H, m), 1.20–1.42 (4H, m), 1.45–1.65 (2H, m), 1.80–1.90 (1H, m), 3.66 (3H, s), 3.88–3.95 (1H, m), 4.51 (1H, d, *J*=3.3 Hz), 6.53 (2H, br d, *J*=8.2 Hz), 6.66 (2H, br d, *J*=8.2 Hz), 7.15–7.30 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 5.6, 14.1, 22.7, 28.3, 35.3, 43.9, 55.6, 64.0, 75.8, 114.6, 116.0, 126.6, 126.7, 128.4, 140.9, 142.3, 152.5; IR (neat): ν 3363, 2956, 2931, 1514, 1493, 1452, 1261, 1234, 1037, 976 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{21}H_{30}NO_2$ 328.2277, found 328.2263.

4.1.6. (1*S*,2*S*,3*R*)-1-(*p*-Anisidino)-2-methyl-1-phenylheptan-3-ol (*anti*-2c). Yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85 (3H, d, *J*=7.2 Hz), 0.89 (3H, t, *J*=7.0 Hz), 1.25–1.63 (6H, m), 1.91 (1H, d of quintet, *J*=3.2, 7.0 Hz), 3.55–3.72 (1H, m), 3.65 (3H, s), 4.69 (1H, d, *J*=3.2 Hz),

6.49 (2H, br d, J=8.9 Hz), 6.64 (2H, br d, J=8.9 Hz), 7.17 (1H, t, J=7.0 Hz), 7.22–7.29 (4H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.5, 14.1, 22.8, 28.1, 35.1, 44.0, 55.6, 58.9, 74.7, 114.7, 115.5, 126.6, 126.9, 128.3, 141.0, 142.1, 152.3; IR (neat): ν 3379, 2956, 2931, 1618, 1601, 1514, 1464, 1452, 1234, 1039 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{21}H_{30}NO_2$ 328.2277, found 328.2286.

4.1.7. (2*S*,3*S*,4*S*)-4-(*p*-Anisidino)-4-(*p*-bromophenyl)-3-methylbutan-2-ol (*syn*-2d). Yellow solid; mp: 138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, d, J=7.2 Hz), 1.21 (3H, d, J=6.3 Hz), 1.72–1.80 (1H, m), 3.67 (3H, s), 4.10 (1H, dq, J=2.3, 6.3 Hz), 6.46 (2H, br d, J=8.9 Hz), 6.66 (2H, br d, J=8.9 Hz), 7.14 (2H, br d, J=8.4 Hz), 7.40 (2H, br d, J=8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 5.1, 21.1, 44.8, 55.7, 63.3, 72.4, 114.9, 116.7, 120.7, 128.3, 131.6, 139.8, 140.7, 153.1; IR (neat): ν 3369, 2970, 1510, 1485, 1403, 1234, 1178, 1039, 1008, 520 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{22}^{79}BrNO_2$ 363.0834, found 363.0832.

4.1.8. (2*R*,3*S*,4*S*)-4-(*p*-Anisidino)-4-(*p*-bromophenyl)-3-methylbutan-2-ol (*anti*-2d). Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (3H, d, J=7.1 Hz), 1.26 (3H, d, J=6.3 Hz), 1.87 (1H, d of quintet, J=3.2, 7.1 Hz), 3.67 (3H, s), 3.76 (1H, quintet, J=6.7 Hz), 4.65 (1H, d, J=3.2 Hz), 6.45 (2H, br d, J=8.9 Hz), 6.66 (2H, br d, J=8.9 Hz), 7.17 (2H, br d, J=8.3 Hz), 7.40 (2H, br d, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 22.0, 45.9, 55.7, 59.0, 70.2, 114.8, 115.2, 120.4, 128.8, 131.4, 141.0, 141.3, 152.3; IR (neat): ν 3379, 2968, 2931, 2360, 1512, 1485, 1234, 1178, 1037, 1008 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{18}H_{23}^{79}BrNO_2$ 364.0912, found 364.0917.

4.1.9. (1*S*,2*S*,3*S*)-1-(*p*-Anisidino)-1-(*p*-bromophenyl)-2-methylheptan-3-ol (*syn*-2e). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.94 (6H, m), 1.20–1.65 (6H, m), 1.76–1.85 (1H, m), 3.67 (3H, s), 3.82–3.88 (1H, m), 4.42 (1H, d, J=4.0 Hz), 6.46 (2H, br d, J=8.9 Hz), 6.66 (2H, br d, J=8.9 Hz), 7.14 (2H, br d, J=8.4 Hz), 7.41 (2H, br d, J=8.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 5.7, 14.0, 22.7, 28.2, 35.4, 43.9, 55.6, 63.5, 75.6, 114.6, 115.7, 120.4, 128.4, 131.5, 140.8, 141.7, 152.5; IR (neat): ν 3367, 2931, 1514, 1484, 1465, 1234, 1039, 1008, 819, 524 cm^{-1}; HRMS (FAB): calcd for $C_{21}H_{28}^{79}BrNO_2$ 405.1303, found 405.1298.

4.1.10. (1*S*,2*S*,3*R*)-1-(*p*-Anisidino)-1-(*p*-bromophenyl)-2-methylheptan-3-ol (*anti*-2e). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, d, J=6.9 Hz), 0.90 (3H, t, J=8.4 Hz), 1.25–1.42 (4H, m), 1.43–1.66 (2H, m), 1.90 (1H, d of quintet, J=3.0, 6.9 Hz), 3.58 (1H, ddd, J=4.0, 6.3, 8.2 Hz), 4.65 (1H, d, J=3.0 Hz), 6.45 (2H, br d, J=8.9 Hz), 6.66 (2H, br d, J=8.9 Hz), 7.15 (2H, br d, J=8.3 Hz), 7.40 (2H, br d, J=8.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.5, 14.1, 22.7, 28.0, 35.1, 44.0, 55.6, 58.6, 74.6, 114.7, 115.3, 120.3, 128.8, 131.4, 140.8, 141.4, 152.3; IR (neat): ν 3367, 2954, 2931, 1532, 1484, 1234, 1039, 1008, 820, 526 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd $C_{21}H_{29}^{79}BrNO_2$ 406.1382, found 406.1353.

4.1.11. (1*R*,2*S*,3*S*)-3-(*p*-Anisidino)-3-(*p*-bromophenyl)-2-methyl-1-phenylpropan-1-ol (*syn*-2f). Colorless solid; ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.82 (3H, d, J=7.0 Hz), 2.05–2.12 (1H, m), 3.68 (3H, s), 4.49 (1H, d, J=3.2 Hz), 5.00 (1H, d, J=3.7 Hz), 6.45 (2H, d, J=8.8 Hz), 6.67 (2H, d, J=8.8 Hz), 7.13 (2H, d, J=8.3 Hz), 7.23–7.26 (1H, m), 7.30–7.33 (4H, m), 7.39 (2H, d, J=8.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 6.4, 47.0, 55.6, 61.9, 77.3, 114.7, 115.6, 120.5, 125.8, 127.4, 128.3, 128.4, 131.5, 140.6, 141.6, 143.3, 152.5; IR (neat): ν 3374, 2931, 2908, 1512, 1484, 1234, 1178, 1035, 1008, 819 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{23}H_{25}^{79}BrNO_2$ 426.1069, found 426.1089; $[\alpha]_D^{20}$ −7.7 (*c* 0.75, $CHCl_3$).

4.1.12. (1*S*,2*S*,3*S*)-3-(*p*-Anisidino)-3-(*p*-bromophenyl)-2-methyl-1-phenylpropan-1-ol (*anti*-2f). Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (3H, d, J=7.1 Hz), 2.25 (1H, d of quintet, J=2.5, 7.1 Hz), 3.68 (3H, s), 4.62–4.66 (2H, m), 6.47 (2H, br d, J=8.9 Hz), 6.67, (2H, br d, J=8.9 Hz), 7.09 (2H, br d, J=8.5 Hz), 7.25–7.35 (5H, m), 7.38 (2H, br d, J=8.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.7, 45.8, 55.6, 58.3, 77.5, 114.7, 115.5, 120.4, 126.3, 127.7, 128.5, 128.8, 131.4, 140.5, 140.9, 143.5, 152.4; IR (neat): ν 3388, 2931, 1512, 1484, 1234, 1072, 1037, 1009, 819, 702 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{23}H_{25}^{79}BrNO_2$ 426.1069, found 426.1040; $[\alpha]_D^{20}$ −30.5 (*c* 0.55, $CHCl_3$).

4.2. Typical experimental procedures for the preparation of 3 (Table 3, entry 1)

To a solution of β-amino alcohol **2a** (205 mg, 0.59 mmol) in CH_2Cl_2 (0.6 mL) was added Et_3N (0.41 mL, 2.96 mmol), DMSO (0.6 mL) and SO_3·pyridine (278 mg, 1.78 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at that temperature. After addition of phosphate buffer, the organic materials were extracted with AcOEt three times and the combined organic phase was dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by TLC (AcOEt/hexane=1:3) to afford β-amino ketone **3a** in 94% yield.

4.2.1. (3*S*,4*S*)-4-(*p*-Anisidino)-3-methyl-4-phenylbutan-2-one (3a). Colorless solid; mp: 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (3H, d, J=7.0 Hz), 2.08 (3H, s), 2.98 (1H, dq, J=5.4, 7.0 Hz), 3.66 (3H, s), 4.00 (1H, br s), 4.65 (1H, d, J=5.4 Hz), 6.44 (2H, br d, J=8.9 Hz), 6.65 (2H, br d, J=8.9 Hz), 7.18–7.24 (1H, m), 7.27–7.30 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.0, 29.3, 53.1, 55.7, 59.7, 114.7, 113.8, 114.7, 114.9, 126.9, 127.2, 128.6, 141.1, 141.3, 152.2; IR (neat): ν 3403, 2933, 1708, 1514, 1452, 1355, 1243, 1002, 796, 648 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{21}NO_2$ 283.1572, found 283.1597; $[\alpha]_D^{20}$ +55 (*c* 0.85, $CHCl_3$).

4.2.2. (2*S*,3*S*)-3-(*p*-Anisidino)-2-methyl-1,3-diphenylpropan-1-one (3b). Colorless solid; mp: 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, d, J=7.0 Hz), 3.64 (3H, s), 3.92 (1H, dq, J=4.8, 7.0 Hz), 4.22 (1H, br s), 4.64 (1H, d, J=4.8 Hz), 6.39 (2H, br d, J=8.9 Hz), 6.60 (2H, br d, J=8.9 Hz), 7.19 (1H, t, J=7.4 Hz), 7.29 (2H, t, J=7.4 Hz), 7.37 (2H, d, J=7.4 Hz), 7.43 (2H, t, J=7.4 Hz), 7.54 (1H, t, J=7.4 Hz), 7.91 (2H, d, J=7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.3, 46.9, 55.6, 59.9, 114.5, 114.9,

126.9, 127.2, 128.3, 128.6, 128.8, 133.3, 136.2, 141.4, 141.8, 152.0, 202.8; IR (neat): ν 3394, 2974, 1672, 1514, 1448, 1294, 1257, 1039, 974, 812 cm^{-1}; HRMS (FAB): calcd for $C_{23}H_{23}NO_2$ 345.1729, found 345.1748; $[\alpha]_D^{22}$ −0.1 (*c* 0.88, MeOH).

4.2.3. (1*S*,2*S*)-1-(*p*-Anisidino)-2-methyl-1-phenylheptan-3-one (3c). Colorless solid; ^1H NMR (400 MHz, CDCl3): δ 0.80 (3H, t, J=7.3 Hz), 1.08 (3H, d, J=7.0 Hz), 1.17 (2H, septet, J=7.2 Hz), 1.42 (2H, m), 2.27 (1H, dt, J=7.3, 17.2 Hz), 2.35 (1H, dt, J=7.3, 17.1 Hz), 2.96 (1H, quintet, J=5.9 Hz), 3.66 (3H, s), 4.57 (1H, d, J=5.7 Hz), 5.43 (2H, br d, J=8.8 Hz), 6.64 (2H, br d, J=8.8 Hz), 7.15–7.24 (1H, m), 7.26–7.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.4, 13.8, 22.1, 25.5, 42.0, 52.5, 55.7, 60.0, 114.7, 114.9, 126.9, 127.2, 128.5, 141.3, 141.5, 152.2, 213.0; IR (neat): ν 3396, 2929, 1702, 1518, 1454, 1295, 1267, 1247, 1232, 1036 cm^{-1}; HRMS (FAB): calcd for $C_{21}H_{27}NO_2$ 325.2042, found 325.2039; $[\alpha]_D^{21}$ +49.9 (*c* 0.27, $CHCl_3$).

4.2.4. (3*S*,4*S*)-4-(*p*-Anisidino)-4-(*p*-bromophenyl)-3-methylbutan-2-one (3d). Colorless solid; ^1H NMR (400 MHz, $CDCl_3$): δ 1.06 (3H, d, J=7.1 Hz), 2.09 (3H, s), 2.94 (1H, dq, J=5.4, 7.1 Hz), 3.66 (3H, s), 3.98 (1H, br s), 4.60 (1H, d, J=5.4 Hz), 6.40 (2H, br d, J=8.9 Hz), 6.65 (2H, br d, J=8.9 Hz), 7.18 (2H, br d, J=8.4 Hz), 7.41 (2H, br d, J=8.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): δ 10.9, 29.3, 52.8, 55.6, 59.1, 114.7, 114.9, 121.0, 128.7, 131.7, 140.5, 140.7, 152.4, 210.2; IR (neat): ν 3392, 2933, 1708, 1514, 1486, 1357, 1241, 1234, 1039, 1009 cm^{-1}; HRMS (FAB): $C_{18}H_{20}^{79}BrNO_2$ 361.0677, found 361.0647; $[\alpha]_D^{20}$ +21.3 (*c* 0.84, $CHCl_3$).

4.2.5. (1*S*,2*S*)-1-(*p*-Anisidino)-1-(*p*-bromophenyl)-2-methylheptan-3-one (3e). Colorless solid; ^1H MNR (600 MHz, $CDCl_3$): δ 0.81 (3H, t, J=7.4 Hz), 1.05 (3H, d, J=7.0 Hz), 1.16 (1H, dq, J=2.9, 7.5 Hz), 1.19 (1H, dq, J=2.9, 7.5 Hz), 1.40–1.44 (2H, m), 2.30 (1H, td, J=7.3, 14.9 Hz), 2.37 (1H, td, J=7.4, 14.9 Hz), 2.92 (1H, quintet, J=6.7 Hz), 3.66 (3H, s), 4.07 (1H, br s), 4.52 (1H, d, J=5.4 Hz), 6.39 (2H, br d, J=8.9 Hz), 6.64 (2H, br d, J=8.9 Hz), 7.18 (2H, br d, J=8.3 Hz), 7.41 (2H, br d, J=8.3 Hz); ^{13}C NMR (150 MHz, $CDCL_3$): δ 11.3, 13.8, 22.1, 25.4, 42.1, 52.1, 55.6, 59.3, 114.6, 114.9, 120.9, 128.7, 131.6, 140.7, 140.8, 152.2, 212.8; IR (neat): ν 3407, 2960, 2931, 1701, 1513, 1460, 1408, 1010, 813, 738 cm^{-1}; HRMS (FAB): calcd for $C_{21}H_{26}^{79}BrNO_2$ 403.1147, found 403.1138; $[\alpha]_D^{20}$ +33.5 (*c* 0.29, $CHCl_3$).

4.2.6. (2*S*,3*S*)-3-(*p*-Anisidino)-3-(*p*-bromophenyl)-2-methyl-1-phenylpropan-1-one (3f). Colorless solid; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, d, J=7.0 Hz), 3.64 (3H, s), 3.87 (1H, dq, J=5.0, 7.0 Hz), 4.22 (1H, br s), 4.59 (1H, d, J=5.0 Hz), 6.37 (2H, br d, J=8.9 Hz), 6.62 (2H, br d, J=8.9 Hz), 7.26 (2H, br d, J=8.3 Hz), 7.41 (2H, br d, J=8.3 Hz), 7.45 (2H, d, J=7.8 Hz), 7.55 (1H, t, J=7.3 Hz), 7.89 (2H, d, J=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 46.8, 55.7, 59.6, 114.7, 115.1, 121.0, 128.2, 128.7, 128.8, 131.7, 133.4, 136.2, 141.0, 141.1, 152.4, 202.5; IR (neat): ν 3380, 2931, 1676, 1512, 1448, 1241, 1236, 1038, 1010, 971 cm^{-1}; HRMS (FAB): calcd for $C_{23}H_{22}^{79}BrNO_2$ 423.0834, found 423.0807; $[\alpha]_D^{20}$ +51.7 (*c* 1.83, $CHCl_3$).

4.3. Typical experimental procedures for the preparation of 2-*anti* by the reduction with $LiAlH(O\text{-}t\text{-}Bu)_3$ (Table 4, entry 1)

To a solution of **3a** (10 mg, 0.035 mmol) in THF (0.5 mL) was added a solution of $LiAlH(O\text{-}t\text{-}Bu)_3$ (1 M in THF, 0.175 mL, 0.175 mmol) at −78 °C and the reaction mixture was stirred for 1 h at that temperature. After addition of a saturated solution of potassium sodium tartrate, the organic materials were extracted with AcOEt three times and the combined organic phase was washed with brine three times and dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were purified by TLC (AcOEt/hexane=1:3) to afford β-amino alcohol **2a** quantitatively (**2a**-*anti*/**2a**-*syn*=86:14). The ratio of *anti*/*syn* was determined by ^1H NMR measurement.

4.4. Typical experimental procedures for the preparation of 2-*syn* by the reduction with catecholborane (Table 4, entry 1)

To a THF solution (1.5 mL) of **3a** (50 mg, 0.15 mmol) was added catecholborane (155 μL, 1.5 mmol) at −10 °C and the reaction mixture was stirred for 3 h at that temperature. After addition of MeOH and a saturated solution of potassium sodium tartrate, the organic materials were extracted with AcOEt three times and the combined organic phase was washed with brine five times and dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were purified by TLC (AcOEt/hexane=1:3) to afford β-amino alcohol **2a** in 90% yield (**2a**-*anti*/**2a**-*syn*=2:98). The ratio of *anti*/*syn* was determined by ^1H NMR measurement.

4.5. The determination of the relative stereochemistry

4.5.1. (1*S*,2*S*,3*S*)-Carbonic acid 3-(*p*-anisidino)-1,2-dimethyl-3-phenylpropyl ester methyl ester (*syn*-4a). To a solution of **2a** (75.7 mg, 0.29 mmol) in CH_2Cl_2 (2.9 mL) was added DMAP (715.9 mg, 5.86 mmol), $ClCO_2$-Me (453 mL, 5.86 mmol) at 0 °C and the reaction mixture was stirred for 2.5 h at room temperature. After addition of phosphate buffer, the organic materials were extracted with AcOEt three times and the combined organic phase was washed with brine and dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by TLC (AcOEt/hexane=1:3) to afford *syn*-**4a** and *anti*-**4a** in 68% yield. *Syn*-**4a** and *anti*-**4a** were separated by TLC.

Yellow solid; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, d, J=6.8 Hz), 1.32 (3H, d, J=6.4 Hz), 1.93–2.02 (1H, m), 3.66 (3H, s), 3.71 (3H, s), 4.40 (1H, d, J=4.8 Hz), 4.81 (1H, dq, J=5.2, 6.4 Hz), 6.41 (2H, br d, J=8.9 Hz), 6.64 (2H, br d, J=8.9 Hz), 7.17–7.30 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 8.8, 18.4, 29.7, 45.1, 54.7, 55.7, 60.4, 114.5, 114.6, 126.7, 127.0, 128.5, 141.3, 142.4, 151.8, 155.3; IR (neat): ν 3415, 2981, 2954, 1743, 1514, 1442, 1271, 1234, 1038, 820 cm^{-1}; HRMS (FAB): calcd for $C_{20}H_{25}NO_4$ 343.1784, found 343.1816; $[\alpha]_D^{21}$ −8.5 (*c* 0.17, MeOH).

4.5.2. (4*S*,5*S*,6*S*)-3-(*p*-Anisidino)-5,6-dimethyl-4-phenyl-[1,3]oxazinan-2-one (5a). To a solution of *syn*-**4a** (25.6 mmol) in THF (0.8 mL) was added NaH (8.95 mmol, 0.373 mmol) at room temperature and the reaction mixture was stirred for 12 h at that temperature. After addition of phosphate buffer, the organic materials were extracted with AcOEt three times and dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by TLC (AcOEt/hexane=1:1) to afford **5a** in 25% yield.

Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, d, J=7.0 Hz), 1.38 (3H, d, J=6.5 Hz), 2.17–2.25 (1H, m), 3.66 (3H, s), 4.85 (1H, dq, J=1.1, 6.5 Hz), 5.26 (1H, d, J=5.0 Hz), 6.68 (2H, br d, J=8.6 Hz), 7.06–7.22 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.8, 18.1, 37.8, 55.2, 67.3, 75.9, 113.7, 127.5, 127.9, 128.3, 133.8, 137.2, 154.2, 157.5; IR (neat): ν 2937, 1689, 1515, 1454, 1402, 1247, 1170, 1033, 1025, 833 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{19}H_{22}NO_3$ 312.1600, found 312.1622; $[\alpha]_D^{20}$ −53.8 (*c* 0.47, $CHCl_3$).

4.6. Experimental procedures of the formal total synthesis of nikkomycin

4.6.1. (2*S*,3*S*)-3-(*N*-*p*-*tert*-Butyldimethylsiloxyphenyl-amino)-3-(2-furyl)-2-methyl-1-(*p*-methoxyphenyl)propan-1-one (14). To a solution of 2-furylaldehyde (0.25 mL, 3.0 mmol) and *p*-*tert*-butyldimethylsiloxyaniline (737 mg, 3.3 mmol) in NMP (3.0 mL) was added L-proline (34.5 mg, 0.03 mmol) and the reaction mixture was stirred for 2 h at room temperature. To this reaction mixture was added pyridine (0.363 mL, 4.5 mmol) and propanal (0.972 mL, 4.5 mmol) at −20 °C, which was further stirred for 20 h at this temperature. After addition of phosphate buffer, the organic materials were extracted with Et_2O three times and the combined organic phase was washed with brine three times and dried over $MgSO_4$. After filtration, the volatile materials were removed under reduced pressure to afford a crude β-amino aldehyde, which was used without further purification in the next reaction.

To a suspension of CuI (2.85 g, 15 mmol) in Et_2O (10 mL) was added a solution of *p*-MeOPhMgBr (2.15 M in Et_2O, 14 mL, 30 mmol) at −7 °C over 5 min and the reaction mixture was stirred for 30 min at this temperature. To this reaction mixture was added a solution of crude β-amino aldehyde in Et_2O (20 mL) at −7 °C and the reaction mixture was stirred for 3 h at this temperature. After addition of phosphate buffer and filtration of the insoluble materials via Celite pad, the organic materials were extracted with AcOEt three times and the combined organic phase was dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was obtained, which was further oxidized.

To a solution of crude amino alcohol **13** in CH_2Cl_2 (2 mL) was added Et_3N (1.3 mL, 10 mmol), DMSO (2 mL) and SO_3·pyridine (937 mg, 6 mmol) at 0 °C, and the reaction mixture was stirred for 30 min at this temperature. After addition of phosphate buffer, the organic materials were extracted with AcOEt three times and the combined organic phase was dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by column chromatography (AcOEt/hexane=1:25) to afford β-amino ketone **14** in 70% yield over three steps.

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (6H, s), 0.92 (9H, s), 1.27 (3H, d, J=6.9 Hz), 3.84 (3H, s), 4.03 (1H, quintet, J=6.9 Hz), 4.75 (1H, d, J=6.5 Hz), 6.09 (1H, d, J=3.2 Hz), 6.17 (1H, dd, J=2.0, 3.2 Hz), 6.44 (2H, br d, J=8.7 Hz), 6.58 (2H, d, J=8.7 Hz), 6.90 (2H, d, J=8.8 Hz), 7.25 (1H, d, J=2.0 Hz), 7.90 (2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5, 13.3, 18.1, 25.7, 44.3, 55.46, 55.49, 107.2, 110.2, 113.8, 115.3, 120.4, 129.3, 130.6, 141.4, 141.6, 148.0, 154.6, 163.6, 200.7; IR (neat): ν 3381, 2956, 2929, 1672, 1601, 1510, 1254, 1173, 924, 841 cm^{-1}; HRMS (FAB): calcd for $C_{27}H_{35}NO_4Si$ 465.2335, found 465.2332; $[\alpha]_D^{22}$ −37.6 (*c* 0.39, $CHCl_3$).

4.6.2. (1*S*,2*S*,3*S*)-3-(*N*-*p*-*tert*-Butyldimethylsiloxyphenyl-amino)-3-(2-furyl)-2-methyl-1-(*p*-methoxyphenyl)propan-1-ol (15). To a solution of **14** (673 mg, 1.44 mmol) in THF (14.4 mL) was of $LiAlH(O\text{-}t\text{-}Bu)_3$ (1 M in THF, 7.2 mL, 7.2 mmol) at −78 °C and the reaction mixture was stirred for 1 h at that temperature. After addition of the saturated solution of potassium sodium tartrate, the organic materials were extracted with AcOEt three times and the combined organic phase was washed with brine three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by column chromatography (AcOEt/hexane=1:15) to afford β-amino alcohol **15** in 98% yield.

The ee was determined by the chiral HPLC analysis: Chiralpak AD-H column (hexane/2-propanol=30:1), 0.5 mL/min, major tr=16.9 min, minor tr=21.5 min.

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.13 (6H, s), 0.84 (3H, d, J=7.4 Hz), 0.94 (9H, s), 2.41 (1H, d of quintet, J=2.5, 7.4 Hz), 3.80 (3H, s), 4.60 (1H, d, J=7.4 Hz), 4.79 (1H, d, J=2.5 Hz), 6.05 (1H, d, J=3.2 Hz), 6.23 (1H, dd, J=1.8, 3.2 Hz), 6.57 (2H, br d, J=8.9 Hz), 6.64 (2H, br d, J=8.9 Hz), 6.87 (2H, br d, J=8.7 Hz), 7.27 (2H, d, J=8.7 Hz), 7.29 (1H, d, J=1.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ −4.5, 12.5, 18.1, 25.7, 43.4, 54.6, 55.2, 106.7, 110.1, 113.8, 116.0, 120.6, 127.5, 128.3, 136.0, 141.2, 141.4, 148.4, 155.4, 158.9; IR (neat): ν 3388, 2956, 2929, 1610, 1508, 1250, 1009, 910, 837, 779 cm^{-1}; HRMS (FAB): calcd for $C_{27}H_{37}NO_4Si$ 467.2492, found 467.2493; $[\alpha]_D^{22}$ −22.4 (*c* 0.81, $CHCl_3$).

4.6.3. (1*S*,2*S*,3*S*)-Benzoic acid 3-{benzoyl-[4-(*tert*-butyl-dimethylsiloxy)-phenyl]-amino}-3(2-furyl)-1-(4-methoxy-phenyl)-2-methylpropyl ester (16). To a solution of **15** (253.1 mg, 0.541 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (0.679 mL, 4.87 mmol), benzoyl chloride (0.377 mL, 3.25 mmol) and catalytic amount of DMAP at 0 °C. After stirring the reaction mixture for 18 h at room temperature, the reaction was quenched by the addition of phosphate buffer. The organic materials were extracted with AcOEt three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude

material was purified by thin-layer chromatography (AcOEt/hexane=1:3) to afford **16** in 61% yield.

Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (6H, s), 0.88 (9H, s), 1.34 (3H, d, J=6.7 Hz), 3.05–3.17 (1H, m), 3.77 (3H, s), 5.85 (1H, d, J=10.7 Hz), 6.10 (1H, d, J=4.5 Hz), 6.24–6.28 (1H, m), 6.41 (1H, d, J=4.1 Hz), 6.45–6.54 (4H, m), 6.84 (2H, d, J=8.2 Hz), 7.05–7.20 (7H, m), 7.28 (1H, s), 7.41 (2H, t, J=7.4 Hz), 7.53 (1H, t, J=7.4 Hz), 8.02 (2H, d, J=7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ −4.5, 11.7, 18.2, 25.6, 39.1, 55.16, 55.20, 76.6, 110.4, 110.5, 113.6, 120.2, 127.4, 128.29, 128.31, 128.6, 128.7, 129.0, 129.6, 130.4, 133.0, 136.5, 141.7, 151.6, 154.6, 159.3, 165.3, 170.7; IR (neat): ν 1718, 1686, 1655, 1647, 1508, 1269, 1252, 912, 711 cm^{-1}; HRMS (FAB): $[M-OBz]^+$ calcd for $C_{34}H_{40}NO_4Si$ 554.2726, found: 554.2714; $[\alpha]_D^{22}$ −68.9 (c 0.79, $CHCl_3$).

4.6.4. (1*S*,2*S*,3*S*)-Benzoic acid 3-benzoylamino-3-(2-furyl)-1-(4-methoxyphenyl)-2-methylpropyl ester (17). To a solution of **16** (251 mg, 0.371 mmol) in THF (7 mL) was added a solution of tetrabutylammonium fluoride (1 M in THF, 0.445 mL, 0.445 mmol) at 0 °C. After stirring the reaction mixture for 10 min at this temperature, the reaction was quenched by the addition of saturated NH_4Cl. The organic materials were extracted with AcOEt three times, and the combined organic phase was washed with brine, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were used directly in the next reaction. To a CH_3CN (1.02 mL) solution of crude phenol derivative was added water (0.5 mL) and iodobenzene diacetate (119.5 mg, 0.371 mmol) at 0 °C. After stirring the reaction mixture for 1 h at that temperature, the reaction was quenched by the addition of solution of $NaHCO_3$ and $Na_2S_2O_3$. The organic materials were extracted with AcOEt three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by thin-layer chromatography (Et_2O/benzene=1:3) to afford **17** in 78% yield over two steps.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, d, J=7.1 Hz), 2.85 (1H, d of quintet, J=3.5, 7.1 Hz), 3.74 (3H, s), 5.63–5.67 (2H, m), 6.23 (1H, d, J=3.3 Hz), 6.27 (1H, dd, J=1.8, 3.3 Hz), 6.80–6.88 (3H, m), 7.23–7.42 (7H, m), 7.45–7.58 (2H, m), 7.68 (2H, d, J=8.0 Hz), 7.98 (2H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 42.3, 50.1, 55.2, 78.5, 107.3, 110.3, 113.9, 127.1, 128.4, 128.5, 128.7, 129.5, 130.6, 131.1, 132.8, 134.4, 142.2, 152.6, 159.5, 165.3, 166.4; IR (neat): ν 3346, 2935, 1720, 1657, 1514, 1269, 1252, 1111, 808, 712 cm^{-1}; HRMS (FAB): $[M-OBz]^+$ calcd for $C_{22}H_{22}NO_3$ 348.1600, found 348.1610; $[\alpha]_D^{22}$ +10.5 (c 0.58, MeOH).

4.6.5. (1*S*,2*S*,3*S*)-Benzoic acid 3-benzoylamino-3-methoxycarbonyl-1-(4-methoxyphenyl)-2-methylpropyl ester (18). To an aqueous solution (AcOEt 1.0 mL and water 0.25 mL) of **17** (8.1 mg, 0.017 mmol) was added RuO_2 (1.0 mg, 0.0075 mmol) and $NaIO_4$ (46 mg, 0.22 mmol) at −6 °C. After stirring the reaction mixture for 2 h at this temperature, the reaction was quenched by the addition of 1 N HCl solution. The organic materials were extracted with $CHCl_3$ three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude materials were dissolved in Et_2O. To an Et_2O solution of crude carboxylic acid was added an Et_2O solution of diazomethane at 0 °C. After 10 min at this temperature, the volatile materials were removed under reduced pressure and the crude methyl ester was purified by thin-layer chromatography (Et_2O/HCO_2H/benzene=1:1:3) to afford methyl ester **18** in 47% yield over two steps.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, d, J=7.1 Hz), 2.86 (1H, dqd, J=2.8, 7.1, 9.8 Hz), 3.75 (3H, s), 3.77 (3H, s), 5.31 (1H, dd, J=2.8, 9.0 Hz), 5.69 (1H, d, J=9.8 Hz), 6.66 (1H, d, J=9.0 Hz), 6.84 (2H, d, J=8.7 Hz), 7.30–7.45 (6H, m), 7.47–7.55 (2H, m), 7.72 (2H, d, J=7.2 Hz), 8.02 (2H, d, J=7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.7, 41.3, 52.7, 53.6, 55.2, 77.4, 113.9, 127.1, 128.4, 128.5, 129.6, 130.4, 131.7, 132.9, 134.0, 159.5, 165.4, 167.3, 172.3; IR (neat): ν 3375, 2926, 1739, 1724, 1668, 1514, 1252, 1215, 1109, 1026, 837, 712 cm^{-1}; HRMS (FAB): $[M-OBz]^+$ calcd for $C_{20}H_{22}NO_4$ 340.1549, found: 340.1526; $[\alpha]_D^{22}$ +22.0 (c 0.19, $CHCl_3$).

4.6.6. (3*S*,4*S*,5*R*)-*N*-[5-(4-Methoxyphenyl)-4-methyl-2-oxo-tetrahydro-furan-3-yl]-benzamide (19). To a solution of **18** (5.0 mg, 0.011 mmol) in MeOH (0.5 mL) was added K_2CO_3 (6.0 mg, 0.044 mmol) at room temperature. After stirring the reaction mixture for 2.5 h at this temperature, the reaction was quenched by the addition of phosphate buffer. The organic materials were extracted with $CHCl_3$ three times, dried over Na_2SO_4, and filtered. After removal of the volatile materials under reduced pressure, the crude material was purified by thin-layer chromatography (Et_2O/HCO_2H/benzene=1:1:3) to afford lactone **19** in 84% yield.

Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.24 (3H, d, J=6.4 Hz), 2.52 (1H, qdd, J=6.4, 10.1, 11.8 Hz), 3.80 (3H, s), 4.80 (1H, dd, J=7.7, 11.8 Hz), 4.93 (1H, d, J=10.1 Hz), 6.71 (1H, d, J=7.2 Hz), 6.90 (2H, d, J=7.7 Hz), 7.33 (2H, t, J=8.8 Hz), 7.42 (2H, t, J=8.0 Hz), 7.52 (1H, t, J=6.5 Hz), 7.81 (2H, d, J=8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.8, 47.2, 55.3, 57.0, 85.3, 114.2, 127.1, 128.0, 128.27, 128.31, 128.7, 132.1, 133.0, 160.3, 167.7, 174.4; IR (neat): ν 2926, 2854, 1780, 1647, 1516, 1250, 1174, 831, 712 cm^{-1}; HRMS (FAB): $[M+H]^+$ calcd for $C_{19}H_{20}NO_4$: 326.1392, found: 326.1400; $[\alpha]_D^{23}$ +9.5 (c 0.13, $CHCl_3$).

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Enantioselective and regioselective nickel-catalyzed multicomponent coupling of chiral allenes, aromatic aldehydes, and silanes

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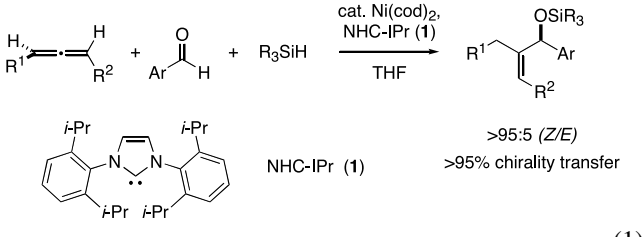
Abstract—A detailed account of the development of a recently developed, nickel-catalyzed multicomponent coupling of chiral allenes, aromatic aldehydes, and silanes is described. The axial chirality of the allene is transferred completely to the product, a trisubstituted *Z*-allylic alcohol protected as a silyl ether. A very high preference for sp rather than sp^2 coupling is observed, and differentially substituted allenes undergo highly site-selective coupling. These transformations represent the first enantioselective multi-component coupling processes of allenes.

1. Introduction

Catalytic, stereoselective multicomponent coupling reactions assemble highly functionalized molecules in a single operation from very simple precursors.[1] Several groups, including our own, have developed a number of nickel-catalyzed reactions of this type in which alkynes are combined with common functional groups, such as aldehydes,[2] epoxides,[3] and imines.[4] We recently described[5] a related, catalytic enantioselective multicomponent coupling, in which an allene takes the place of the alkyne (Eq. 1).[6] These functional groups are related to alkynes in that they possess an sp-hybridized carbon atom, compared to the two that comprise an alkyne, but in contrast to an alkyne, an allene may be chiral about the axis of its cumulated π bonds.[7]



(1)

Prior to our studies, the majority of intermolecular reactions of allenes and aldehydes involved the union of one of the sp^2-hybridized carbons of the allene with the carbonyl group of the aldehyde, affording homoallylic alcohols in the case of multi-component coupling reactions[6] and, in allenylmetal addition reactions, homopropargylic alcohols.[8] Ours is a rare example of the alternative-intermolecular addition of an electrophile (aldehyde) to the sp-hybridized[9] and ostensibly least nucleophilic carbon of an unactivated allene.[10] Among intermolecular transition metal-catalyzed multi-component coupling reactions involving allenes and aldehydes, these were the first that gave allylic (as opposed to homoallylic)[6] alcohol derivatives, the first that were reductive (instead of alkylative),[6] and finally, the first that were highly enantioselective.[11] Herein, we provide a full account of the development of this transformation, a nickel-catalyzed, multi-component coupling reaction that transmits the axial chirality of a 1,3-disubstituted allene to a stereogenic center in the product with very high fidelity.

2. Development of an enantioselective multi-component coupling reaction of a chiral, 1,3-disubstituted allene

We began our investigations by examining reactions of 4,5-nonadiene, benzaldehyde, and a variety of reducing agents and found that a species derived from $Ni(cod)_2$ and an organophosphine ligand (R_3P) catalyzed a novel, efficient, and selective three-component coupling process (Table 1).[12] Larger, trialkylphosphines proved to be superior in these reactions (entries 4–6), relative to smaller phosphines (entries 1–3). In all cases where coupling was observed, the ratio of allylic and homoallylic products (i.e., coupling

Keywords: Nickel; Allene; Asymmetric catalysis; Chirality transfer; *N*-Heterocyclic carbene.
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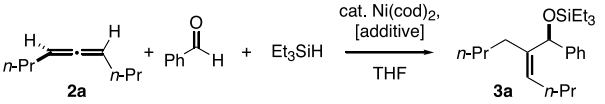
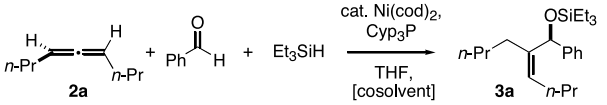
Table 1. Evaluation of organophosphine additives[a]



Entry	Additive	Yield **3a** (%)[b]	*Z*/*E*[c]
1	Ph_3P	Trace	na
2	$(n\text{-Octyl})_3P$	Trace	na
3	$(o\text{-Anisyl})_3P$	Trace	na
4	Cy_3P	54	>95:5
5	$(i\text{Pr})_3P$	63	>95:5
6	Cyp_3P	77	>95:5

[a] Standard procedure: to a solution of $Ni(cod)_2$ (20 mol%), the additive indicated (20 mol%), benzaldehyde (300 mol%), and triethylsilane (300 mol%) in THF at ambient room temperature was added a THF solution of (±)-4,5-nonadiene (100 mol%, 0.1 mmol) over 4.5 h. The mixture was stirred an additional 8 h and filtered through SiO_2.
[b] NMR yield versus an internal standard.
[c] Determined by ^1H NMR analysis of unpurified reaction mixture.

Table 2. Evaluation of cosolvents[a]



Entry	Cosolvent	Yield **3a** (%)[b]	*Z*/*E*[c]
1	DMI	75	>95:5
2	DMF	65	>95:5
3	Acetone	63	>95:5
4	MeOH	55	>95:5
5	DMSO	39	>95:5
6	CH_3CN	24	>95:5

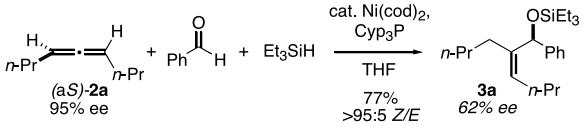
[a] Standard procedure: to a solution of $Ni(cod)_2$ (20 mol%), Cyp_3P (20 mol%), benzaldehyde (300 mol%), triethylsilane (300 mol%), and the cosolvent indicated (50 μL) in THF at ambient room temperature was added a THF solution of (±)-4,5-nonadiene (100 mol%, 0.1 mmol) over 4.5 h. The mixture was stirred an additional 8 h and filtered through SiO_2.
[b] NMR yield versus an internal standard.
[c] Determined by ^1H NMR analysis of unpurified reaction mixture.

at the sp vs an sp^2 carbon) was >95:5, and only the *Z* allylic alcohol was detected.[13] Among all the organophosphine ligands studied, tricyclopentylphosphine (Cyp_3P) was found to be the most effective (entry 6).

With the hope of enhancing the chemical yield of the reaction, we conducted a brief survey of cosolvents (Table 2). With the exception of 1,3-dimethylimidazolin-2-one (DMI, entry 1), the presence of each of these diminished the yield of allylic alcohol **3a**. As the improvement in yield was negligible, we did not included DMI in future experiments, instead utilizing THF as the exclusive solvent.

We then turned our attention to the issue of chirality transfer, and for these studies we prepared enantiomerically enriched (a*S*)-4,5-nonadiene ((a*S*)-**2a**, Scheme 1). Addition of a lithium acetylide derived from 1-pentyne to butyraldehyde provided racemic 5-pentyn-4-ol (**4**) in near quantitative yield, and lipase-catalyzed resolution, using vinylacetate as the acylating agent, afforded enantiomerically enriched (*S*)-**4** (95% ee). Finally, following the procedure developed by Myers, this propargyl alcohol was transformed to the desired (a*S*)-allene ((a*S*)-**2a**, 95% ee) in 60% yield.

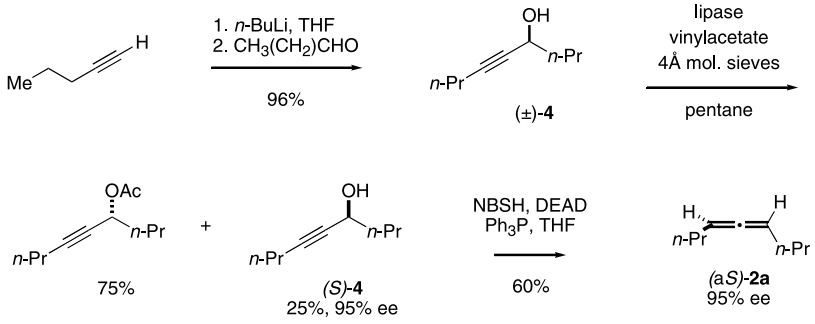
As noted above, the conditions that we found to be the highest yielding employed Cyp_3P as a substoichiometric additive. Similarly, in the analogous experiment using enantiomerically enriched **2a**, the product **3a** was obtained in 77% and with >95:5 *Z*/*E* selectivity (Eq. 2). However, while the starting allene had an ee of 95%, the ee of the product in the coupling reaction was substantially lower (62%). We thus, conducted another evaluation of supporting ligands in this transformation with the aim of finding one that was not only efficacious, but also transferred the axial chirality of the allene to the product to a greater extent than Cyp_3P did.



(2)

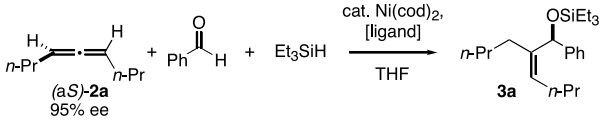
In the past several years, carbenes derived from imidazole have been utilized with great success in a wide range of transition metal catalyzed reactions,[14] and nickel complexes supported by these *N*-heterocyclic carbene (NHC) ligands catalyze aldehyde addition reactions of both alkynes[15] and 1,3-dienes.[16] As shown in Table 3, this family of ligands provided a solution to the erosion of enantiomeric purity that we observed using Cyp_3P.

The method of generating the catalytically competent ligand (the 'free carbene') from an imidazolium salt precursor had significant effects on both yield and the degree of chirality transfer (entries 1–4). In all cases in which the free carbene was generated in situ (entries 2–4), either the yield or ee of the product was lower than that obtained with Cyp_3P (Eq. 2). However, using of the free carbene *i*Pr itself afforded the product in near identical yield as Cyp_3P and



Scheme 1.

Table 3. Evaluation of NHC ligands[a]



Entry	[Ligand]	Yield **3a** (%)[b]	ee (%)
1	*i*Pr(**1**)	78	95
2	*i*PrHCl, Cs_2CO_3	65	23
3	*i*PrHCl, KO*t*Bu	71	95
4	S*i*PrHBF$_4$, KO*t*Bu	36	95
5[c]	*i*Pr(**1**)	88	95
6[c]	*i*Pr(**1**)	80[d]	95

[a] See Section 7 for details.
[b] NMR yield versus an internal standard. In all cases, the *Z*/*E* selectivity was >95:5 (^{1}H NMR of unpurified reaction mixture).
[c] Allene **2a** was added at −78 °C, and the mixture was allowed to warm to ambient room temperature.
[d] Isolated yield of **3a**.

with complete transfer of chirality, giving product of 95% ee.

Slow addition of the allene to the other components of the reaction in THF at ambient room temperature was used during the early stages of development of this transformation in order to minimize side reactions involving allene–allene coupling. We later found that these byproducts were suppressed by adding the allene to the reaction mixture at reduced temperature (−78 °C). The need for slow addition was thus obviated, and this modification also resulted in a further increased yield (entries 5–6).

It should be noted that with the use of an NHC ligand, homoallylic products arising from reaction of the aldehyde at the sp^2 carbon of the allene could be detected in the unpurified reaction mixtures (^{1}H NMR). (When Cyp_3P was employed, only the Et_3Si ether of an allylic alcohol (**3a**) was detectable.) In the case at hand, the ratio of the allylic product to the sum of all homoallylic products was nevertheless still rather high (94:6). The latter were removed by straightforward column chromatography (SiO_2), and the yield of the allylic product (**3a**) is reported in each case in Table 3.

Mosher ester analysis of the product was accomplished by removing the Et_3Si group (TBAF/THF) from racemic **3a** and esterifying with the *R* enantiomer of the Mosher acid, and this sequence was repeated with 95% ee product (Scheme 2). ^{1}H NMR analysis of both products indicated that the vinylic proton of the major diastereomer of the ester formed using the enantiomerically enriched material was upfield (5.45 ppm) relative to that of the minor diastereomer (5.51 ppm). These results suggested that the configuration of the product of the nickel-catalyzed reaction was *R*.

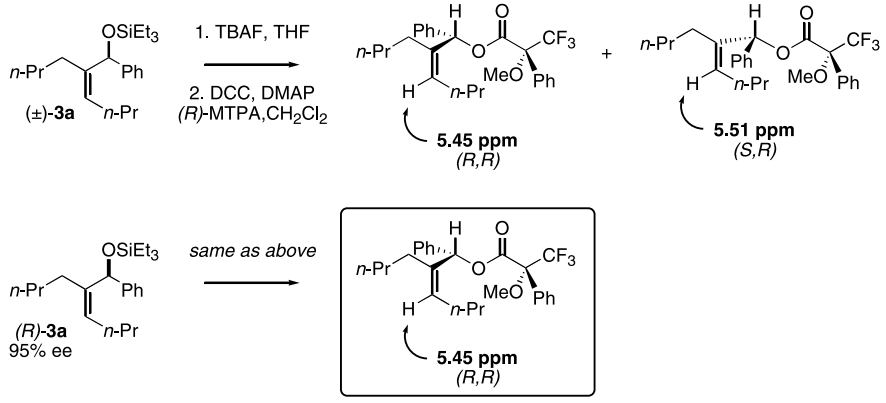
3. Reaction scope

With reaction conditions in hand that provided a good chemical yield of stereochemically pure material in the multicomponent coupling reaction, the scope of this novel transformation was examined (Table 4). In all cases examined, the degree of chirality transfer was 100%, and the *Z*/*E* selectivity was uniformly >95:5.

A methyl group para to the carbonyl of the aldehyde had little effect on both the allylic:homoallylic selectivity and the *Z*/*E* selectivity (entries 1–2), whereas an ortho methyl substituent resulted in slightly diminished reaction yield (70%) and a slight increase in the amount of homoallylic products formed (90:10, entry 3).

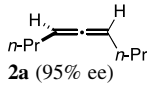
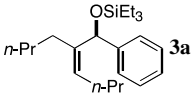
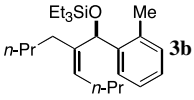
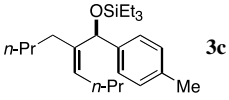
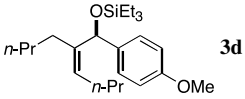
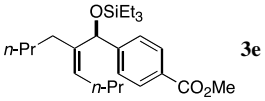
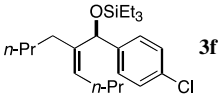
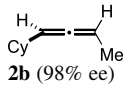
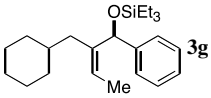
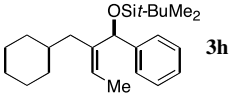
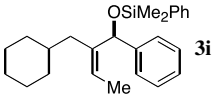
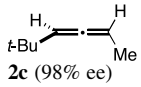
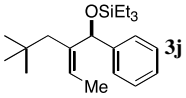
A noteworthy feature is the compatibility of these carbon–carbon bond-forming reactions with Lewis-basic ethers, esters, and aryl chlorides (entries 4–6). An electron-donating MeO group in the para position (entry 4) had little effect on the transformation, but an electron-withdrawing CO_2Me substituent reduced the chemical yield to 56% and the allylic:homoallylic selectivity to 90:10 (entry 5). In the case of a para Cl substituent, a small amount of **3a**, corresponding to reductive dechlorination of **3f**, could be detected by ^{1}H NMR analysis of the crude reaction mixture (**3f**:**3a** = 94:6), but this impurity was easily removed by SiO_2 chromatography.

We next, examined coupling reactions of enantiomerically enriched 1,3-allenes in which the two allene substituents were different, adding yet another selectivity variable in these reactions, site selectivity. In other words, two different allylic products are possible, depending upon which double bond of the allene reacts (entries 7–10).



Scheme 2. Mosher ester analysis of **3a**.

Table 4. Reaction scope[a]

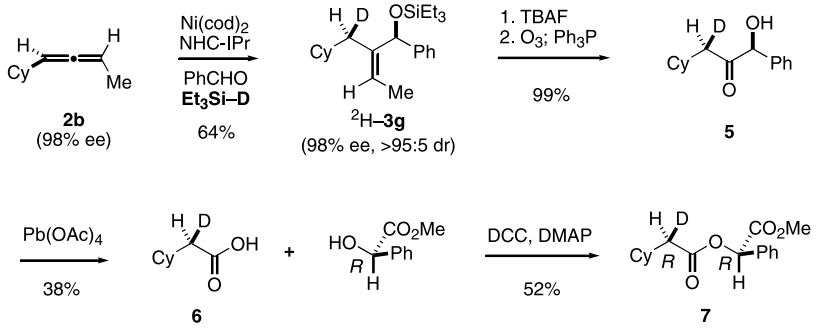
Entry	Allene	Product	Allylic: homoallylic[b,c]	Yield (allylic),[d] Z/E[c]	Site selectivity[c]	ee (%)[e]
1	 **2a** (95% ee)	 **3a**	94:6	80%, >95:5	na	95
2	**2a**	 **3b**	90:10	70%, >95:5	na	95
3	**2a**	 **3c**	95:5	74%, >95:5	na	95
4	**2a**	 **3d**	93:7	75%, >95:5	na	95
5	**2a**	 **3e**	90:10	56%, >95:5	na	95
6[f]	**2a**	 **3f**	90:10	66%, >95:5	na	95
7	 **2b** (98% ee)	 **3g**	93:7	76%, >95:5	>95:5	98
8	**2b**	 **3h**	90:10	68%, >95:5	>95:5	98
9	**2b**	 **3i**	93:7	65%, >95:5	>95:5	98
10	 **2c** (98% ee)	 **3j**	85:15	40%, >95:5	>95:5	98

[a] See Eq. 1. Standard conditions: to a solution of $Ni(cod)_2$ (20 mol%), **1** (40 mol%) in THF at −78 °C were added the allene (100 mol%, 0.5 mmol), aldehyde (300 mol%), and silane (300 mol%). The mixture was warmed to ambient room temperature over 6 h, stirred 12 h, and purified by chromatography (SiO_2). Absolute configuration determined by Mosher ester analysis. See Section 7.
[b] Ratio of allylic to the sum of all homoallylic products.
[c] Determined by ^1H NMR of unpurified reaction mixtures.
[d] Isolated yield of allylic alcohol shown.
[e] Determined by chiral HPLC.
[f] ^1H NMR of crude reaction mixture indicated a 94:6 ratio of **3f**:**3a** (reductive dechlorination).

(*S*)-1-cyclohexyl-1,2-butadiene (**2b**, 98% ee), prepared using a similar sequence to that illustrated in Scheme 2 for (*S*)-4,5-nonadiene, underwent multicomponent coupling in 76% yield with benzaldehyde under the catalytic reaction conditions used in the previous examples (entry 7). The ratio of allylic to homoallylic products was similarly high (93:7), as were both the *Z*/*E* selectivity and the enantiomeric purity of the product (**3g**, 98% ee). On the issue of site selectivity, a single allylic product was isolated, corresponding to exclusive reaction of the more hindered double bond of the allene.

These trends and high selectivity were preserved in analogous coupling reactions employing different organosilanes (entries 8 and 9). The reactions leading to allylic products **3h** and **3i** proceeded with excellent allylic:homoallylic selectivity, in good yield, and with high enantio-, *Z*/*E*-, and site selectivity. These results also demonstrate a degree of flexibility as to which silyl 'protective group' is incorporated into the product.

Finally, the multicomponent coupling of (*S*)-1-*tert*-butyl-1,2-butadiene, benzaldehyde, and Et_3SiH afforded **3j** in reduced yield and allylic:homoallylic selectivity, but with the same level of *Z*/*E*-, enantio-, and site selectivity as that observed in all other cases (entry 10).[17]



Scheme 3. Deuterium labeling experiment.

4. Deuterium labeling experiment

The results of a deuterium labeling experiment provided information critical to the development of mechanistic framework and stereochemical model for these transformations. We repeated a previous experiment (Table 4, entry 7), using Et_3SiD (97% D) in place of Et_3SiH (Scheme 3). Slightly lower allylic:homoallylic selectivity (89:11) was observed, but ^{2}H-**3g** had the same ee, *Z*/*E* ratio, and site selectivity as **3g**. Moreover, deuterium incorporation occurred at a single site and with >95:5 diastereoselectivity.

Mosher ester analysis confirmed that the sense of chirality transfer from the allene to the carbinol stereogenic center in the product was *R*, that is, unchanged by replacing Et_3SiH with Et_3SiD. The configuration of the deuterium labeled stereogenic center was assigned as *R* by the sequence shown in Scheme 3. The triethylsilyl group of labeled coupling product ^{2}H-**3g** was removed with tetrabutylammonium fluoride, and ozonolysis of the double bond afforded hydroxyketone **5** in near quantitative yield. Lead tetraacetate cleavage of this functional group pair provided 2-deuterio-2-cyclohexylacetic acid (**6**). Esterification of **6** with methyl (*R*)-mandelate (DCC, DMAP) yielded **7**, and comparison of the ^{1}H NMR spectra of this compound to those of the unlabeled corresponding ester allowed for assignment of the labeled stereogenic center as the *R* configuration.[18]

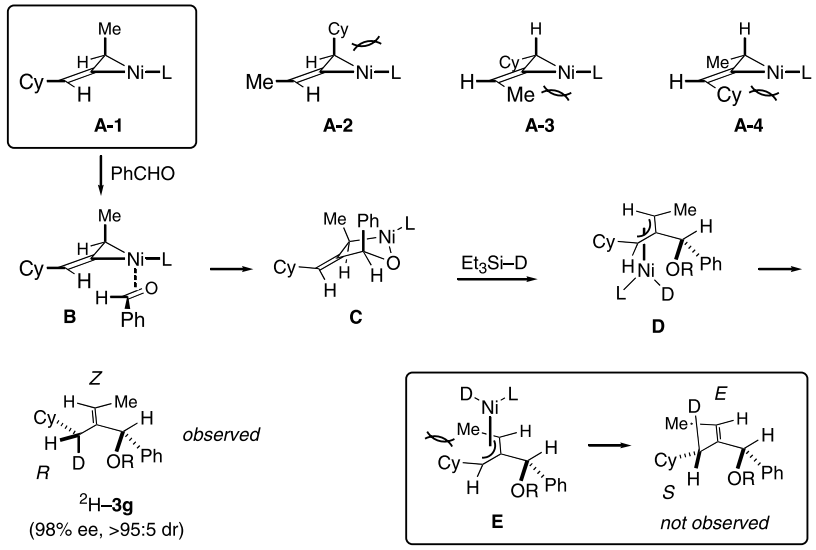
5. Discussion

5.1. Chirality transfer

As described above, the use of an imidazolinyl carbene ligand NHC-*i*Pr completely suppressed the erosion of enantiomeric purity observed with an organophosphine ligand, a case of a dependence of enantioselectivity upon the nature of an achiral ligand. Chirality transfer is commonly observed in intramolecular reactions of enantiomerically enriched allenes,[19] but the vast majority of intermolecular examples[20] involve allenylmetal additions.[7,8c] Moreover, only achiral, racemic, or 1:1 mixtures of diastereomeric allenes were used in all previously reported multicomponent coupling reactions.[6] Thus, the transfer of allene axial chirality in such processes is now documented for the first time in these investigations.

5.2. *Z*/*E* selectivity

Two aspects of the complete preference for the *Z* alkene geometry deserve further comment. In related reductive coupling reactions involving alkynes, *E*-allylic alcohols are



Scheme 4. Mechanistic proposal and stereochemical model.

formed exclusively (cis addition of H and RCHO across the triple bond).[2] Allenes and alkynes are thus, complementary to one another in this regard. Second, the *Z* geometry corresponds to attachment of the aldehyde to the more hindered face of the allene. In a similar vein, the site selectivity observed with allenes **2b** and **2c** (entries 7–10) suggests addition across the more hindered double bond.

5.3. Deuterium labelling

The results of the deuterium labeling experiment (Scheme 3) can be accounted for by the sequence of events shown in Scheme 4. Backbonding likely induces significant deformation from linearity of the allene, and of the 4 isomeric 1:1:1 complexes of Ni, NHC-*i*Pr (L), and allene **2b** (**A**-**1**, **A**-**2**, **A**-**3**, and **A**-**4**), only **A**-**1** places the large Ni–L complex on the less hindered allene face and less substituted double bond. The sense of induction may be explained by benzaldehyde coordination away from the methyl group with the Ph group placed between L and (cyclohexyl)-methylidene (**B**), reorganization to allow overlap between a C–Ni bond and π^*, and oxidative addition to give metallacyle **C**.

We believe that there is a direct link between the selectivity for the *Z* alkene geometry and the sense of induction of deuterium labeling. Sigma bond metathesis between **C** and Et_3SiD could afford η^3-allyl-Ni complex **D**. Reductive elimination with retention leads to the observed *Z* alkene and *R* configuration at the labeled carbon. Conversely, the alternative complex (**E**) gives the opposite sense of selectivity in both cases (*E* and *S*, respectively). Our explanation for the absence of this product is the severe 1,3-interaction between the Me and Cy groups present in **E**. Finally, the overall site selectivity avoids formation of the more congested alkene (Cy vs Me), and this bias appears to be operative in the transition state of reductive elimination from **D**.

Mori proposed a similar sequence of events in nickel-mediated carboxylations of allenes that afford α,β-unsaturated carboxylic acids.[9d,f] These products are analogous to what we observe in nickel-catalyzed couplings of allenes, aldehydes, and silanes, in that they are the result of C–C bond formation between the allene sp carbon and that of the electrophile (CO_2).

6. Conclusion

In summary, this enantioselective, three-component coupling occurs by way of a previously unobserved process in allene–aldehyde reactions and is promoted by a Ni–NHC complex that transfers the axial chirality of the allene to the product with very high fidelity. This catalyst also possesses the qualities necessary to induce a surprising sense and degree of *Z*/*E*- and site selectivity. The implementation of this single-step formation of synthetically useful, silyl-protected *Z* allylic alcohols in the synthesis of complex molecules is currently under investigation.

7. Experimental

7.1. General information

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Tetrahydrofuran was distilled from a blue solution of sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Triethylsilane, *tert*-butyl- dimethylsilane and dimethylphenylsilane were purchased from Aldrich Chemical Co. and were saturated with nitrogen before use. Benzaldehyde was purchased from Aldrich Chemical Co. distilled by bulb to bulb distillation and then saturated with nitrogen before storage under nitrogen. Other aromatic aldehydes were purchased from Aldrich Chemical Co. and were used without further purification. Bis(cyclooctadienyl)nickel(0) ($Ni(cod)_2$) and tricyclopentylphosphine were purchased from Strem Chemicals, Inc., stored under nitrogen atomosphere and used without further purification. 1,3-Bis-(2,6-di-isopropylphenyl)imidazol-2-ylidene (NHC-*i*Pr) was prepared according to literature procedure.[21] Triethylsilane-*d* was prepared according to literature procedure.[22] Cyclohexanecarboxaldehyde, methyl lithium, Amano lipase, vinylacetate, acetaldehyde, methyl-(*R*)-mandelate, cyclohexaneacetic acid and Mosher's acid were purchased from Aldrich Chemical Co. and used as received (unless otherwise noted). Carbontetrabromide, triphenylphosphine and 4-(dimethylamino)-pyridine were purchased from Alfa Aesar and used as received. *tert*-Butylacetylene and 1-pentyne were purchased from GFS and used as received. Diethylazodicarboxylate was purchased from Lancaster and used as received. Dicyclohexylcarbodiimide was purchased from Pierce and used as received.

Analytical thin-layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate ($KMnO_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz or Bruker 400 MHz spectrometer in $CDCl_3$ or C_6D_6, unless otherwise noted. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm) or residual benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrument Facility. Chiral GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. Chiral HPLC analysis was

performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD or OD-H columns. Specific rotations ($[\alpha]_D$) were measured on a Perkin-Elmer 241 polarimeter at 589 nm.

7.2. Preparation of 1,3-disubstituted allenes

7.2.1. (a*S*)-Buta-1,2-dienyl-cyclohexane (2b). This was prepared according to Myers' procedure.[26] Carbontetrabromide (73 g, 220 mmol) was dissolved in anhydrous dichloromethane (150 mL). The solution was cooled to 0 °C, triphenylphosphine (115 g, 440 mmol) was added. The mixture was stirred 30 min at 0 °C. Cyclohexanecarboxaldehyde (10 mL, 110 mmol) was added and the reaction mixture was slowly warmed to room temperature and stirred 12 h. The brown precipitate was removed by filtering the CH_2Cl_2 solution through silica gel and the silica gel was washed with hexane. Evaporation of the solvents gave an oil with white precipitate. The crude was diluted with hexane and filtered through silica gel to yield a colorless oil (2,2-dibromo-vinyl)-cyclohexane as a colorless oil (21.62 g, 74% yield). It was used without further purification. (2,2-Dibromo-vinyl)-cyclohexane (9.18 g, 34 mmol) was dissolved in anhydrous THF (40 mL) and was cooled to −78 °C. Methyllithium (55 mL, 88 mmol, 1.6 M in ether) was added to the solution over 5 min and the mixture was stirred 2.5 h at −78 °C. Acetaldehyde was added in one portion and the mixture was stirred 1.5 h and was warmed to room temperature. The reaction was quenched with water and extracted with diethylether (1× 80 mL), which was washed with water and dried with $MgSO_4$. Column chromatography afforded a yellow oil (+/−)-4-cyclohexyl-but-3-yn-2-ol (4.9 g, 94% yield). This racemic alcohol was subjected to lipase resolution.[23] In an oven-dried round bottom flask, (+/−)-4-cyclohexyl-but-3-yn-2-ol (2.28 g, 15 mmol) was dissolved in anhydrous pentane (50 mL) at room temperature. 4 Å molecular sieves (approximately half the volume of the solvent), Amano lipase AK from *Pseudomonas fluorescens* (2 g) followed by freshly distilled vinyl acetate (4 mL, 40 mmol) were added. The slurry was stirred 5 h at room temperature. NMR of the crude reaction mixture indicated that the ratio of acetate to alcohol was approximately 1:1. The mixture was stirred for 30 more minutes, filtered through Celite and washed with pentane. Column chromatography afforded (*S*)-4-cyclohexyl-but-3-yn-2-ol as a colorless oil (1.1 g, 99% yield based on 50% conversion) that was at least 98% ee according to Mosher's ester analysis. The absolute configuration was determined by Mosher's ester analysis.[24] The alcohol was consistent with the specific rotations of similar compounds prepared from the same method.[23]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.53 (m, 1H), 2.42–2.30 (m, 1H), 1.9–1.2 (m, 10H), 1.43 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 89.0, 82.3, 58.8, 32.8, 29.1, 26.0, 25.1; IR (NaCl, thin film): 3333, 2931, 2854, 2240, 1449, 1158, 1078, 897; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{10}H_{16}O$, 175.109; found, 175.109; $[\alpha]_D^{20}$ −23.0 (c 1.00, $CHCl_3$)

Mosher's ester analysis: (+/−)-4-cyclohexyl-but-3-yn-2-ol was converted into a pair of diastereomers of (*R*)-Mosher's esters (DCC, DMAP, (*R*)-Mosher's acid, CH_2Cl_2).[25] The methyl doublets (δ 1.50 and 1.56 ppm) of the two diastereomers were well resolved by ^{1}H NMR and were assigned according to the method of Mosher.[24]

The enantiomerically-enriched alcohol was then converted to (*R*)-Mosher's ester, and a doublet was observed at δ 1.56 ppm. Therefore, 4-cyclo-hexyl-but-3-yn-2-ol prepared from lipase resolution had an absolute configuration of (*S*).

Triphenylphosphine (5 g, 15 mmol) was dissolved in THF (20 mL). The solution was cooled in a MeOH/ice bath, and diethylazodicarboxylate (DEAD) (2.4 mL, 15 mmol) was added to the solution over 1 min. The solution was stirred 10 min below −10 °C. (*S*)-4-cyclohexyl-but-3-yn-2-ol (1.52 g, 10 mmol) in THF (10 mL) was added. THF (5 mL) was used to rinse the rest of the alcohol into the reaction mixture. The mixture was stirred 10 min, and *o*-nitrobenzenesulfonyl-hydrazine[27] (3.3 g, 15 mmol in 20 mL THF) was added. The mixture was kept below 0 °C for 2 h and was allowed to warm to room temperature and stirred 16 h. The reaction was cooled to 0 °C, diluted with pentane (200 mL) and washed 10 times with ice cold water to remove THF. Column chromatography in pentane afforded (a*S*)-buta-1,2-dienyl-cyclohexane as a colorless oil (0.95 g, 70% yield, 98% ee based on chiral GC analysis). The absolute configuration of the allene was determined[26] based on the absolute configuration of the alcohol and was consistent with Lowes-Brewster rule.[28] The spectral data are consistent with literature values.[29] ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.09 (m, 1H), 5.04 (m, 1H), 2.00–1.91 (m, 1H), 1.80–1.00 (m, 10H), 1.65 (dd, J=3.4, 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 203.7, 96.7, 86.5, 37.4, 33.3, 26.4, 26.3, 15.0; IR (NaCl, thin film): 2924, 2852, 1965, 1448, 960, 869, 711; HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{10}H_{16}$, 136.125; found, 136.125; $[\alpha]_D^{20}$ +76.7 (c 1.46, $CHCl_3$); Chiral GC analysis: (Chiraldex B-DA, 60 °C isotherm, 1.5 mL/min): t_R(a*S*)=21.1 min; t_R(a*R*)=22.6 min.

7.2.2. (a*S*)-5,5-Dimethyl-hexa-2,3-diene (2c). THF (80 mL) was cooled to −78 °C. *tert*-Butylacetylene (7.35 mL, 60 mmol) was added. MeLi (56 mL, 90 mmol, 1.6 M in diethylether) was added via a syringe pump over 10 min. The mixture was stirred 1 h at −78 °C. Acetaldehyde (6.7 mL, 120 mmol) was added. The mixture was stirred at −78 °C for one more hour and warmed to room temperature. The reaction was cooled to 0 °C and quenched with water. The cold mixture was diluted with diethylether (150 mL) and washed two times with water. The ether solution was dried by $MgSO_4$ and was filtered through silica gel. The silica gel was washed with diethyl ether. The NMR of the crude reaction mixture indicated 5,5-dimethyl-hex-3-yn-2-ol along with some cyclotrimer of acetaldehyde (pale yellow oil). (53.4 mmol alcohol based on NMR integration, 89% yield). The crude product was subjected to lipase resolution without further purification, using the same lipase resolution procedure as described above (lipase, 4 Å MS, vinylacetate, pentane, room temperature, 5.5 h. 88.5% isolated yield. >98% ee based on chiral GC analysis and Mosher's ester analysis). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.49 (q, J=6.5 Hz, 1H), 2.1 (br s, 1H), 1.39 (d, J=6.5 Hz, 3H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 92.9, 80.9, 68.1, 58.6, 31.2, 25.0; IR (NaCl, thin film): 3336,

2971, 2237, 1363, 1263, 1125, 1050, 973, 882; $[\alpha]_D^{20}$ −27.3 (*c* 1.06, $CHCl_3$).

Mosher's ester analysis: (+/−)-5,5-dimethyl-hex-3-yn-2-ol was converted into a pair of diastereomers of (*R*)-Mosher's esters (DCC, DMAP, (*R*)-Mosher's acid, CH_2Cl_2).[25] The methyl doublets (δ 1.48 and 1.54 ppm) and *t*-Bu singlets (δ 1.19 and 1.21 ppm) of the two diastereomers were well resolved by ^{1}H NMR and were assigned according to the method of Mosher.[24] The enantiomerically-enriched alcohol was converted to (*R*)-Mosher's ester. A doublet was observed at δ 1.54 ppm, and a singlet was observed at δ 1.19 ppm. Therefore, 5,5-dimethyl-hex-3-yn-2-ol prepared from lipase resolution had an absolute configuration of (*S*). Chiral GC analysis: (Chiraldex B-PH, 60 °C isotherm, 0.3 mL/min): $t_R(S)=69.0$ min; $t_R(R)=72.3$ min.

(*S*)-5,5-dimethyl-hex-3-yn-2-ol was converted to **2c** using the same method as described above for **2b**. After the removal of THF by an aqueous workup, the pentane solution was filtered through a pad of silica gel to remove most of the by-products. The pentane was removed by rotary evaporator at atmospheric pressure, and the last traces of pentane were removed by fractional distillation. Finally, the product was separated from the crude mixture by distilling under high vacuum at room temperature, collecting in a cooled flask, affording 60% of (a*S*)-5,5-dimethyl-hexa-2,3-diene as a colorless oil. The absolute configuration of the allene was assigned[26] based on the absolute configuration of the alcohol and was consistent with Lowe-Brewster rule.[28] ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.12 (quintet, $J=6.8$ Hz, 1H), 5.06 (dq, $J=3.3$, 6.42 Hz, 1H), 1.67 (dd, $J=3.3$, 6.9 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 202.1, 102.6, 87.4, 31.9, 30.4, 15.1; IR (NaCl, thin film): 2962, 1962, 1462, 1363, 1192, 873, 725; $[\alpha]_D^{20}$ +67.7 (*c* 1.24, $CHCl_3$) (consistent with similar compounds).[30]

7.2.3. (a*S*)-Nona-4,5-diene (2a). Prepared using the same method as **2b** and **2c** from (*S*)-non-5-yn-4-ol, which was prepared by lipase resolution using the procedure described above (60% yield from (*S*)-non-5-yn-4-ol, 95% ee, as a colorless oil). The absolute configuration was assigned by comparing the specific rotation of **2a** with the literature value[31] and is also consistent with the Lowes-Brewster rule.[28] ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.07 (m, 2H), 1.97 (m, 4H), 1.44 (sextet, $J=7.3$ Hz, 4H), 0.94 (t, $J=7.3$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 204.2, 90.8, 31.4, 22.7, 13.9; IR (NaCl, thin film): 2960, 2931, 1963, 1464, 879; $[\alpha]_D^{20}$ +64.0 (*c* 1.00, $CHCl_3$); $[\alpha]_D^{20}$ +84.7 (*c* 0.72, EtOH); lit.[31] $[\alpha]_D^{20}$ +80.0 (*c* 0.69, EtOH); Chiral GC analysis: (Chiraldex B-PH, 35 °C isotherm, 0.1 mL/min): t_R(a*R*)=74.7 min; t_R(a*S*)=81.2 min.

7.2.4. (+/−)-Deca-2,3-diene (2d). Prepared using the same method as **2b** and **2c** from (+/−)-dec-3-yn-2-ol. Isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.04 (m, 2H), 1.96 (m, 2H), 1.65 (dd, $J=5.2$, 10 Hz, 3H), 1.45–1.23 (m, 8H), 0.90 (t, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 204.9, 90.5, 85.2, 31.9, 29.3, 29.1, 28.9, 22.9, 14.8, 14.3; IR (NaCl, thin film): 2963, 2928, 2857, 1967, 1460; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{10}H_{18}$, 138.1403; found, 138.1406.

7.3. Nickel-catalyzed reductive couplings of allenes and aldehdyes

7.3.1. Standard procedure A. (0.1 mmol scale). A 7 mL vial and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 20 mol%) and the specified ligand were added to the vial, the vial was sealed with a septum, and the sealed vial was brought out of the glove box and connected to an argon line. An allene stock solution was prepared by dissolving the specified allene in THF to make a 0.06 M solution in an oven dried, nitrogen purged round bottom flask. The catalyst mixture was dissolved in 0.5 mL THF at room temperature under argon and stirred 10 min at room temperature. Triethylsilane (50 μL, 0.3 mmol, 300 mol%) was added in one portion. Benzaldehyde (32 μL, 0.3 mmol, 300 mol%) was added in one portion. Finally, 1.5 mL allene solution was added into the reaction mixture via a syringe pump over 4.5 h. Reaction was stirred at room temperature for another 8 h. THF and excess silane were removed under reduced pressure, and the crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic alcohol coupling product.

7.3.2. Standard procedure B. A 25 mL round bottom flask and a stir bar were oven-dried and brought into a glove box. $Ni(cod)_2$ (28 mg, 0.1 mmol, 20 mol%) and NHC-*i*Pr (78 mg, 0.2 mmol, 40 mol%) were added to the round bottom flask, the flask was sealed with a septum, and the sealed flask was brought out of the glove box and connected to an argon line. The catalyst mixture was dissolved in THF (7.5 mL) under argon and stirred 10 min at room temperature. The solution was cooled to −78 °C in a dry ice/acetone bath. After 10 min of cooling, triethylsilane (240 μL, 1.5 mmol, 300 mol%), *tert*-butyldimethylsilane (250 μL, 1.5 mmol, 300 mol%), or dimethylphenylsilane (233 μL, 1.5 mmol, 300 mol%), as specified below, was added in one portion. Next, the aldehyde (1.5 mmol, 300 mol%) was added in one portion. The mixture was stirred 5 min at −78 °C. The allene (0.5 mmol, 100 mol%) was added to the reaction mixture in one portion. The reaction was kept in the dry ice/acetone bath and the bath was allowed to warm to room temperature over 6 h. The reaction was stirred an additional 12 h at room temperature. ^{1}H NMR of an aliquot of the crude (after filtering through a plug of silica) indicated the allylic alcohol was the major coupling product along with minor impurities assigned as various homoallylic alcohols. The ratio of the allylic to homoallylic products was determined by the ^{1}H NMR integration of spectrum of the crude mixture (refer to Table 4 for the ratio). THF and excess silane were removed under reduced pressure and the crude mixture was diluted in hexane. Purification via flash chromatography on silica afforded the allylic alcohol coupling product.

7.3.3. (2-Butyl-1-phenyl-hex-2-enyloxy)-triethyl-silane (3a). The reaction of (a*S*)-nona-4,5-diene (**2a**) (82 μL, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and triethylsilane in THF following the standard procedure B described above afforded **3a** in 77% isolated yield as a colorless oil and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was determined by Mosher's ester analysis to be *R*. The

olefin geometry was determined to be *Z* by a NOE experiment (see below). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.16–7.40 (m, 5H), 5.76 (s, 1H), 5.24 (t, J=7.3 Hz, 1H), 2.27 (q, J=7.5 Hz, 2H), 2.02 (m, 1H), 1.74 (m, 1H), 1.51 (sextet, J=7.5 Hz, 2H), 1.14–1.34 (m, 4H), 1.01 (t, J=6.7 Hz, 3H), 0.97 (t, J=7.6 Hz, 9H), 0.81 (t, J=7.0 Hz, 3H), 0.64 (q, J=7.9 Hz), ^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.5, 141.9, 128.0, 126.5, 125.6, 125.4, 71. 3, 31.0, 30.4, 29.6, 23.6, 22.9, 14.34, 14.26, 7.11, 7.07; IR (NaCl, thin film): 2957, 2875, 1458, 1063, 742, 698; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{38}OSi$, 369.258; found, 369.259; $[\alpha]_D^{20}$ −75.2 (*c* 1.07, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the corresponding free alcohol, obtained by the deprotection of **3a** (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$=9.7 min; $t_R(R)$=10.8 min.

Mosher's ester analysis: (+/−)-**3a** was first converted into the free alcohol (TBAF, THF) and was then converted into a pair of diastereomers of (*R*)-Mosher's esters (DCC, DMAP, (*R*)-Mosher's acid, CH_2Cl_2).[25] The vinyl triplets (δ 5.45 and 5.51 ppm) of the two diastereomers were well resolved by ^{1}H NMR and were assigned according to the method of Mosher.[24] The enantiomerically-enriched **3a** was then converted to (*R*)-Mosher's ester using the same procedure.[25] The vinyl triplet was observed at δ 5.46 ppm. Therefore, **3a** had an absolute configuration of (*R*).

NOE DIFF experiment: pre-saturation of the carbinol proton of **3a** gave no NOE to the vinylic proton (δ 5.24 ppm), but 13% NOE was observed for the allylic protons indicated (δ 2.27 ppm). These results supported a *Z* olefin geometry.

7.3.4. (2-Butyl-1-*o*-tolyl-hex-2-enyloxy)-triethyl-silane (3b). The reaction of (a*S*)-nona-4,5-diene (**2a**) (82 μL, 0.5 mmol) and *o*-tolualdehyde (174 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and triethylsilane in THF following the standard procedure B described above afforded **3b** in 66% yield as a colorless oil and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **3a** and **3j** whose configurations were established by Mosher's ester analysis. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.71 (br d, J=7.6 Hz, 1H), 7.21 (bt, J=7.4 Hz, 1H), 7.13 (dt, J=1.4, 7.4 Hz, 1H), 7.04 (br d, J=7.4 Hz, 1H), 5.75 (s, 1H), 5.20 (t, J=6.6 Hz, 1H), 2.38–2.22 (dq, J=7.5, 14.8 Hz, 2H), 2.20 (s, 3H), 1.91 (ddt, J=1.1, 5.4, 10.32 Hz, 1H), 1.65 (ddt, J=1.0, 6.7, 9.8 Hz, 1H), 1.49 (sextet, J=6.9 Hz, 2H), 1.16 (m, 3H), 1.03 (t, J=5.6 Hz, 4H), 0.94 (t, J=8.0 Hz, 9H), 0.77 (t, J=7.1 Hz, 3H), 0.60 (q, J=7.5 Hz, 6H), ^{13}C NMR (100 MHz, $CDCl_3$, δ): 142.2, 139.1, 134.2, 129.8, 126.9, 126.7, 126.5, 125.6, 69.1, 31.7, 30.6, 30.5, 23.5, 22.8, 19.6, 14.4, 14.2, 7.1, 5.2; IR (NaCl, thin film): 2957, 2875, 1462, 1061, 1006, 744; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{40}OSi$, 383.274; found, 383.274; $[\alpha]_D^{20}$ −75.2 (*c* 1.25, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the corresponding free alcohol, obtained by the deprotection of **3b** (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$=11.4 min; $t_R(R)$=14.1 min.

7.3.5. (2-Butyl-1-*p*-tolyl-hex-2-enyloxy)-triethyl-silane (3c). The reaction of (a*S*)-nona-4,5-diene (**2a**) (82 μL, 0.5 mmol) and *p*-tolualdehyde (177 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and triethylsilane in THF following the standard procedure B described above afforded **3c** in 74% yield as a colorless oil and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **3a** and **3j** whose configuration were established by Mosher's ester analysis. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.24 (d, J=7.9 Hz, 2H), 7.11 (d, J=7.6 Hz, 2H), 5.74 (s, 1H), 5.22 (t, J=7.0 Hz, 1H), 2.34 (s, 3H), 2.27 (q, J=7.3 Hz, 2H), 2.03 (m, 1H), 1.74 (m, 1H), 1.50 (sextet, J=7.3 Hz, 2H), 1.38–1.18 (m, 4H), 1.00 (t, J=7.3 Hz, 3H), 0.97 (t, J=7.9 Hz, 9H), 0.82 (t, J=7.0 Hz, 3H), 0.63 (q, J=7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 142.0, 141.5, 136.0, 128.7, 125.6, 125.1, 71.2, 31.0, 30.3, 29.6, 23.6, 22.9, 21.3, 14.33, 14.28, 7.1, 5.1; IR (NaCl, thin film): 2957, 2875, 1458, 1073, 1006, 741; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{40}OSi$, 383.274; found, 383.275; $[\alpha]_D^{20}$ −83.8 (*c* 1.05, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the corresponding free alcohol, obtained by the deprotection of **3c** (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 100:0, 1.5 mL/min): $t_R(R)$=37.7 min; $t_R(S)$=49.1 min.

7.3.6. 2-Butyl-1-(4-methoxy-phenyl)-hex-2-enyloxy]-triethyl-silane (3d). The reaction of (a*S*)-nona-4,5-diene (**2a**) (82 μL, 0.5 mmol) and *p*-anisaldehyde (183 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and triethylsilane in THF following the standard procedure B described above afforded **3d** in 75% yield as a colorless oil and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **3a** and **3j** whose configuration were established by Mosher's ester analysis. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.28 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.4 Hz, 2H), 5.73 (s, 1H), 5.23 (t, J=7.2 Hz, 1H), 3.82 (s, 3H), 2.26 (q, J=7.6 Hz, 2H), 2.05 (m, 1H), 1.76 (m, 1H), 1.50 (sextet, J=7.2 Hz, 2H), 1.40–1.15 (m, 4H), 1.01 (t, J=7.2 Hz, 3H), 0.98 (t, J=8.0 Hz, 9H), 0.84 (t, J=7.0, 3H), 0.64 (q, J=7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 158.3, 142.1, 136.7, 126.7, 125.1, 113.4, 71.0, 55.4, 31.0, 30.3, 29.6, 23.6, 22.9, 14.33, 14.28, 7.1, 5.1; IR (NaCl, thin film): 2956, 2875, 1510, 1464, 1246, 1071, 741; $[\alpha]_D^{20}$ −67.5 (*c* 1.14, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the corresponding free alcohol, obtained by the deprotection of **3d** (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(R)$=14.3 min; $t_R(S)$=17.0 min.

7.3.7. 4-(2-Butyl-1-triethylsilanyloxy-hex-2-enyl)-benzoic acid methyl ester (3e). The reaction of (a*S*)-nona-4,5-diene (**2a**) (82 μL, 0.5 mmol) and methyl 4-formyl-benzoate (246 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and triethylsilane in THF following the standard procedure B described above afforded **3e** in 56% yield (co-eluted with a small amount of homoallylic alcohol minor products) as a colorless oil and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **3a** and **3j** whose configuration were established by Mosher's ester analysis. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.98 (d, J=7.5 Hz, 2H), 7.43 (d, J=8.0 Hz, 2H), 5.79 (s, 1H), 5.26 (t, J=7.0 Hz, 1H), 3.90 (s, 3H), 2.28 (q, J=7.1 Hz, 2H), 1.95 (m, 1H), 1.72 (m, 1H), 1.55 (sextet, J=7.0 Hz, 2H), 1.30–1.10 (m, 4H), 1.01 (t, J=7.0 Hz, 3H), 0.96 (t, J=7.6 Hz, 9H), 0.79 (t, J=7.3 Hz, 3H), 0.63 (q, J=7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$,

δ): 167.4, 150.1, 141.3, 129.4, 128.5, 126.1, 125.6, 71.2, 52.2, 31.0, 30.4, 29.6, 23.5, 22.8, 14.3, 14.2, 7.06, 5.01; IR (NaCl, thin film): 2956, 1727, 1277, 1075, 1018, 743; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{24}H_{40}O_3Si$, 427.264; found, 427.266; $[\alpha]_D^{20}$ −108.6 (*c* 1.28, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the corresponding free alcohol, obtained by the deprotection of **3e** (TBAF, THF): (Chiralcel OD, hexanes: 2-propanol, 95:5, 1.0 mL/min): $t_R(R)=7.5$ min; $t_R(S)=19.7$ min.

7.3.8. [2-Butyl-1-(4-chloro-phenyl)-hex-2-enyloxy]-triethyl-silane (3f). The reaction of (a*S*)-nona-4,5-diene (**2a**) (82 μL, 0.5 mmol) and *p*-chlorobenzaldehyde solution (211 μL aldehyde, 1.5 mmol in 1 mL THF) with $Ni(cod)_2$, NHC-*i*Pr and triethylsilane in THF following the standard procedure B described above yielded **3f** in 65% yield and 1% of dechlorinated product, that is, **3a** (total 66% isolated yield as a colorless oil, ratio of **3f**:**3a** in crude NMR is 94:6) and 95% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **3a** and **3j** whose configuration were established by Mosher's ester analysis. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.4–7.2 (m, 4H), 5.73 (s, 1H), 5.26 (t, $J=7.0$ Hz, 1H), 2.27 (q, $J=7.3$ Hz, 2H), 2.00 (m, 1H), 1.72 (m, 1H), 1.51 (sextet, $J=7.4$ Hz, 2H), 1.40–1.10 (m, 4H), 1.02 (t, $J=7.3$ Hz, 3H), 0.97 (t, $J=7.8$ Hz, 9H), 0.83 (t, $J=7.3$ Hz, 3H), 0.64 (q, $J=8.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 143.2, 141.5, 132.2, 128.1, 127.1, 125.8, 70.9, 31.0, 30.4, 29.6, 23.6, 22.9, 14.3, 14.2, 7.1, 5.1; IR (NaCl, thin film): 2957, 1488, 1074, 1014, 726; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{37}OClSi$, 403.219; found, 403.220; $[\alpha]_D^{20}$ −88.9 (*c* 1.17, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the corresponding free alcohol, obtained by the deprotection of **3f** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)=7.4$ min; $t_R(R)=8.6$ min.

7.3.9. (2-Cyclohexylmethyl-1-phenyl-but-2-enyloxy)-triethyl-silane (3g). The reaction of **2b** (68 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and triethylsilane in THF following the standard procedure B described above afforded **3g** in 76% isolated yield as a colorless oil and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **3a** and **3j** whose configuration were established by Mosher's ester analysis. The olefin geometry was determined to be *Z* by a NOE experiment (see below). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.35 (d, $J=7.6$ Hz, 2H), 7.29 (t, $J=7.3$ Hz, 2H), 7.20 (t, $J=7.3$ Hz, 1H), 5.79 (s, 1H), 5.30 (q, $J=7.0$ Hz, 1H), 1.88 (d, $J=6.7$ Hz, 3H), 1.80 (dd, $J=6.5$, 14.5 Hz, 1H), 1.68 (dd, $J=7.0$, 14.5 Hz), 1.64–1.54 (m, 6H), 1.28–1.18 (m, 1H), 1.12–1.00 (m, 3H), 0.97 (t, $J=7.9$ Hz, 9H), 0.76–0.58 (m, 1H), 0.64 (q, $J=7.9$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.6, 140.8, 128.0, 126.5, 125.6, 120.4, 70.9, 39.2, 36.1, 33.8, 33.5, 27.0, 26.7, 13.9, 7.1, 5.1; IR (NaCl, thin film): 2954, 2921, 1449, 1091, 1064, 863, 737; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{38}OSi$, 381.258; found, 381.259; $[\alpha]_D^{20}$ −58.0 (*c* 1.12, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the corresponding free alcohol, obtained by the deprotection of **3g** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)=11.3$ min; $t_R(R)=17.4$ min.

NOE DIFF experiment: pre-saturation of the carbinol proton (δ 5.79 ppm) of **3g** gave no NOE to the vinylic proton (δ 5.30 ppm). A 10.7% NOE to the methyl group, however, was observed. Similarly, pre-saturation of the methyl protons (δ 1.88 ppm) did not show any NOE to the cyclohexyl protons. A 4.5% NOE to the carbinol proton (δ 5.79 ppm), however, was observed.

7.3.10. *tert*-Butyl-(2-cyclohexylmethyl-1-phenyl-but-2-enyloxy)-dimethyl-silane (3h). The reaction of **2b** (68 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and *tert*-butyldimethyl-silane in THF following the standard procedure B described above afforded **3h** in 68% isolated yield as a colorless oil and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **3a** and **3j** whose configuration were established by Mosher's ester analysis. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40–7.10 (m, 5H), 5.80 (s, 1H), 5.31 (q, $J=7.0$ Hz, 1H), 1.88 (d, $J=7.0$ Hz, 3H), 1.77 (dd, $J=7.1$, 14.8 Hz, 1H), 1.66 (dd, $J=7.0$, 14.6 Hz, 1H), 1.57 (m, 6H), 1.30–0.50 (m, 5H), 0.96 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.5, 140.5, 127.9, 126.5, 125.6, 120.5, 71.1, 39.1, 35.9, 33.8, 33.5, 26.9, 26.6, 26.2, 18.6, 13.8, −4.6, −4.8; IR (NaCl, thin film): 2926, 2854, 1449, 1252, 1090, 1064, 876, 835, 775, 698; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{38}OSi$, 381.258; found, 381.260; $[\alpha]_D^{20}$ −55.9 (*c* 1.11, $CHCl_3$); Chiral HPLC analysis: analysis was performed **3h** without the deprotection of the silane protected alcohol: (Chiralcel OD-H, hexanes: 2-propanol, 100:0, 0.8 mL/min): $t_R(R)=4.1$ min; $t_R(S)=4.4$ min.

7.3.11. (2-Cyclohexylmethyl-1-phenyl-but-2-enyloxy)-dimethyl-phenyl-silane (3i). The reaction of **2b** (68 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and dimethylphenylsilane in THF following the standard procedure B described above afforded **3i** in 65% isolated yield as a colorless oil and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was assigned as *R* in analogy to **3a** and **3j** whose configuration were established by Mosher's ester analysis. ^{1}H NMR (500 MHz, C_6D_6, δ): 7.66–7.61 (m, 2H), 7.49 (d, $J=7.6$ Hz, 2H), 7.24–7.18 (m, 5H), 7.09 (t, $J=7.3$ Hz, 1H), 5.89 (s, 1H), 5.25 (q, $J=6.7$ Hz, 1H), 2.02 (dd, $J=7.0$, 14.7 Hz, 1H), 1.93 (dd, $J=7.0$, 14.7 Hz, 1H), 1.74–1.58 (m, 5H), 1.56 (d, $J=7.0$ Hz, 3H), 1.35 (m, 1H), 1.10 (m, 3H), 0.82–0.60 (m, 2H), 1.57 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.0, 139.9, 138.2, 133.8, 129.7, 127.99, 127.96, 126.6, 125.6, 121.1, 71.4, 39.1, 36.1, 33.8, 33.5, 26.9, 26.6, 13.6, −0.9, −1.0; IR (NaCl, thin film): 2921, 2850, 1449, 1428, 1251, 1118, 1088, 1057, 881, 829, 785, 737, 698; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{34}OSi$, 401.227; found, 401.227; $[\alpha]_D^{20}$ −19.0 (*c* 1.00, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the corresponding free alcohol, obtained by the deprotection of **3i** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)=11.3$ min; $t_R(R)=17.4$ min.

7.3.12. Triethyl-(2-ethylidene-4,4-dimethyl-1-phenyl-pentyloxy)-silane (3j). The reaction of **2c** (55 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and triethylsilane in THF following the

standard procedure B described above afforded **3j** in 40% isolated yield as a colorless oil (co-eluted with a homoallylic alcohol minor product) and 98% ee as determined by chiral HPLC. The absolute configuration of the stereocenter was determined by Mosher's ester analysis to be *R*. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.34 (d, J=7.6 Hz, 2H), 7.29 (t, J=7.3 Hz, 2H), 7.20 (t, J=7.3 Hz, 1H), 5.72 (s, 1H), 5.46 (q, J=7.0 Hz, 1H), 1.91 (d, J=7.0 Hz, 3H), 1.86 (d, J=14.6 Hz, 1H), 1.77 (d, J=14.6 Hz, 1H), 0.95 (t, J=7.9 Hz, 9H), 0.80 (s, 9H), 0.61 (qd, J=2.4, 7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.7, 140.5, 127.8, 126.4, 125.9, 122.9, 71.7, 43.3, 30.7, 22.7, 14.0, 6.9, 4.9; IR (NaCl, thin film): 2954, 1463, 1091, 1065, 1006, 742; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{36}OSi$, 355.2428; found, 355.2427; $[\alpha]_D^{20}$ −29.8 (*c* 1.14, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the corresponding free alcohol, obtained by the deprotection of **3j** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$=10.4 min; $t_R(R)$=13.3 min.

Mosher's ester analysis: (+/−)-**3j** was first converted into the free alcohol (TBAF, THF) and then into a pair of diastereomers of (*R*)-Mosher's esters (DCC, DMAP, (*R*)-Mosher's acid, CH_2Cl_2).[25] The vinylic quartets (δ 5.63 and 5.70 ppm) and the *t*-Bu singlets (δ 0.76 and 0.80 ppm) of the two diastereomers were well resolved by ^{1}H NMR and were assigned according to the method of Mosher.[24] The enantiomerically-enriched **3j** was then converted to (*R*)-Mosher's ester using the same procedure.[25] The vinylic quartet was observed at δ 5.64 ppm, and the *t*-Bu singlet was observed at δ 0.75 ppm. Therefore, **3a** had an absolute configuration of (*R*).

7.3.13. (+/−)-Triethyl-(2-ethylidene-1-phenyl-nonyloxy)-silane (3k) and (+/−)-triethyl-(2-ethyl-1-phenyl-non-2-enyloxy)-silane (3l). The reaction of **2d** (13.8 mg, 0.1 mmol) and benzaldehyde (32 μL, 0.3 mmol) with $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 20 mol%), NHC-*i*Pr (16 mg, 0.04 mmol, 40 mol%) and triethylsilane (50 μL, 0.3 mmol, 300 mol%) in THF (1.5 ml) following standard procedure B described above afforded **3k** and **3l** as a colorless oil in 1:1 ratio in 73% yield as determined by NMR versus an internal standard. **3k**: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.35 (d, J=6.9 Hz, 2H), 7.29 (t, J=7.6 Hz, 2H), 7.20 (t, J=7.3 Hz, 1H), 5.79 (s, 1H), 5.34 (q, J=7.0 Hz, 1H), 1.99 (m, 1H), 1.86 (d, J=7.0 Hz, 1H), 1.73 (m, 1H), 1.36–1.10 (m, 10H), 0.97 (t, J=8.2, 9H), 0.86 (t, J=7.0 Hz, 3H), 0.63 (q, J=7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.6, 143.1, 128.0, 126.5, 125.6, 118.9, 70.7, 32.1, 30.0, 29.8, 29.5, 28.7, 22.9, 14.4, 13.8, 7.1, 5.1. **3l**: ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.36 (d, J=7.0 Hz, 2H), 7.29 (t, J=7.3 Hz, 2H), 7.20 (t, J=7.0 Hz, 1H), 5.78 (s, 1H), 5.23 (t, J=7.0 Hz, 1H), 2.29 (m, 2H), 2.10 (sextet, J=7.6 Hz, 1H), 1.73 (sextet, J=7.6 Hz, 1H), 1.52–1.28 (m, 8H), 0.96 (t, J=8.2 Hz, 9H), 0.92 (t, J=7.0 Hz, 3H), 0.87 (t, J=7.3 Hz, 3H), 0.63 (q, J=7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.6, 143.1, 128.0, 126.5, 125.7, 124.7, 71.3, 32.1, 30.5, 29.6, 28.3, 22.9, 22.3, 14.4, 12.8, 7.1, 5.1.

7.4. Deuterium labeling experiment

^{2}H-**3g** was converted to a mandelic acid derivative **7** to determine the absolute configuration of the deuterated stereocenter using ^{1}H NMR by Parker's method.[32] The same mandelic acid derivative was also prepared by Fleming[33] and was also analyzed by the method of Parker.[32]

7.4.1. (2-Cyclohexyl-acetoxy)-phenylacetic acid methyl ester (^{1}H-7). Cyclohexylacetic acid (31.3 mg, 0.22 mmol), methyl-(*R*)-mandelate (33.2 mg, 0.2 mmol), dicyclohexylcarbodiimide (61.9 mg, 0.3 mmol) and 4-(dimethylamino)-pyridine (2.4 mg, 0.02 mmol) were mixed together and dissolved in anhydrous CH_2Cl_2 (2 mL). The mixture was stirred 6 h at room temperature. The CH_2Cl_2 solution was filtered through a plug of silica, the silica was washed with CH_2Cl_2. The filtrate was concentrated and column chromatography afforded ^{1}H-**7** as a colorless oil (45.1 mg, 78% yield). ^{1}H NMR (400 MHz, C_6D_6, δ): 7.46 (d, J=7.2 Hz, 2H), 7.10–7.00 (m, 3H), 6.09 (s, 1H), 3.18 (s, 3H), 2.22 (dd, J=7.1, 14.9 Hz, 1H), 2.12 (dd, J=7.1, 14.9 Hz, 1H), 1.86 (m, 1H), 1.73 (m, 2H), 1.60–1.40 (m, 3H), 1.22–1.10 (m, 2H), 1.10–0.90 (m, 1H), 0.90–0.75 (m, 2H); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.50–7.35 (m, 5H), 5.93 (s, 1H), 3.73 (s, 3H), 2.37 (dd, J=7.0, 15.0 Hz, 1H), 2.31 (dd, J=7.0, 14.9 Hz, 1H), 1.92–1.61 (m, 6H), 1.36–0.60 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 172.6, 169.6, 134.1, 129.4, 128.9, 127.7, 74.4, 52.7, 41.9, 35.0, 33.1, 26.3, 26.2; IR (NaCl, thin film): 2925, 2852, 1760, 1743, 1450, 1216, 1159, 1114, 1044, 734; $[\alpha]_D^{20}$ −90.3 (*c* 1.03, $CHCl_3$).

7.4.2. (2-Cyclohexylmethyl-2-deuterio-1-phenyl-but-2-enyloxy)-triethylsilane (^{2}H-3g). The reaction of **2b** (68 mg, 0.5 mmol) and benzaldehyde (152 μL, 1.5 mmol) with $Ni(cod)_2$, NHC-*i*Pr and triethylsilane-*d* (239 μL, 1.5 mmol) in THF, following the general procedure described above afforded ^{2}H-**3g** as a colorless oil (111 mg, 64% yield) in 98% ee as determined by chiral HPLC and > 95:5 dr as determined by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.35 (d, J=8.0 Hz, 2H), 7.28 (t, J=7.5 Hz, 2H), 7.19 (t, J=7.5 Hz, 1H), 5.78 (s, 1H), 5.28 (q, J=6.9 Hz, 1H), 1.87 (d, J=7.0 Hz, 3H), 1.76 (br d, J=6.6 Hz, 1H), 1.62–1.52 (m, 6H), 1.26–1.16 (m, 1H), 1.12–1.00 (m, 3H), 0.95 (t, J=7.9 Hz, 9H), 0.76–0.58 (m, 1H), 0.62 (q, J=7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 144.6, 140.7, 127.9, 126.5, 125.6, 120.4, 70.9, 38.8 (t, J=19.5 Hz), 36.0, 33.8, 33.5, 26.9, 26.6, 13.9, 7.1, 5.1; IR (NaCl, thin film): 2920, 1448, 1090, 1064, 731; HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{37}DOSi$, 382.265; found, 382.264; $[\alpha]_D^{20}$ −57.8 (*c* 1.02, $CHCl_3$); Chiral HPLC analysis: analysis was performed on the deprotected ^{2}H-**3g** (TBAF, THF): (Chiralcel OD-H, hexanes: 2-propanol, 99:1, 1.0 mL/min): $t_R(S)$=11.1 min; $t_R(R)$=17.3 min.

7.4.3. 3-Cyclohexyl-3-deuterio-1-hydroxy-1-phenyl-propan-2-one (5). ^{2}H-**3g** (96 mg, 0.27 mmol) was stirred 30 min in TBAF (1 mL, 0.5 mmol, 0.5 M in THF). The mixture was diluted in diethylether and washed with water. The ether solution was dried in $MgSO_4$, and the solvent was removed under reduced pressure. The crude was dissolved in CH_2CL_2 (5 mL) and was cooled to −78 °C. Ozone was bubbled through the solution for 20 min, and the solution turned blue. After purging with oxygen (2 min) triphenylphosphine (157 mg, 0.6 mmol in 5 mL CH_2Cl_2) was added in one portion at −78 °C, stirred 5 min, and warmed to room temperature. CH_2Cl_2 was removed under reduced

pressure. Column chromatography first with 20% CH_2Cl_2/hexane removed triphenylphosphine. A gradient of 10–20% EtOAc/Hexane afforded **5** as a colorless oil (62 mg, 99% yield) in >95:5 dr as determined by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40–7.27 (m, 5H), 5.04 (d, J=4.4 Hz, 1H), 4.43 (d, J=4.5 Hz, 1H), 2.14 (dt, J=2.0, 6.9 Hz, 1H), 1.90–0.55 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 209.3, 138.1, 129.1, 128.8, 127.7, 80.2, 45.2 (t, J=19.0 Hz), 34.0, 33.2, 26.2, 26.1, 26.0; IR (NaCl, thin film): 3458, 2923, 2851, 1711, 1450, 756, 670; $[\alpha]_D^{20}$ +231.7 (*c* 1.23, $CHCl_3$).

7.4.4. 2-Cyclohexy-(2*R*)-deuterio-acetic acid (6). A 7 mL glass vial was charged with **5** (60 mg, 0.26 mmol) and lead tetraacetate (115 mg, 0.26 mmol). The vial was purged with nitrogen, CH_2Cl_2 (2.5 mL, saturated with nitrogen) was added. The reaction mixture was stirred 8 h at room temperature, and the CH_2Cl_2 solution was passed through a dry silica gel column (purged with argon) and eluted with CH_2Cl_2 (saturated with argon) under argon to remove benzaldehyde and other low polarity byproducts. **6** and a minor impurity were eluted with 30% ethylacetate/hexane. Column chromatography with a gradient of 5–30% EtOAc/hexane afforded **6** as a colorless oil (14 mg, 38% yield). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 12.2–11.0 (br s, 1H), 2.21 (br d, J=6.5 Hz, 1H), 1.85–1.65 (m, 6H), 1.40–0.80 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 180.0, 41.8 (t, J=19.5 Hz), 34.8, 33.2, 33.1, 26.3, 26.2; IR (NaCl, thin film): 2925, 2852, 1705, 1414, 1295.

7.4.5. (2-Cyclohexyl-(2*R*)-2-deuterio-acetoxy)-phenyl-acetic acid methyl ester (7). Compound **6** (12 mg, 0.084 mmol), methyl-(*R*)-mandelate (21 mg, 0.09 mmol), dicyclohexylcarbodiimide (26 mg, 0.126 mmol), 4-(dimethyl)-aminopyridine (2 mg, 0.016 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and stirred 12 h at room temperature. The crude reaction mixture was filtered through a plug of silica, and the silica was washed with CH_2Cl_2. Column chromatography in 1–5% EtOAc/hexane afforded **7** as a colorless oil (15.6 mg, 52% yield). ^{1}H NMR indicated slight erosion of dr (>90:10) at the deuterated stereocenter as compared to ^{2}H-**3g** before conversion to **7**. The deuterated stereocenter was assigned to be of the *R* configuration, according to the method of Parker,[32] and the analysis was consistent with Fleming's result.[33] (refer to ^{1}H NMRs of ^{1}H-**7**, **7** and **8** for comparison of chemical shifts). ^{1}H NMR (400 MHz, C_6D_6, δ): 7.48 (d, J=6.9 Hz, 2H), 7.07 (t, J=6.0 Hz, 2H), 7.03 (t, J=7.4 Hz, 1H), 6.10 (s, 1H), 3.18 (s, 3H), 2.20 (dt, J=1.7, 6.9 Hz, 1H), 1.92–1.80 (m, 1H), 1.80–1.68 (m, 2H), 1.61–1.42 (m, 3H), 1.22–1.07 (m, 2H), 1.07–0.91 (m, 1H), 0.90–0.75 (m, 2H); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.50–7.40 (m, 2H), 7.44–7.37 (m, 3H), 5.93 (s, 1H), 3.73 (s, 3H), 2.35 (br d, J=6.9 Hz, 1H), 1.90–1.60 (m, 6H), 1.55–0.90 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 172.7, 169.6, 134.1, 129.4, 129.0, 127.8, 74.4, 52.8, 41.6 (t, J=20.0 Hz), 35.0, 33.11, 33.08, 26.3, 26.2; IR (NaCl, thin film): 2924, 2851, 1760, 1743, 1450, 1436, 1216, 1163; $[\alpha]_D^{20}$ +112.0 (*c* 1.25, $CHCl_3$)

7.4.6. (2*R*)-(2-Cyclohexyl-(2)-deuterio-acetoxy)-phenyl-acetic acid methyl ester and (2*S*)-(2-cyclohexyl-(2)-deuterio-acetoxy)-phenyl-acetic acid methyl ester (8). Prepared using the same method as **7** except that (±)-**2b** was used to give a 1:1 mixture of diastereomers of **8** as a colorless oil. ^{1}H NMR (400 MHz, C_6D_6, δ): 7.48 (d, J=7.2 Hz, 2H), 7.07 (t, J=7.0 Hz, 2H), 7.04 (t, J=7.1 Hz, 1H), 6.11 (s, 2H), 3.18 (s, 6H), 2.20 (dt, J=1.8, 6.9 Hz, 1H), 2.12 (dt, J=1.8, 7.1 Hz, 1H), 1.92–1.80 (m, 1H), 1.80–1.68 (m, 2H), 1.61–1.42 (m, 3H), 1.22–1.07 (m, 2H), 1.07–0.91 (m, 1H), 0.90–0.75 (m, 2H); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.50–7.40 (m, 2H), 7.44–7.37 (m, 3H), 5.93 (s, 1H), 3.73 (s, 3H), 2.35 (dt, J=1.9, 6.9 Hz, 1H), 2.30 (br d, J=1.8, 7.0 Hz, 1H), 1.90–1.60 (m, 6H), 1.55–0.90 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 172.7, 169.6, 134.1, 129.4, 129.0, 127.8, 74.4, 52.8, 41.6 (t, J=20.0 Hz), 35.0, 33.11, 33.08, 26.3, 26.2; IR (NaCl, thin film): 2923, 1850, 1760, 1742, 1215, 1163.

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Preparation of functionalized primary chiral amines and amides via an enantioselective three-component synthesis of propargylamines

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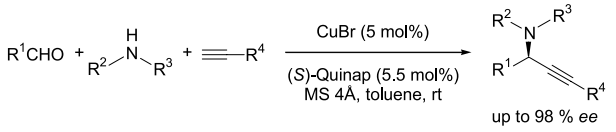
Abstract—A general preparation of functionalized primary chiral amines and amides from propargylamines has been developed. The chirality is established by an enantioselective three-component reaction of an aldehyde, a terminal alkyne and a secondary amine in the presence of copper(I) bromide/Quinap as the catalytic system leading to chiral propargylamines in high yields and enantioselectivities. Functionalization and reduction leads to various primary amines and amides.

1. Introduction

Multicomponent reactions play an important role in modern organic chemistry, since they exhibit generally a higher atom economy[1] and selectivity, as well as lower level of by-products compared to classical stepwise synthesis routes. Furthermore, in many cases multicomponent reactions are easy to perform leading to simpler experimental procedures[2] as well as lower costs, time and energy. The Strecker-reaction, developed in 1850, has been recognized as the first multi-component reaction.[3] This three-component coupling of an amine, a carbonyl compound and hydrogen cyanide giving α-aminonitriles establishes an important indirect route to α-amino acids. The amine group itself is one of the fundamental structures in organic chemistry. In particular, optically active primary amines, in which the nitrogen atom is attached to a stereogenic center play a crucial role as characteristic structural features in bioactive natural products and pharmaceutically important compounds. Several methods have been developed for their synthesis. One possibility, similar to the addition of carbanions to a carbonyl group, is the addition of organometallic reagents to the C=N double bonds of imines and imine derivatives. A new stereogenic center and a C–C– bond are formed during this addition reaction.[4] Recently, we[5] and others[6] have developed an asymmetric multicomponent one-pot synthesis[7] for the preparation of propargylamines by the addition of alkynes to in situ generated imminium ions from aldehydes and secondary amines in the presence of copper(I) bromide/Quinap[8] as the catalytic system (Scheme 1).



Scheme 1. Asymmetric three-component synthesis of propargylamines.

In this article, we wish to describe the use of our multicomponent asymmetric propargylamine synthesis for the preparation of enantiomerically enriched functionalized and primary amines.

2. Results and discussion

In a recent communication,[5a] we have described the asymmetric three-component synthesis of propargylamines. This method is superior to our previously reported method[9] using a two-step sequence consisting of the preparation of an enamine followed by the copper-catalyzed addition of a terminal alkyne in a separate step. Using the multicomponent protocol, it was possible to improve the enantioselectivity of the reaction and the use of aromatic aldehydes was now possible. From these aldehydes, no enamines could be obtained. Furthermore, the need to prepare and purify sensitive enamines is abandoned. This new multicomponent protocol allows the enantioselective

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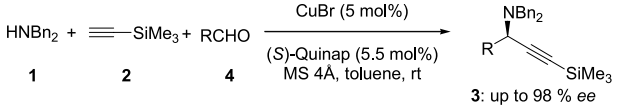
preparation of propargylamines by simple mixing of the commercially available starting materials (aldehyde, terminal alkyne and secondary amine) with the catalyst consisting of copper(I) bromide and Quinap at rt.

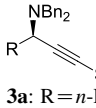
2.1. The preparation of enantiomerically enriched propargylamines

During our studies, we have observed that the use of dibenzylamine (**1**) leads to propargylamines with high enantiomeric purity. As the alkyne component, we have found trimethylsilylacetylene (**2**) to be the substrate of choice. It is also leading to products with exceptionally high enantiomeric excess. Furthermore, after removal of the trimethylsilyl group, it is possible to convert the propargylic amine to various substituted derivatives. A number of chiral propargylamines **3** have been prepared using different aldehydes **4** (Scheme 2 and Table 1).



Scheme 2. Asymmetric three-component synthesis of benzyl-protected propargylamines.

Table 1. Asymmetric three-component synthesis of propargylamines

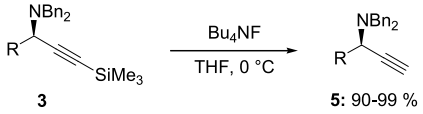
Entry	RCHO **4**	Product of type **3**	Yield (%)[a]	ee (%)[b]
				
1	**4a**: *n*-Pr	**3a**: R=*n*-Pr	98	90
2	**4b**: *n*-Bu	**3b**: R=*n*-Bu	75	90
3	**4c**: *n*-Pent	**3c**: R=*n*-Pent	97	88
4	**4d**: *s*-Pent	**3d**: R=*s*-Pent	97	98
5	**4e**: *c*-Hex	**3e**: R=*c*-Hex	92	97
6	**4f**: $C_6H_5(CH_2)_2$	**3f**: R=$C_6H_5(CH_2)_2$	76	88

[a] Isolated yield of analytically pure product.
[b] Enantiomeric excess determined by HPLC using Chiracel OD-H column (*n*-heptane/*i*-PrOH).

Propargylamines **3a–f** were obtained in good to excellent yields and uniformly high enantioselectivities. The sterically most hindered 2-ethylbutyraldehyde **4d** furnished the propargylamine **3d** with the highest selectivity (98% ee, see entry 4, Table 1). Similarly, the *c*-hexyl-substituted propargylamine **3e** was obtained with 97% ee (entry 5, Table 1).

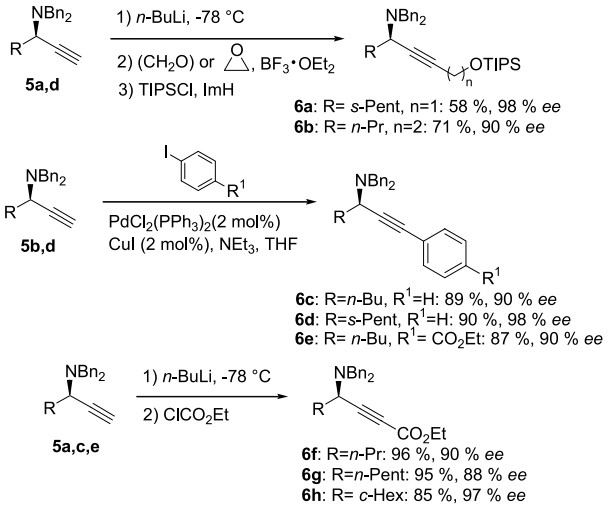
2.2. Functionalization of chiral propargylamines

The trimethylsilyl group was readily removed from the propargylamines **3** using Bu_4NF as solution in THF at 0 °C giving terminal propargylamines **5** in very good yields (generally >90%) (Scheme 3).



Scheme 3. Removal of the trimethylsilyl group.

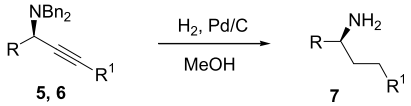
The resulting terminal propargylamines **5** could be further functionalized using known methods (Scheme 4). For example, deprotonation of **5a** and **5d** with *n*-BuLi in THF at −78 °C and alkylation with either paraformaldehyde[10] or ethylene oxide in the presence of boron trifluoride–etherate[11] yielded the corresponding alcohols. These were subsequently silylated with TIPSCl in the presence of imidazole giving the protected aminoalcohols **6a–b** in 58–71% yield over two steps with 98 and 90% ee, respectively, (Scheme 4). Sonogashira cross-coupling[12] of **5b** and **5d** with iodobenzene or ethyl 4-iodobenzoate in the presence of $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (2 mol%) led to the functionalized phenylacetylene derivatives **6c–e** in 87–90% yield and 90–98% ee (see Scheme 4). Finally, the reaction of the alkynyllithiums derived from **5a**, **5c** and **5e** with ethyl chloroformiate provided the chiral alkynyl esters **6f–h** in 85–96% yield and 88–97% ee (Scheme 4).



Scheme 4. Preparation of chiral functionalized propargylamines **6**.

2.3. Reduction to functionalized primary chiral amines and amides

We have investigated the reduction of the propargylamines **5** and **6** in the presence of Pd on charcoal in methanol under hydrogen atmosphere (1 bar) (Scheme 5).

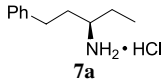
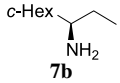
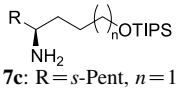
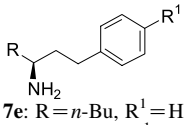
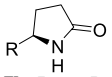


Scheme 5. Hydrogenation of propargylamines **5** and **6**.

Hydrogenation of the dihydrocinnamaldehyde derived propargylamine **5f** under the described conditions at rt led to the desired primary amine **7a** in 92% yield after transformation to the hydrochloride (entry 1, Table 2).

The unfunctionalized propargylamine **5e** was succesfully reduced to the chiral primary amine **7b** in 84% yield and 97% ee (entry 2, Table 2). Hydrogenation of the TIPS-ether substituted propargylamines **6a–b** also leads to the aminoalcohols **7c–d** in 66 and 99% yield and 98 and 90% ee, respectively, (entries 3 and 4, Table 2).

Table 2. Functionalized primary amines and amides

Entry	Propargylamine	Reduction product **7**	Yield (%)/ee (%)[a]
1			92/88
	5f	**7a**	
2			84/97
	5e	**7b**	
3			66/98
	6a	**7c**: R=*s*-Pent, *n*=1	
4	**6b**	**7d**: R=*n*-Pr, *n*=2	99/90
5			72/90
	6c	**7e**: R=*n*-Bu, R^1=H	
6	**6d**	**7f**: R=*s*-Pent, R^1=H	88/98
7	**6e**	**7g**: R=*n*-Bu, R^1=CO_2Et	72/90
			
8	**6f**	**7h**: R=*n*-Pr	75/90
9	**6g**	**7i**: R=*n*-Pent	87/88
10	**6h**	**7j**: R=*c*-Hex	85/97

[a] Isolated yield of analytically pure compound.

The phenylacetylene-derivatives **6c** and **6d** underwent equally smooth reduction to the β-phenyl-substituted amines **7e–f** in good yields (entries 5 and 6, Table 2). Furthermore, the ester functionality in **6e** was perfectly tolerated and the aminoester **7g** was obtained in 72% yield and 90% ee. Finally, reduction of the alkynyl esters **6f–h** under the standard conditions led directly to the cyclic amides **7h–j** in good yields (75–85%) and selectivities (88–97% ee) (entries 8–10, Table 2).

3. Conclusion

In summary, we have developed a convenient synthesis of functionalized chiral primary amines and amides in 88–98% ee. The key step and source of chirality is the asymmetric one-pot three-component synthesis of propargylamines from aldehydes, dibenzylamine and terminal alkynes like trimethylsilylacetylene. This reaction leads to the desired propargylamines in high yields and excellent selectivities (88–98% ee). Functionalization and reduction with Pd on charcoal under hydrogen atmosphere proceeds under mild conditions and is compatible with functional groups, such as silyl ethers and ester groups leading to functionalized primary amines. Furthermore, the use of alkynyl esters in the reduction reaction is leading directly to chiral cyclic amides in good yields.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere in dried glassware. All starting materials were purchased from commercial sources and used without further purification. Toluene was predried over KOH and continuously refluxed and freshly distilled from sodium. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Preparative chromatography was performed on silica gel 60 (0.063–0.200 mm) from Merck. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR and capillary GC.

4.2. Typical procedure A (racemic propargylamine synthesis)

In a dry and argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, CuBr (0.075 mmol, 5 mol%) was suspended in dry toluene (3 mL). MS 4 Å (750 mg) and *n*-decane (100 mg) were added, followed by trimethylsilylacetylene (1.5 mmol), the aldehyde (1.5 mmol) and dibenzylamine (1.5 mmol). The reaction mixture was stirred at rt until GC-analysis showed full conversion (12–48 h). MS 4 Å was filtered and washed with diethyl ether. The crude product was concentrated in vacuo and purified by column chromatography on silica gel.

4.3. Typical procedure B (chiral propargylamine synthesis)

In a dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, CuBr (0.015 mmol, 5 mol%) and (*R*)-Quinap (0.017 mmol, 5.5 mol%) were suspended in dry toluene (1.5 mL) and stirred for 30 min at rt. MS 4 Å (150 mg) and *n*-decane (30 mg) were added, followed by trimethylsilylacetylene (0.3 mmol), the aldehyde (0.3 mmol) and dibenzylamine (0.3 mmol). The reaction mixture was stirred at rt until GC-analysis showed full conversion (24 h–6 days). MS 4 Å was filtered and washed with diethyl ether. The crude product was concentrated in vacuo and purified by column chromatography on silica gel.

4.3.1. *N,N*-Dibenzyl-1-(trimethylsilyl)-1-hexyn-3-amine (3a). Prepared according to typical procedure A and B. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield (racemic): 90% (2.0 mmol scale, 628 mg); (nonracemic): 98% (0.3 mmol scale, 103 mg) as a colorless oil. $[\alpha]_D^{20}-166$ (*c* 0.96, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.43–7.23$ (m, 10H), 3.84 (d, $J=13.7$ Hz, 2H), 3.43 (t, $J=7.6$ Hz, 1H), 3.41 (d, $J=13.7$ Hz, 2H), 1.79–1.34 (m, 4H), 0.82 (t, $J=7.5$ Hz, 3H), 0.28 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=139.9$, 128.8, 128.2, 126.8, 104.7, 89.0, 54.8, 52.1, 35.8, 19.5, 13.7, 0.4. MS (70 eV, EI): *m/z* (%): 349 (M+, <1), 307 (25), 306 (100), 91 (33). HRMS (EI): calcd for $C_{23}H_{31}NSi$ [M^+]: 349.2226, found: 349.2198. IR (film): 2958 (s), 2935 (m), 2158 (m), 1495 (m), 1454 (m), 1250 (s), 842 (vs), 698 (s). Anal. Calcd for $C_{23}H_{31}NSi$: C, 79.02; H, 8.94; N, 4.01. Found: C, 79.01; H, 9.06; N, 3.96.

4.3.2. *N,N*-Dibenzyl-1-(trimethylsilyl)-1-heptyn-3-amine (3b). Prepared according to typical procedure A and B. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield (racemic): 82% (2.0 mmol scale, 596 mg); (nonracemic): 75% (0.3 mmol scale, 82 mg) as a colorless oil. $[\alpha]_D^{20}-186$ (*c* 0.69, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.22–7.00$ (m, 10H), 3.62 (d, $J=13.7$ Hz, 2H), 3.19 (d, $J=13.7$ Hz, 2H), 3.21–3.15 (m, 1H), 1.59–1.35 (m, 2H), 1.30–1.10 (m, 2H), 1.10–0.94 (sext, $J=7.3$ Hz, 2H), 0.66 (t, $J=7.3$ Hz, 3H), 0.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=139.5$, 128.4, 127.7, 126.4, 104.3, 88.6, 54.4, 51.9, 32.9, 28.0, 21.8, 13.5, 0.4. MS (70 eV, EI): *m/z* (%): 348 (5, M^+-CH_3), 306 (100), 214 (4), 91 (85), 73 (12). HRMS (EI): calcd for $C_{24}H_{32}NSi$ [M^+-H]: 362.2304, found: 362.2333. IR (film): 3064 (w), 3029 (w), 2958 (s), 2159 (m), 1495 (m), 1454 (m), 1250 (s), 842 (vs), 698 (s). Anal. Calcd for $C_{24}H_{33}NSi$: C, 79.28; H, 9.15; N, 3.85. Found: C, 79.19; H, 9.15; N, 3.83.

4.3.3. *N,N*-Dibenzyl-1-(trimethylsilyl)-1-octyn-3-amine (3c). Prepared according to typical procedure A and B. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield (racemic): 99% (10.0 mmol scale, 3.74 g); (nonracemic): 97% (0.3 mmol scale, 110 mg) as a colorless oil. $[\alpha]_D^{20}-152$ (*c* 0.45, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.43–7.40$ (m, 4H), 7.36–7.22 (m, 6H), 3.83 (d, $J=13.8$ Hz, 2H), 3.43–3.37 (m, 3H), 1.77–1.56 (m, 2H), 1.48–1.11 (m, 6H), 0.87 (t, $J=7.7$ Hz, 3H), 0.27 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=139.9$, 128.8, 128.2, 126.8, 104.7, 89.0, 54.8, 52.3, 33.5, 31.3, 25.9, 22.5, 14.0, 0.4. MS (70 eV, EI): *m/z* (%): 377 (M^+, <1), 307 (25), 306 (100), 91 (45). HRMS (EI): calcd for $C_{25}H_{34}NSi$ [M^+-H]: 376.2461, found: 376.2448. IR (film): 2957 (s), 2933 (s), 2159 (m), 1494 (m), 1454 (m), 1250 (s), 842 (vs), 698 (s). Anal. Calcd for $C_{25}H_{35}NSi$: C, 79.51; H, 9.34; N, 3.71. Found: C, 79.39; H, 9.40; N, 3.64.

4.3.4. *N,N*-Dibenzyl-4-ethyl-1-(trimethylsilyl)-1-hexyn-3-amine (3d). Prepared according to typical procedure A and B. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield (racemic): 99% (5.0 mmol scale, 1.87 g); (nonracemic): 97% (0.3 mmol scale, 110 mg) as a colorless oil. $[\alpha]_D^{20}-199$ (*c* 0.41, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.43–7.40$ (m, 4H), 7.36–7.31 (m, 4H), 7.28–7.23 (m, 2H), 3.82 (d, $J=13.5$ Hz, 2H), 3.37 (d, $J=13.5$ Hz, 2H), 3.19 (d, $J=10.1$ Hz, 1H), 1.75–1.27 (m, 5H), 0.81 (t, $J=7.9$ Hz, 3H), 0.59 (t, $J=7.9$ Hz, 3H), 0.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=139.7$, 129.1, 128.1, 126.8, 104.0, 90.0, 55.6, 55.0, 41.4, 22.1, 20.1, 10.6, 8.9, 0.5. MS (70 eV, EI): 362 (M^+-Me, 1), 307 (30), 306 (100), 91 (29). HRMS (EI): calcd for $C_{25}H_{36}NSi$ [$M^+ + H$]: 378.2617, found: 378.2617. IR (film): 2962 (s), 2158 (m), 1494 (m), 1454 (m), 1250 (s), 842 (vs), 747 (m), 698 (s). Anal. Calcd for $C_{25}H_{36}NSi$: C, 79.51; H, 9.34; N, 3.71. Found: C, 79.49; H, 9.37; N, 3.69.

4.3.5. *N,N*-Dibenzyl-1-cyclohexyl-3-(trimethylsilyl)-2-propyn-1-amine (3e). Prepared according to typical procedure A and B. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield (racemic): 99% (2.0 mmol scale, 770 mg); (nonracemic): 92% (0.3 mmol scale, 107 mg) as a colorless solid. Mp 81–82 °C. $[\alpha]_D^{20}-185$ (*c* 0.89, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.44–7.42$ (m, 4H), 7.37–7.32 (m, 4H), 7.28–7.23 (m, 2H), 3.83 (d, $J=13.6$ Hz, 2H), 3.39 (d, $J=13.6$ Hz, 2H), 3.06 (d, $J=10.9$ Hz, 1H), 2.32–2.28 (m, 1H), 2.04–2.00 (m, 1H), 1.73–1.55 (m, 4H), 1.28–1.07 (m, 3H), 0.89–0.67 (m, 2H), 0.28 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=139.8$, 128.8, 128.2, 126.8, 103.5, 90.1, 58.6, 54.9, 39.5, 31.2, 30.3, 26.6, 26.2, 25.9, 0.5. MS (70 eV, EI): 307 (M^+-c-Hex, 27), 306 (100), 91 (34). HRMS (EI): calcd for $C_{26}H_{35}NSi$ [M^+]: 389.2539, found: 389.2506. IR (KBr): 2924 (s), 2852 (m), 2160 (m), 1494 (m), 1451 (m), 1248 (s), 1006 (m), 844 (vs), 737 (s), 698 (s). Anal. Calcd for $C_{26}H_{35}NSi$: C, 80.14; H, 9.05; N, 3.59. Found: C, 79.90; H, 9.07; N, 3.54.

4.3.6. *N,N*-Dibenzyl-5-phenyl-1-(trimethylsilyl)-1-pentyn-3-amine (3f). Prepared according to typical procedure A and B. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield (racemic): 78% (1.0 mmol scale, 321 mg); (nonracemic): 76% (0.3 mmol scale, 94 mg) as a colorless oil. $[\alpha]_D^{20}-114$ (*c* 0.38, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.44–7.14$ (m, 13H), 7.09–7.06 (m, 2H), 3.88 (d, $J=13.6$ Hz, 2H), 3.50 (d, $J=7.6$ Hz, 1H), 3.45 (d, $J=13.6$ Hz, 2H), 2.85–2.75 (m, 1H), 2.69–2.59 (m, 1H), 2.12–1.88 (m, 2H), 0.28 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=141.9$, 139.7, 128.9, 128.4, 128.3, 128.2, 126.9, 125.7, 104.2, 89.6, 55.0, 52.2, 35.6, 32.6, 0.4. MS (70 eV, EI): 411 (M^+, <1), 307 (25), 306 (100), 91 (60). HRMS (EI): calcd for $C_{28}H_{33}NSi$ [M^+]: 411.2382, found: 411.2406. IR (film): 3027 (m), 2956 (m), 2158 (m), 1495 (s), 1454 (s), 1250 (s), 842 (vs), 746 (s), 698 (vs). Anal. Calcd for $C_{28}H_{33}NSi$: C, 81.69; H, 8.08; N, 3.40. Found: C, 81.92; H, 8.56; N, 3.37.

4.4. Typical procedure C (TMS-deprotection)

The amine of type **3** (1.0 mmol) was dissolved in dry THF (5 mL) and cooled to 0 °C. Bu_4NF (0.3 mL, 0.3 mmol, 1 M in THF) was added dropwise and the mixture was stirred at this temperature for 15 min. Water (20 mL) was added and the aq phase was extracted with diethyl ether (3×25 mL). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated in vacuo and the crude product was purified by column chromatography on silica gel.

4.4.1. *N,N*-Dibenzyl-1-hexyn-3-amine (5a). The reaction was carried out according to typical procedure C. Column

chromatographic purification: SiO_2, pentane/ether 99:1. Yield: 98% (1.0 mmol scale, 272 mg) as a colorless oil. $[\alpha]_D^{20}$ −160 (*c* 0.77, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=7.44–7.42 (m, 4H), 7.37–7.32 (m, 4H), 7.29–7.24 (m, 2H), 3.87 (d, *J*=13.7 Hz, 2H), 3.45 (td, *J*=8.1, 2.2 Hz, 1H), 3.43 (d, *J*=13.7 Hz, 2H), 2.35 (d, *J*=2.2 Hz, 1H), 1.83–1.36 (m, 4H), 0.83 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=139.7, 128.8, 128.2, 126.9, 82.2, 72.3, 54.8, 51.2, 35.9, 19.5, 13.6. MS (70 eV, EI): *m/z* (%): 377 (M^+, <1), 235 (17), 234 (100), 91 (65). HRMS (EI): calcd for $C_{20}H_{23}N$ [M^+]: 277.1830, found: 277.1838. IR (film): 3301 (m), 2958 (s), 2935 (m), 1495 (m), 1454 (s), 748 (s), 698 (vs). Anal. Calcd for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.52; H, 8.46; N, 5.02. HPLC (OD-H, 100% *n*-heptane/0% *i*-propanol, 0.8 mL/min): t_r(min)=11.3 (+), 12.9 (−).

4.4.2. *N,N*-Dibenzyl-1-heptyn-3-amine (5b). The reaction was carried out according to typical procedure C. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield: 92% (1.0 mmol scale, 268 mg) as a colorless oil. $[\alpha]_D^{20}$ −190 (*c* 0.87, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ=7.41 (d, *J*=7.7 Hz, 4H), 7.33 (t, *J*=7.3 Hz, 4H), 7.25 (t, *J*=7.3 Hz, 2H), 3.85 (d, *J*=13.8 Hz, 2H), 3.46–3.40 (m, 3H), 2.33 (d, *J*=1.3 Hz, 1H), 1.83–1.73 (m, 1H), 1.71–1.63 (m, 1H), 1.50–1.33 (m, 2H), 1.25–1.17 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=139.7, 128.8, 128.2, 126.9, 82.2, 72.4, 54.7, 51.5, 33.4, 28.4, 22.2, 13.9. MS (70 eV, EI): *m/z* (%):290 (1, M^+−H), 235 (22), 234 (98), 181 (11), 92 (100), 65 (10). HRMS (EI): calcd for $C_{21}H_{25}N$ [M^+−H]: 290.1909, found: 290.1885. IR (film): 3302 (m), 2956 (s), 2934 (s), 2860 (m), 1494 (m), 1454 (s), 746 (s), 698 (vs). Anal. Calcd for $C_{21}H_{25}N$: C, 86.55; H, 8.65; N, 4.81. Found: C, 86.84; H, 8.80; N, 4.97. HPLC (OD-H, 100% *n*-heptane/0% *i*-propanol, 0.8 mL/min): t_r(min)=11.3 (+), 12.9 (−).

4.4.3. *N,N*-Dibenzyl-1-octyn-3-amine (5c). The reaction was carried out according to typical procedure C. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield: 96% (9.8 mmol scale, 2.87 g) as a colorless oil. $[\alpha]_D^{20}$ −115 (*c* 0.41, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ=7.44 (d, *J*=7.2 Hz, 4H), 7.35 (t, *J*=7.2 Hz, 4H), 7.29–7.26 (m, 2H), 3.87 (d, *J*=13.7 Hz, 2H), 3.44 (d, *J*=13.7 Hz, 2H), 3.44–3.43 (m, 1H), 2.35 (d, *J*=2.3 Hz, 1H), 1.80–1.74 (m, 1H), 1.70–1.64 (m, 1H), 1.49–1.37 (m, 2H), 1.30 (sext, *J*=7.2 Hz, 2H), 1.20–1.15 (m, 2H), 0.88 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=139.7, 128.8, 128.2, 126.9, 82.2, 72.4, 54.7, 51.4, 33.6, 31.3, 25.9, 22.5, 14.0. MS (70 eV, EI): *m/z* (%): 305 (M^+, <1), 235 (18), 234 (93), 91 (100). HRMS (EI): calcd for $C_{22}H_{27}N$ [M^+]: 305.2143, found: 305.2165. IR (film): 3304 (m), 2954 (s), 2933 (s), 1495 (m), 1454 (s), 746 (s), 698 (vs). Anal. Calcd for $C_{22}H_{27}N$: C, 86.51; H, 8.91; N, 4.59. Found: C, 86.31; H, 8.99; N, 4.55. HPLC (after acylation with benzoyl chloride)(OD-H, 99% *n*-heptane/1% *i*-propanol, 0.2 mL/min): t_r(min)=22.6 (−), 25.9 (+).

4.4.4. *N,N*-Dibenzyl-4-ethyl-1-hexyn-3-amine (5d). The reaction was carried out according to typical procedure C. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield: 98% (4.0 mmol scale, 1.20 g) as a colorless oil. $[\alpha]_D^{20}$ −199 (*c* 0.41, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=7.43–7.41 (m, 4H), 7.37–7.32 (m, 4H), 7.29–7.24 (m, 2H), 3.84 (d, *J*=13.7 Hz, 2H), 3.40 (d, *J*=13.7 Hz, 2H), 3.21 (dd, *J*=10.1, 2.3 Hz, 1H), 2.38 (d, *J*=2.3 Hz, 1H), 1.79–1.62 (m, 3H), 1.50–1.28 (m, 2H), 0.81 (t, *J*=7.3 Hz, 3H), 0.60 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=139.6, 129.0, 128.2, 126.9, 81.3, 73.3, 55.0, 54.6, 41.4, 21.9, 19.9, 10.4, 8.9. MS (70 eV, EI): 235 (20), 234 (M^+−1-ethylpropyl, 100), 91 (74). HRMS (EI): calcd for $C_{22}H_{26}N$ [M^+−H]: 304.2065, found: 304.2075. IR (film): 3302 (m), 2963 (s), 2937 (m), 1495 (m), 1454 (m), 748 (m), 698 (s). Anal. Calcd for $C_{22}H_{27}N$: C, 86.51; H, 8.91; N, 4.59. Found: C, 86.45; H, 9.07; N, 4.57. HPLC (OD-H, 100% *n*-heptane/0% *i*-propanol, 0.2 mL/min): t_r(min)=28.4 (−), 31.9 (+).

4.4.5. *N,N*-Dibenzyl-1-cyclohexyl-2-propyn-1-amine (5e). The reaction was carried out according to typical procedure C. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield: 93% (1.5 mmol scale, 442 mg) as a colorless solid. Mp 75–76 °C. $[\alpha]_D^{20}$ −157 (*c* 0.35, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=7.44–7.41 (m, 4H), 7.36–7.31 (m, 4H), 7.27–7.23 (m, 2H), 3.85 (d, *J*=13.7 Hz, 2H), 3.41 (d, *J*=13.7 Hz, 2H), 3.07 (dd, *J*=10.6, 2.2 Hz, 1H), 2.37 (d, *J*=2.2 Hz, 1H), 2.35–2.28 (m, 1H), 2.06–2.00 (m, 1H), 1.72–1.59 (m, 4H), 1.31–1.07 (m, 3H), 0.91–0.72 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=139.7, 128.8, 128.2, 126.8, 81.0, 73.4, 57.6, 54.8, 39.5, 31.2, 30.2, 26.5, 26.1, 25.9. MS (70 eV, EI): 235 (21), 234 (M^+−*c*-Hex, 100), 91 (88). HRMS (EI): calcd for $C_{23}H_{27}N$ [M^+]: 317.2143, found: 317.2139. IR (KBr): 3302 (s), 2926 (vs), 2851 (s), 1495 (m), 1448 (m), 746 (s), 698 (s). Anal. Calcd for $C_{23}H_{27}N$: C, 87.02; H, 8.57; N, 4.41. Found: C, 86.74; H, 8.37; N, 4.32. HPLC (OD-H, 100% *n*-heptane/0% *i*-propanol, 0.2 mL/min): t_r(min)=31.7 (−), 36.0 (+).

4.4.6. *N,N*-Dibenzyl-5-phenyl-1-pentyn-3-amine (5f). The reaction was carried out according to typical procedure C. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield: 98% (0.5 mmol scale, 166 mg) as a colorless oil. $[\alpha]_D^{20}$ −83 (*c* 0.46, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=7.45–7.15 (m, 13H), 7.09–7.07 (m, 2H), 3.91 (d, *J*=13.8 Hz, 2H), 3.52 (dd, *J*=8.0, 2.2 Hz, 1H), 3.48 (d, *J*=13.8 Hz, 2H), 2.87–2.77 (m, 1H), 2.72–2.62 (m, 1H), 2.39 (d, *J*=2.2 Hz, 1H), 2.16–1.93 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=141.7, 139.5, 128.9, 128.3, 128.3, 128.2, 126.9, 125.7, 81.7, 72.9, 54.9, 51.2, 35.5, 32.5. MS (70 eV, EI): 339 (M^+, 1), 235 (18), 234 (100), 91 (94). HRMS (EI): calcd for $C_{25}H_{25}N$ [M^+]: 339.1987, found: 339.1975. IR (film): 3295 (m), 3027 (m), 1495 (s), 1454 (s), 746 (s), 698 (vs). Anal. Calcd for $C_{25}H_{25}N$: C, 88.45; H, 7.42; N, 4.13. Found: C, 88.30; H, 7.47; N, 4.01. HPLC (OD-H, 99% *n*-heptane/1% *i*-propanol, 0.15 mL/min): t_r(min)=38.6 (+), 42.5 (−).

4.4.7. *N,N*-Dibenzyl-5-ethyl-1-[(triisopropylsilyl)oxy]-2-heptyn-4-amine (6a). Propargylamine **5d** (305 mg, 1.0 mmol) was dissolved in dry THF (5 mL) and cooled to −78 °C. *n*-BuLi (0.67 mL, 1.55 M in hexane, 1.05 mmol) was added dropwise and the reaction was stirred for 10 min. Paraformaldehyde (95 mg, 1.05 mmol) was suspended in dry THF (7 mL) and added to the reaction mixture. Stirring was continued for 30 min at −78 °C and then at rt overnight. Water (20 mL) was added to the reaction mixture and the aq phase was extracted with diethyl ether (3×

25 mL). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated in vacuo and the crude product was purified by column chromatography (SiO_2, pentane/ether 4:1) leading to the alcohol (83%, 278 mg). The alcohol (268 mg, 0.8 mmol) was dissolved in dry DMF (4 mL) and imidazole (65 mg, 1.0 mmol) and DMAP (25 mg) were added as solids. The reaction mixture was cooled to 0 °C and TIPSCl (170 mg, 0.9 mmol) was added. The reaction was allowed to warm to rt overnight. Water (20 mL) was added to the reaction mixture and the aq phase was extracted with diethyl ether (3×25 mL). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated in vacuo and the crude product was purified by column chromatography (SiO_2, pentane/ether 98:2) leading to **6a** (70%, 276 mg, 0.6 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.38–7.36 (m, 4H), 7.32–7.27 (m, 4H), 7.24–7.19 (m, 2H), 4.54 (d, J=1.7 Hz, 2H), 3.79 (d, J=13.8 Hz, 2H), 3.38 (d, J=13.8 Hz, 2H), 3.18 (td, J=10.2, 1.8 Hz, 1H), 1.72–1.57 (m, 3H), 1.48–1.32 (m, 2H), 1.03 (s, 21H), 0.74 (t, J=7.5 Hz, 3H), 0.56 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=139.8, 129.0, 128.1, 126.8, 84.5, 82.1, 55.0, 54.8, 52.3, 41.6, 22.0, 20.0, 18.0, 12.1, 10.4, 8.9. MS (70 eV, EI): *m/z* (%): 490 (M^+-H, <1), 421 (32), 420 (100), 91 (30). HRMS (EI): calcd for $C_{32}H_{48}NOSi$ [M^+-H]: 490.3505, found: 490.3545. IR (KBr): 2962 (vs), 2942 (vs), 2866 (vs), 1495 (m), 1454 (s), 1369 (m), 1119 (s), 1068 (s), 883 (m), 747 (s), 698 (s). Anal. Calcd for $C_{32}H_{49}NOSi$: C, 78.15; H, 10.04; N, 2.85. Found: C, 77.92; H, 10.07; N, 2.99.

4.4.8. *N*,*N*-Dibenzyl-8-[(triisopropylsilyl)oxy]-5-octyn-4-amine (6b). Propargylamine **5a** (277 mg, 1.0 mmol) was dissolved in dry THF (2 mL). The mixture was cooled to −78 °C and *n*-BuLi (0.92 mL, 1.2 mmol, 1.3 M in hexane) was added. After stirring at this temperature for 30 min, oxirane (0.15 mL, 3.0 mmol,) followed by $BF_3\cdot OEt_2$ (170 mg, 1.2 mmol) were added and the mixture was kept at −78 °C for 2 h. Satd NH_4Cl-solution was added and the aq layer was extracted with diethyl ether and dried (Na_2SO_4). Column chromatographic purification (SiO_2, pentane/diethyl ether 2:1) furnished the desired alcohol as a colorless oil (244 mg, 76%). Silylation was carried out as described for **6a** leading to compound **6b** (0.5 mm scale, 93%, 22 2mg) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40–7.37 (m, 4H), 7.32–7.19 (m, 6H), 3.86 (t, J=7.3 Hz, 2H), 3.79 (d, J=13.8 Hz, 2H), 3.38 (d, J=13.8 Hz, 2H), 3.39–3.34 (m, 1H), 2.54 (td, J=7.0, 2.2 Hz, 2H), 1.70–1.30 (m, 4H), 1.10 (s, 21H), 0.78 (t, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=140.1, 128.8, 128.1, 126.7, 81.8, 79.0, 62.7, 54.8, 51.5, 36.3, 23.4, 19.6, 18.0, 13.7, 12.0. MS (70 eV, EI): *m/z* (%): 477 (M^+, <1), 435 (25), 434 (100). HRMS (EI): calcd for $C_{31}H_{47}NOSi$ [M^+]: 477.3427, found: 477.3436. IR (film): 2942 (vs), 2867 (vs), 1495 (m), 1463 (s), 1454 (s), 1110 (s), 1071 (m), 883 (m), 745 (m), 698 (s). Anal. Calcd for $C_{31}H_{47}NOSi$: C, 77.93; H, 9.91; N, 2.93. Found: C, 78.10; H, 9.94; N, 2.88.

4.5. Typical procedure D (Sonogashira-coupling)

$PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol) and CuI (3.8 mg, 0.02 mmol) were charged in a 10 mL Schlenk-flask and dried in vacuo. After 15 min, the catalyst was suspended in dry THF (1.5 mL) and NEt_3 (152 mg, 1.5 mmol) was added. After 10 min of stirring at rt, the iodobenzene-derivative (1.1 mmol) was added. Propargylamine **5** (1 mmol) was dissolved in THF (3.5 mL) and added in one portion. After stirring at rt for 20 h, TLC-analysis showed full conversion and the reaction mixture was quenched with water (25 mL) and the aq layer was extracted with diethyl ether (3× 30 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo and the crude product was purified by column chromatography on silica gel.

4.5.1. *N*,*N*-Dibenzyl-1-phenyl-1-heptyn-3-amine (6c). The reaction was carried out according to typical procedure D with iodobenzene. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield: 89% (1.0 mmol scale, 314 mg) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.44–7.10 (m, 15H), 3.80 (d, J=13.7 Hz, 2H), 3.51 (t, J=7.4 Hz, 1H), 3.40 (d, J=13.8 Hz, 2H), 1.78–1.56 (m, 2H), 1.46–1.23 (m, 2H), 1.14 (sext, J=7.2 Hz, 2H), 0.78 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=139.9, 131.8, 128.8, 128.3, 128.2, 127.8, 126.8, 123.6, 88.1, 85.2, 55.0, 52.2, 33.6, 28.6, 22.3, 13.5. MS (70 eV, EI): *m/z* (%): 310 (100, $M^+-C_4H_9$), 218 (3), 128 (2), 115 (7), 91 (57). HRMS (EI): calcd for $C_{27}H_{33}N$ [M^+-H]: 366.2222, found: 366.2215. IR (film): 3062 (w), 3029 (w), 2955 (s), 2932 (s), 1599 (m), 1490 (s), 1454 (s), 755 (vs), 698 (vs). Anal. Calcd for $C_{27}H_{34}N$: C, 88.24; H, 7.95; N, 3.81. Found: C, 87.85; H, 7.84; N, 3.73.

4.5.2. *N*,*N*-Dibenzyl-4-ethyl-1-phenyl-1-hexyn-3-amine (6d). The reaction was carried out according to typical procedure D with iodobenzene. Column chromatographic purification: SiO_2, pentane/ether 99:1. Yield: 90% (1.0 mmol scale, 343 mg) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.59–7.56 (m, 2H), 7.48–7.46 (m, 4H), 7.42–7.34 (m, 7H), 7.31–7.26 (m, 2H), 3.93 (d, J=13.6 Hz, 2H), 3.51 (d, J=13.6 Hz, 2H), 3.43 (d, J=9.6 Hz, 1H), 1.83–1.69 (m, 3H), 1.57–1.37 (m, 2H), 0.87 (t, J=7.7 Hz, 3H), 0.66 (t, J=7.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=142.5, 128.3, 128.3, 125.7, 52.1, 47.3, 36.7, 33.3, 22.4, 21.4, 12.2, 12.1. MS (70 eV, EI): *m/z* (%): 380 (M^+-H, <1), 311 (22), 310 (100), 91 (23). HRMS (EI): calcd for $C_{28}H_{30}N$ [M^+-H]: 380.2378, found: 380.2374. IR (film): 2961 (s), 2935 (m), 2803 (m), 1489 (m), 1453 (m), 754 (s), 746 (s), 698 (vs), 690 (vs). Anal. Calcd for $C_{28}H_{31}N$: C, 88.14; H, 8.19; N, 3.67. Found: C, 87.96; H, 8.18; N, 3.65.

4.5.3. Ethyl 4-[3-(dibenzylamino)-1-heptynyl]benzoate (6e). The reaction was carried out according to typical procedure D with ethyl 4-iodobenzoate. Column chromatographic purification: SiO_2, pentane/ether 98:2. Yield: 87% (1.0 mmol scale, 382 mg) as a light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.06 (d, J=8.5 Hz, 2H), 7.59 (d, J=8.5 Hz, 2H), 7.46 (d, J=7.8 Hz, 4H), 7.36 (t, J=7.8 Hz, 4H), 7.29–7.27 (m, 2H), 4.44 (q, J=7.1 Hz, 2H), 3.95 (d, J=13.5 Hz, 2H), 3.67 (t, J=7.8 Hz, 1H), 3.53 (d, J=13.5 Hz, 2H), 1.89–18.3 (m, 1H), 1.80–1.74 (m, 1H), 1.55–1.49 (m, 1H), 1.46 (t, J=7.2 Hz, 3H), 1.48–1.40 (m, 1H), 1.30–1.24 (m, 2H), 0.91 (t, J=7.8 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=166.1, 139.7, 131.7, 129.5, 129.4, 128.8, 128.2, 128.1, 126.9, 91.6, 84.7, 61.1, 55.0, 52.3, 33.4, 28.5, 22.3, 14.3, 14.0. MS (70 eV, EI): *m/z* (%): 439 (<1, M^+), 383 (28), 382 (100), 91 (53). HRMS (EI): calcd for

$C_{30}H_{32}NO_2$ [M^+-H]: 438.2433, found: 438.2405. IR (film): 2956 (m), 2933 (m), 1720 (vs), 1606 (m), 1454 (m), 1367 (m), 1272 (vs), 1174 (m), 1106 (s), 769 (m), 747 (m), 698 (m).

4.6. Typical procedure E (alkynyl ester synthesis)

Propargylamine of type **5** (1.0 mmol) was dissolved in dry THF (2 mL) and cooled to −78 °C. *n*-BuLi (0.67 mL, 1.0 mmol, 1.5 M in hexane) was added. After stirring at this temperature for 30 min, ethyl chloroformiate (217 mg, 2.0 mmol) was added and the mixture was allowed to warm to rt. The reaction mixture was quenched with water (25 mL) and the aq phase was extracted with diethyl ether (3×30 mL) and dried (Na_2SO_4). Column chromatographic purification (SiO_2, pentane/diethyl ether 98:2) furnished the desired alkynyl esters.

4.6.1. Ethyl 4-(dibenzylamino)-2-heptynoate (6f). Prepared according to typical procedure E from **5a**. Yield: 96% (2.0 mmol scale, 673 mg), colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.42–7.40 (m, 4H), 7.37–7.32 (m, 4H), 7.29–7.24 (m, 2H), 4.31 (q, J=7.0 Hz, 2H), 3.90 (d, J=13.8 Hz, 2H), 3.57 (t, J=8.0 Hz, 1H), 3.45 (d, J=13.8 Hz, 2H), 1.83–1.62 (m, 2H), 1.56–1.34 (m, 3H), 1.39 (t, J=7.1 Hz, 3H), 0.82 (t, J=7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=153.7, 139.1, 128.8, 128.3, 127.1, 86.8, 77.2, 62.0, 54.9, 51.3, 35.0, 19.4, 14.1, 13.5. MS (70 eV, EI): 348 (M^+-H, <1), 307 (19), 306 (100), 91 (45). HRMS (EI): calcd for $C_{25}H_{29}NO_2$ [M^+-2H]: 375.2198, found: 375.2166. IR (film): 2960 (m), 2936 (m), 2220 (m), 1713 (vs), 1454 (m), 1242 (vs), 750 (m), 699 (m).

4.6.2. Ethyl 4-(dibenzylamino)-2-nonynoate (6g). Prepared according to typical procedure E from **5c**. Yield: 95% (1.0 mmol scale, 390 mg), colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.42 (d, J=7.7 Hz, 4H), 7.35 (t, J=7.7 Hz, 4H), 7.29–7.26 (m, 2H), 4.32 (q, J=7.3 Hz, 2H), 3.90 (d, J=13.8 Hz, 2H), 3.56 (t, J=7.7 Hz, 1H), 3.45 (d, J=13.8 Hz, 2H), 1.84–1.67 (m, 2H), 1.51–1.43 (m, 2H), 1.40 (t, J=7.3 Hz, 3H), 1.31–1.25 (m, 2H), 1.18–1.13 (m, 2H), 0.87 (t, J=7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=153.7, 139.1, 128.8, 128.3, 127.1, 86.9, 77.4, 62.0, 54.9, 51.5, 32.8, 31.1, 25.7, 22.4, 14.1, 14.0. MS (70 eV, EI): 375 (M^+-2H<1), 307 (18), 306 (100), 91 (53). HRMS (EI): calcd for $C_{25}H_{29}NO_2$ [M^+-2H]: 375.2198, found: 375.2166. IR (film): 2956 (m), 2933 (m), 2222 (m), 1713 (vs), 1454 (m), 1242 (vs), 749 (m), 699 (m).

4.6.3. Ethyl 4-cyclohexyl-4-(dibenzylamino)-2-butynoate (6h). Prepared according to typical procedure E from **5e**. Yield: 85% (1.0 mmol scale, 393 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.43–7.41 (m, 4H), 7.37–7.32 (m, 4H), 7.29–7.24 (m 2H), 4.32 (q, J=7.1 Hz, 2H), 3.90 (d, J=13.8 Hz, 2H), 3.44 (d, J=13.8 Hz, 2H), 3.21 (d, J=10.5 Hz, 1H), 2.30 (d, J=14.1 Hz, 1H), 1.99 (d, J=12.1 Hz, 1H), 1.75–1.61 (m, 4H), 1.40 (t, J=7.1 Hz, 3H), 1.34–1.06 (m, 3H), 0.97–0.68 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.8, 139.0, 128.8, 128.3, 127.1, 86.1, 78.5, 61.9, 57.8, 55.0, 39.2, 31.0, 30.2, 26.4, 25.9, 25.7, 14.1. MS (70 eV, EI): *m/z* (%): 389 (M^+, <1), 307 (20), 306 (100), 91 (66). HRMS (EI): calcd for $C_{26}H_{31}NO_2$ [M^+]: 389.2355, found: 389.2347. IR (KBr): 2928 (s), 2852 (m), 2219 (m), 1712 (vs), 1495 (m), 1452 (m), 1366 (m), 1241 (vs), 749 (s), 699 (s).

4.7. Typical procedure F (hydrogenation)

Propargylamine of type **5** or **6** (1.0 mmol) was dissolved in MeOH (5 mL). KOH (3 drops of a 1 M soln) and Pd on charcoal (100 mg, 10%) were added and the reaction mixture was stirred under H_2 (1 atm) until TLC-analysis showed the disappearance of the starting material. Filtration over celite (washing with EtOAc) and concentration in vacuo furnished the crude product. Purification was carried out as described for each compound.

4.7.1. 1-Ethyl-3-phenylpropylamine hydrochloride (7a). The reaction was carried out according to typical procedure F from **5f**. The crude product was taken up in diethyl ether and HCl in Et_2O was added dropwise. A light yellow precipitate was formed and collected by filtration (1.0 mmol scale, 183 mg, 0.92 mmol, 92%). ^{1}H NMR (300 MHz, D_2O): δ=7.47–7.26 (m, 5H), 3.22 (quint, J=6.4 Hz, 1H), 2.73 (t, J=7.3 Hz, 2H), 2.07–1.87 (m, 2H), 1.83–1.62 (m, 2H), 0.97 (t, J=7.6 Hz, 3H). ^{13}C NMR (75 MHz, D_2O): δ=141.4, 129.2, 128.8, 126.8, 53.0, 33.6, 31.0, 25.1, 8.8. MS (70 eV, EI): *m/z* (%): 163 (M^+-HCl, 1), 146 (17), 134 (42), 117 (25), 106 (16), 91 (85), 58 (100). HRMS (EI): calcd for $C_{11}H_{17}N$ [M^+-HCl]: 163.1361, found: 163.1330. IR (film): 3437 (s), 3029 (vs), 2970 (vs), 2933 (vs), 1602 (m); 1502 (m), 1455 (m), 700 (m).

4.7.2. 1-Cyclohexyl-1-propanamine (7b). The reaction was carried out according to typical procedure F from **5e**. The crude product was already analytically pure, yielding **7b** as a colorless liquid (2.0 mmol scale, 236 mg, 1.67 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.40–2.38 (m, 1H), 1.77–1.60 (m, 5H), 1.54–1.42 (m, 1H), 1.28–0.98 (m, 8H), 0.90 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=57.6, 43.3, 29.8, 27.9, 27.3, 26.7, 26.6, 26.5, 10.8. MS (70 eV, EI): *m/z* (%): 142 (M^++H, 2), 112 (31), 95 (14), 58 (100), 41 (10). HRMS (EI): calcd for $C_9H_{20}N$ [M^++H]: 142.1596, found: 142.1592. IR (KBr): 2924 (vs), 2852 (s), 1565 (m), 1463 (m), 1449 (m).

4.7.3. 5-Ethyl-1-[(triisopropylsilyl)oxy]-4-heptanamine (7c). The reaction was carried out according to typical procedure F from **6a**. Distillation in Kugelrohr (1.0×10^{-1} mbar, 150 °C) leads to the desired amine (0.50 mmol scale, 104 mg, 0.33 mmol, 66%) as a colorless oil, which solidified upon standing. Mp 67–69 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.07 (br s, 2H), 3.79–3.58 (m, 2H), 3.28–3.19 (m, 1H), 1.91–1.33 (m, 9H), 1.03 (s, 21H), 0.93 (t, J=7.0 Hz, 3H), 0.92 (t, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=62.2, 53.9, 43.4, 29.2, 25.8, 21.8, 18.0, 12.0, 11.9, 11.8, 11.6. MS (70 eV, EI): *m/z* (%): 315 (M^+, 8), 273 (19), 272 (81), 245 (21), 244 (100), 157 (15), 131 (18), 130 (40), 123 (14), 103 (23), 100 (26). HRMS (EI): calcd for $C_{18}H_{41}NOSi$ [M^+]: 315.2957, found: 315.2957. IR (KBr): 2942 (vs), 2867 (vs), 1605 (w), 1521 (m), 1463 (m), 1100 (s), 883 (m), 678 (m).

4.7.4. 1-Propyl-5-[(triisopropylsilyl)oxy]pentylamine (7d). The reaction was carried out according to typical

procedure F from **6b**. Kugelrohr distillation (160 °C, 7×10^{-2} mbar) yielded the desired product **7d** (3.0 mmol scale, 861 mg, 2.9 mmol, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.67$ (t, $J=6.0$ Hz, 2H), 2.70 (br s, 2H), 1.56–1.12 (m, 9H), 1.08–1.00 (m, 2H), 1.03 (s, 21H), 0.90 (t, $J=6.6$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 63.3, 50.9, 40.2, 37.9, 33.1, 22.4, 19.3, 18.0, 14.2, 12.0. MS (70 eV, EI): *m/z* (%): 299 (M^+-2H, 23), 298 (100), 258 (75), 241 (21), 199 (51), 170 (66), 130 (35), 115 (20), 75 (20), 72 (20). IR (film): 2941 (vs), 2866 (vs), 1463 (m), 1105 (s). Anal. Calcd for $C_{17}H_{39}NOSi$: C, 67.70; H, 13.03; N, 4.64. Found: C, 67.61; H, 12.71; N, 4.36.

4.7.5. 1-(2-Phenylethyl)pentylamine (7e). The reaction was carried out according to typical procedure F from **6c**. The crude product was already analytically pure (0.90 mmol scale, 123 mg, 0.64 mmol, 72%) and obtained as a colorless oil, which slowly solidified upon standing. Mp 152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.56$ (br s, 2H), 7.35–7.16 (m, 5H), 3.21 (quint, $J=6.3$ Hz, 1H), 2.93–2.74 (m, 2H), 2.17–1.96 (m, 2H), 1.85–1.67 (m, 2H), 1.51–1.23 (m, 4H), 0.88 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 140.3, 128.5, 128.4, 126.2, 52.0, 34.5, 32.5, 31.4, 27.3, 22.3, 13.7. MS (70 eV, EI): *m/z* (%): 190 (M^+-H, 1), 134 (68), 117 (36), 104 (11), 91 (92), 86 (100). HRMS (EI): calcd for $C_{13}H_{20}N$ [M^+-H]: 190.1596, found: 190.1591. IR (KBr): 3436 (m), 3027 (s), 2932 (vs), 1602 (m), 1498 (m), 1455 (m), 747 (w), 699 (m).

4.7.6. 4-Ethyl-1-phenyl-3-hexanamine (7f). The reaction was carried out according to typical procedure F from **6d**. Distillation in Kugelrohr (1.0×10^{-1} mbar, 120–140 °C) leads to the desired amine (0.85 mmol scale, 150 mg, 0.75 mmol, 88%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.33$–7.28 (m, 2H), 7.24–7.17 (m, 3H), 2.82–2.78 (m, 2H), 2.67–2.57 (m, 1H), 1.82–1.71 (m, 1H), 1.65–1.53 (m, 1H), 1.46–1.13 (m, 7H), 0.91 (t, $J=7.5$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=142.5$, 128.3, 128.3, 125.7, 52.1, 47.3, 36.7, 33.3, 22.4, 21.4, 12.2, 12.1. MS (70 eV, EI): *m/z* (%): 206 (M^++H, 2), 134 (100), 117 (11), 91 (23). HRMS (EI): calcd for $C_{14}H_{24}N$ [M^++H]: 206.1909, found: 206.1901. IR (film): 2961 (vs), 2931 (s), 2874 (m), 1454 (m), 699 (m). Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.32; H, 11.19; N, 6.69.

4.7.7. Ethyl 4-(3-aminoheptyl)benzoate (7g). The reaction was carried out according to typical procedure F from **6e**. The crude product was washed with diethyl ether and dried in vacuo. Aminoester **7g** (0.30 mmol scale, 57 mg, 0.22 mmol, 72%) was obtained as a colorless solid. Mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.55$ (br s, 2H), 7.90 (d, $J=8.4$ Hz, 2H), 7.28 (d, $J=8.3$ Hz, 2H), 4.35 (q, $J=7.4$ Hz, 2H), 3.18 (quint, $J=6.0$ Hz, 1H), 2.96–2.77 (m, 2H), 2.14–1.94 (m, 2H), 1.82–1.59 (m, 2H), 1.34 (t, $J=$ 7.4 Hz, 3H), 1.31–1.19 (m, 4H), 0.84 (t, $J=7.3$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=166.4$, 145.5, 129.7, 128.7, 128.4, 60.8, 52.1, 34.2, 32.6, 31.4, 27.3, 22.2, 14.3, 13.7. MS (70 eV, EI): *m/z* (%): 263 (M^+, 2), 207 (11), 206 (94), 163 (42), 86 (100). HRMS (EI): calcd for $C_{16}H_{25}NO_2$ [M^+]: 263.1885, found: 263.1882. IR (KBr): 3436 (s), 2959 (vs), 2931 (vs), 1716 (vs), 1612 (m), 1279 (vs), 1111 (m).

4.7.8. 5-Propyl-2-pyrrolidinone (7h). The reaction was carried out according to typical procedure F from **6f**. Distillation in Kugelrohr (4.5×10^{-1} mbar, 160 °C) leads to the desired amide (0.90 mmol scale, 95 mg, 0.68 mmol, 75%) as a colorless solid. Mp 48–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.96$ (br s, 1H), 3.61 (quint, $J=$ 6.7 Hz, 1H), 2.33–2.14 (m, 3H), 1.72–1.59 (m, 1H), 1.54–1.26 (m, 4H), 0.90 (t, $J=7.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.5$, 54.5, 38.9, 30.3, 27.2, 19.1, 13.9. MS (70 eV, EI): *m/z* (%): 127 (M^+, 2), 84 (100), 41 (21). HRMS (EI): calcd for $C_7H_{13}NO$ [M^+]: 127.0997, found: 127.1002. IR (KBr): 3194 (s), 2963 (s), 2931 (s), 2871 (s), 1707 (vs), 1662 (s), 1461 (m), 1390 (m), 1347 (m), 1318 (m), 1290 (m), 766 (m). Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10. 30; N, 11.01. Found: C, 66.27; H, 9.94; N, 10.75.

4.7.9. 5-Pentyl-2-pyrrolidinone (7i). The reaction was carried out according to typical procedure F from **6g**. Distillation in Kugelrohr (1.0×10^{-1} mbar, 170 °C) leads to the desired amide (0.75 mmol scale, 100 mg, 0.65 mmol, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$ 6.86 (br s, 1H), 3.59 (quint, $J=6.2$ Hz, 1H), 2.32–2.14 (m, 3H), 1.71–1.59 (m, 1H), 1.54–1.37 (m, 2H), 1.33–1.25 (m, 6H), 0.85 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.4$, 54.7, 36.6, 31.6, 30.3, 27.2, 25.4, 22.4, 13.9. MS (70 eV, EI): *m/z* (%): 154 (M^+, 100), 110 (70), 100 (32), 97 (65), 84 (55), 69 (32), 43 (23), 41 (28). HRMS (EI): calcd for $C_9H_{16}NO$ [M^+-H]: 154.1232, found: 154.1222. IR (KBr): 3208 (m), 2956 (m), 2928 (s), 2859 (m), 1698 (vs), 1463 (m), 1284 (m).

4.7.10. 5-Cyclohexyl-2-pyrrolidinone (7j). The reaction was carried out according to typical procedure F from **6h**. The crude product was dissolved in EtOH (3 mL) and concd H_2SO_4 (3 drops) was added. After stirring overnight, the reaction was quenched with $NaHCO_3$ (30 mL) and the aq phase was extracted with EtOAc (3×40 mL) and dried over Na_2SO_4. Concentration under reduced pressure leads to the amide **7j** (1.4 mmol scale, 202 mg, 1.2 mmol, 85%) as a yellow solid. Mp 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=6.23$ (br s, 1H), 3.35 (q, $J=6.7$ Hz, 1H), 2.49–2.34 (m, 1H), 2.21–2.09 (m, 1H), 1.86–1.62 (m, 6H), 1.56–1.42 (m, 1H), 1.30–1.13 (m, 4H), 1.05–0.83 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.3$, 59.5, 43.4, 30.3, 29.4, 28.6, 26.3, 25.8, 25.7, 25.0. MS (70 eV, EI): *m/z* (%): 167 (M^+, <1), 85 (7), 84 (100), 55 (3), 40 (7). HRMS (EI): calcd for $C_{10}H_{17}NO$ [M^+]: 167.1310, found: 167.1295. IR (KBr): 3182 (m), 2923 (s), 2855 (s), 1689 (vs), 1453 (m), 1279 (m), 1264 (m), 808 (m).

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Synthesis of C-5 substituted nucleosides via palladium-catalyzed coupling of dienes and amines

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Abstract—The palladium-catalyzed coupling of C-5 iodopyrimidine nucleosides; 1,2-, 1,3-, or 1,ω-dienes; and amines provides a novel and efficient method for the preparation of a wide variety of C-5 aminoalkyl-substituted nucleosides. Adding certain Lewis acids, particularly zinc salts, improves the yields significantly. Secondary amines are the most effective amines for this process. Acyclic and cyclic dienes have been successfully employed. Protection of the 3′- and 5′-hydroxyl groups of iodouridine is required in order to obtain good yields when the coupling process is carried out on 1,3-dienes or long chain or branched non-conjugated dienes.

1. Introduction

Uridine (pyrimidine nucleoside) and its nucleotide derivatives have attracted great attention as potential novel therapeutic agents for a variety of diseases.[1] Among the uridines, C-5 substituted 2′-deoxyuridines have played very important roles in many therapeutic areas. They have shown potent inhibition against viruses as diverse as herpes simplex virus (HSV-1 and HSV-2),[2] vaccinia virus (VV),[3] hepatitis B virus (HBV)[4] and varicella zoster virus (VZV).[5] 5-Fluoro-2′-deoxyuridine has been used for decades to treat various types of solid tumors. However, its usage is limited due to toxic side effects. Modification of the uridine core to increase antitumor efficacy and decrease toxicity has been actively pursued.[6] Uridine analogs have also been widely used for DNA analysis employing fluorescence spectroscopy[7] and radioactive labeling.[8] Fluorophores can be introduced into oligonucleotides in different ways, but one of the most common is to label the pyrimidine ring at the C-5 position. This position is exposed to the major groove of the DNA double-helix, and most functionality here has little effect on hybridization. The fluorescent labels can be attached to the pyrimidine ring either directly[9] or by a linker arm.[10] The length of the linker arm has a significant effect on the thermal stability of the DNA duplexes.[11] Hydroxy[10] and amino[11] groups are most commonly used to attached fluorescent labels at the end of the linker arm.

Many of the procedures for modification of the pyrimidine nucleosides at C-5 have involved palladium-catalyzed coupling reactions. In early studies, mercuriopyrimidine nucleosides were often used as starting materials.[12] More recently, procedures have been developed employing the palladium-catalyzed coupling of commercially available 5-iodo-2′-deoxyuridine (IdU=**1**) and terminal alkynes,[5,8a,10] electron-deficient alkenes,[13] arylboronic acids,[14] or arylstannanes.[15]

Recently, we have successfully developed the palladium-catalyzed three component coupling of aryl iodides, non-conjugated dienes and nucleophiles, such as amines[16] and carbanions.[17] In this paper, we present our efforts on the synthesis of amine-containing C-5 substituted 2′-deoxyuridines using this methodology with extentions to 1,2- and 1,3-dienes. This methodology readily allows one to change the length of the carbon linker chain and the functional groups introduced at the distal end of the chain. This is particularly noteworthy for the modification of nucleosides, since it has been found that the stabilization of DNA duplexes by a terminal amino group depends on the length of the linker arm.[11] Furthermore, increasing the length of the side chain at C-5, while retaining substituents, increases the antiviral activity at the same time it substantially decreases toxicity.[18]

2. Results and discussion

2.1. Non-conjugated dienes

Based on our previous success with the palladium-catalyzed

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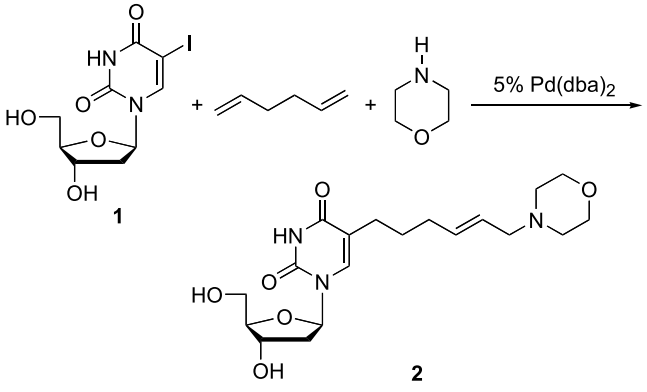
Table 1. Palladium-catalyzed coupling of 5-iodo-2′-deoxyuridine (**1**), 1,5-hexadiene and morpholine (Eq. 1)[a]

Entry	Solvent	Chloride (equiv)	Temperature (°C)	Time (days)	Isolated yield of **2** (%)
1[b]	DMF	*n*-Bu_4NCl (2)	100	1	0
2	DMF	LiCl (2)	100	2	0
3	CH_3CN	LiCl (2)	80	2	0
4	MeOH	*n*-Bu_4NCl (2)	80	2	25
5	MeOH	LiCl (2)	80	2	>18
6	DMSO	LiCl (2)	80	2	41
7	DMSO	LiCl (2)	100	2	38
8	DMSO	LiCl (2)	60	2	28
9	DMSO	LiCl (3)	80	2	28
10	DMSO	*n*-Bu_4NCl (2)	80	2	30
11	DMSO	*n*-Bu_4NCl (3)	80	2	43 (35)[c]
12[d]	DMSO	*n*-Bu_4NCl (3)	80	2	21
13	DMSO	*n*-Bu_4NCl (3)	80	4	30
14	1:1 MeOH/CH_2Cl_2	*n*-Bu_4NCl (2)	80	4	29
15	$HOCH_2CH_2OH$	*n*-Bu_4NCl (2)	80	2	4
16	Dioxane	*n*-Bu_4NCl (2)	100	1	0
17	4:1 DMSO/H_2O	*n*-Bu_4NCl (2)	100	1	30
18	1:4 DMSO/H_2O	*n*-Bu_4NCl (2)	100	1	Trace
19	4:1 CH_3CN/H_2O	*n*-Bu_4NCl (2)	100	1	21
20	1:4 CH_3CN/H_2O	*n*-Bu_4NCl (2)	100	1	0
21	H_2O	*n*-Bu_4NCl (2)	100	1	0

[a] All reactions were run in the presence of 5 mol% $Pd(dba)_2$, 5 equiv of 1,5-hexadiene and 5 equiv of morpholine.
[b] Two equivalents of morpholine were used.
[c] The same reaction was run twice and gave different yields of the product.
[d] Two equivalents of Na_2CO_3 added.

coupling of aryl iodides, non-conjugated dienes and amines,[16] the reaction of 5-iodo-2′-deoxyuridine (IdU= **1**), 1,5-hexadiene and morpholine was chosen as a model system in which to optimize yields (Eq. 1). First, the reaction was run under our best previous conditions for secondary amines. Unfortunately, none of the desired product was obtained (Table 1, entry 1). We then increased the amount of morpholine to 5 equiv, extended the reaction time to 2 days and used LiCl instead of *n*-Bu_4NCl, but still no coupling product was formed (entry 2). Other solvents were next examined. At the same time, the temperature was lowered to 80 °C, because we were concerned that the starting material IdU (**1**) might not be very stable at higher temperatures. Although the use of acetonitrile as the solvent again failed to provide any of the desired coupling product (entry 3), the solvents MeOH or DMSO provided the desired coupling product **2** in low yields (entries 4–13). This might be due to the higher solubility of IdU in MeOH or DMSO than in DMF or CH_3CN. The reaction was also examined at different temperatures (compare entries 6–8). The reaction gave the highest yield of the desired product when run at 80 °C. In an attempt to further improve the yield, the amount of LiCl added was increased to 3 equiv, but the yield appeared to drop (entries 6 and 9). Switching to 2 equiv of *n*-Bu_4NCl as the chloride source gave a slight reduction in yield (entry 10), but increasing the amount of *n*-Bu_4NCl to 3 equiv afforded better results, although they did not seem to be very reproducible (entry 11). The addition of 2 equiv of an inorganic base Na_2CO_3 (entry 12) or extending the reaction time (entry 13) only lowered the yield.

Since the solubility of IdU in the reaction system appeared to be a critical factor, several other solvents were examined, especially aqueous media (entries 14–21). Unfortunately, none of the solvent systems examined gave very satisfactory results. Using water as the sole solvent failed to give any of the desired product, although it is a good solvent for IdU (entry 21).

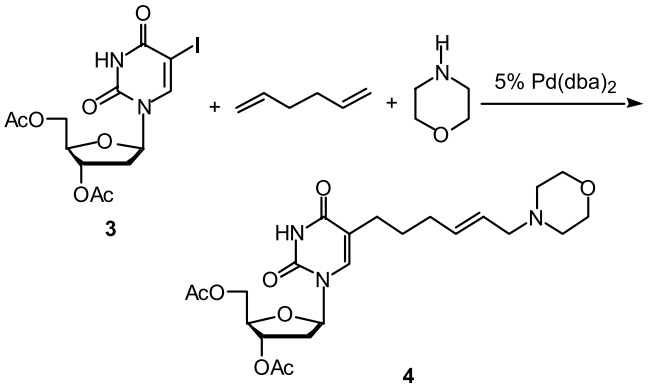


(1)

Interestingly, in all of these reactions a single regio- and stereoisomer, compound **2**, has been observed, although two regioisomers have normally been observed in almost all previous examples of this process.[16] The addition of simple aryl or heteroaryl groups to non-conjugated dienes has previously been observed to give significant amounts of product in which the organic moiety adds to the internal carbon of the carbon–carbon double bond. It is unclear whether the organopalladium intermediate resulting from IdU affords much higher regioselectivity because of increased steric effects or some electronic effect present in this species or whether the modified reaction conditions employed here have a substantial effect.

Because of its polarity, IdU only dissolves easily in a few very polar solvents, such as DMSO, MeOH, and water. To solve this solubility problem, the two hydroxyl groups in IdU were protected as acetoxy groups. The resulting acetyl 5-iodo-2′-deoxyuridine (AcIdU=**3**) was then employed in the coupling process with 1,5-hexadiene and morpholine (Eq. 2). The results shown in Table 2 were somewhat unexpected. No more than a 40% yield of the coupling product **4** could be obtained under a variety of reaction

conditions. Among all of the solvents tested, DMSO appeared to be the best for this process. Surprisingly, MeOH, a relatively good solvent for the coupling of IdU, produced a messy reaction mixture in this case (entry 8). Aqueous solutions were also tested, but water appeared to make the reaction worse (entries 10–13). The reactions run at 100 °C gave somewhat higher yields than those run at 80 °C in most cases. As a chloride source, *n*-Bu_4NCl was better than LiCl for this coupling reaction.



(2)

At this stage, the low yields from the coupling reactions involving IdU (**1**) or AcIdU (**3**) were quite disappointing. Reasoning that perhaps the relatively electron-rich nature of the uracil ring might be inhibiting oxidative addition of the iododeoxyuridines to Pd(0), we decided to examine the effect that the addition of Lewis acids might have on this reaction, figuring that the Lewis acid should coordinate to the carbonyl groups of the uracil ring and thus, facilitate the oxidative addition step, which exhibits characteristics of a nucleophilic aromatic substitution process. After testing several common Lewis acids, we found that the use of zinc chloride ($ZnCl_2$) significantly improved the reaction described in Eq. 1. Some results are summarized in Table 3.

Acetonitrile was initially chosen as the solvent instead of DMSO in order to avoid possible strong coordination between $ZnCl_2$ and the solvent. The coupling reaction run without any Lewis acid added provided only a 30% yield of the desired product (Table 3, entry 1), while the reaction run in the presence of 1 equiv of $ZnCl_2$ gave a 61% yield (entry 2). To confirm that this improvement is due to the presence of the Zn cation and not the presence of additional chloride,

Table 3. Palladium-catalyzed coupling of 5-iodo-2′-deoxyuridine (**1**), 1,5-hexadiene and morpholine[a]

Entry	$ZnCl_2$ (equiv)	Chloride (equiv)	Solvent	Isolated yield of **2** (%)
1	0	*n*-Bu_4NCl (2)	CH_3CN	30
2	1	*n*-Bu_4NCl (2)	CH_3CN	61
3	0	*n*-Bu_4NCl (2)+ LiCl (2)	CH_3CN	Trace
4	0	LiCl (4)	CH_3CN	0
5	1	*n*-Bu_4NCl (2)	4:1 CH_3CN/H_2O	38
6	1	*n*-Bu_4NCl (2)	DMSO	55

[a] All reactions were run in the presence of 5 mol% $Pd(dba)_2$, 5 equiv of 1, 5-hexadiene and 2 equiv of morpholine at 100 °C for 1 day.

we compared the results obtained by the addition of 2 equiv of LiCl, instead of 1 equiv of $ZnCl_2$ (entry 3), and we also ran a reaction with 4 equiv of LiCl and no *n*-Bu_4NCl (entry 4). Neither reaction gave more than trace amounts of the desired product. Thus, the presence of the Zn cation dramatically improves the yields of coupling product. Since IdU is not particularly soluble in acetonitrile, an aqueous solution of acetonitrile was employed as the solvent, but the yield dropped (entry 5). Although it was originally thought that DMSO would not be a very good solvent for this process, because it might strongly coordinate the Lewis acid, the results with DMSO as the solvent were almost as good as those obtained using acetonitrile as the solvent (entry 6).

Since the Lewis acid $ZnCl_2$ might tie up the base morpholine, it was of interest to examine the stoichiometry

Table 4. Effects of the morpholine/$ZnCl_2$ stoichiometry (Eq. 1)[a]

Entry	Morpholine (equiv)	$ZnCl_2$ (equiv)	Isolated yield of **2** (%)
1	1.5	0.5	52
2	1.5	1.0	42
3	1.5	2.0	Trace
4	1.5	4.0	0
5	2.0	0.5	45
6	2.0	1.0	61
7	2.0	2.0	<5
8	3.0	2.0	60
9	4.0	3.0	54
10	5.0	4.0	15

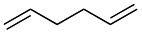
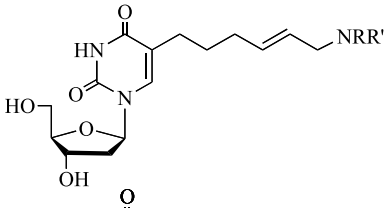
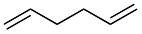
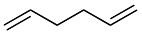
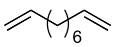
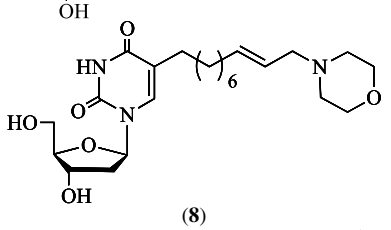
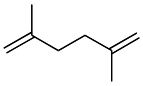
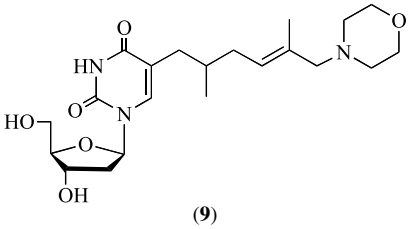
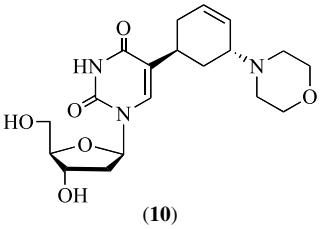
[a] All reactions were run in the presence of 5 mol% $Pd(dba)_2$, 2 equiv of *n*-Bu_4NCl and 5 equiv of 1,5-hexadiene in CH_3CN at 100 °C for 1 day.

Table 2. Palladium-catalyzed coupling of acetyl 5-iodo-2′-deoxyuridine (**3**), 1,5-hexadiene and morpholine (Eq. 2)[a]

Entry	Solvent	Chloride (equiv)	Temperature (°C)	Time (days)	Isolated yield of **4** (%)
1	DMF	*n*-Bu_4NCl	80	2	25
2	DMF	LiCl	80	2	15
3	DMF	LiCl	100	2	29
4	DMSO	*n*-Bu_4NCl	80	2	40
5	DMSO	*n*-Bu_4NCl	100	1	40
6	DMSO	LiCl	80	2	26
7	DMSO	LiCl	100	2	35
8	MeOH	LiCl	100	2	Messy
9	Dioxane	*n*-Bu_4NCl	100	1	0
10	4:1 DMSO/H_2O	*n*-Bu_4NCl	100	1	25
11	1:4 DMSO/H_2O	*n*-Bu_4NCl	100	1	0
12	4:1 CH_3CN/H_2O	*n*-Bu_4NCl	100	1	38
13	1:4 CH_3CN/H_2O	*n*-Bu_4NCl	100	1	0

[a] All reactions were run in the presence of 5 mol% $Pd(dba)_2$ and 2 equiv of chloride using 5 equiv of 1,5-hexadiene and 5 equiv of morpholine.

Table 5. Palladium-catalyzed coupling of 5-iodo-2′-deoxyuridine (**1**), non-conjugated dienes and amines

Entry	Diene	Amine	Product	Yield (%)
1		CH_3NHCH_2Ph		NRR′, $N(CH_3)CH_2Ph$ (**5**) 67[a]
2		*n*-Pr_2NH		$N(n\text{-}Pr)_2$ (**6**) 42
3		*t*-$BuNH_2$		NH(*t*-Bu) (**7**) 0
4			 (**8**)	31
5			 (**9**)	8[b]
6			 (**10**)	30[c] (dr=1:1)

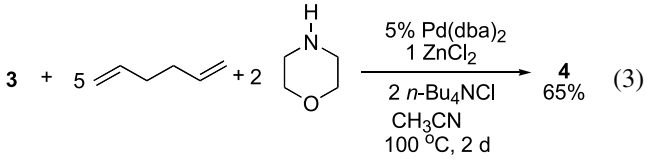
[a] Accompanied by benzylmethylamine (40% recovered).
[b] Accompanied by a 43% yield of side product deoxyuridine (**11**).
[c] Deoxyuridine (**11**) was isolated in 40% yield.

of this reaction. The results shown in Table 4 indicate that the presence of equal amounts of $ZnCl_2$ and morpholine or an excess of $ZnCl_2$ leads to a sharp reduction in the yield of compound **2**. Increasing the amount of $ZnCl_2$, while keeping the amount of morpholine constant, reduced the yield of the product dramatically (entries 1–4). Interestingly, the best results were usually obtained when the amount of morpholine used in the reaction was 1 equiv more than that of $ZnCl_2$ (entries 1, 6, 8, and 9).

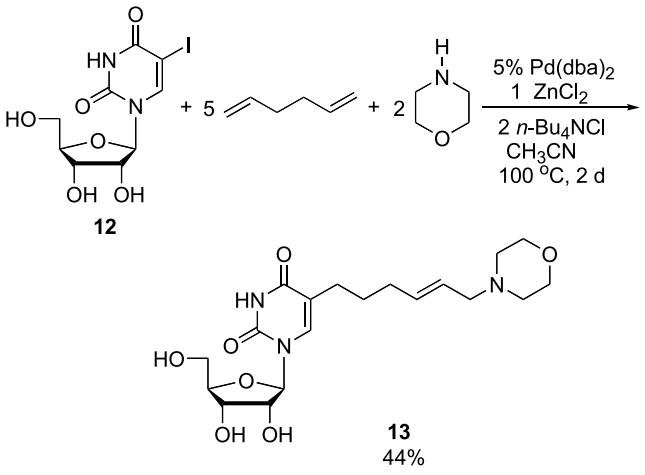
The best reaction conditions described in entry 6 of Table 4 were then applied to the reaction of IdU, and several other non-conjugated dienes and amines. The results are summarized in Table 5. When coupled with IdU and 1,5-hexadiene, benzylmethylamine provided a 62% yield of the desired product (entry 1). This is as good as the reaction of morpholine. Di-*n*-propylamine, however, gave a somewhat lower yield (entry 2). The primary amine *t*-butylamine was also examined in this coupling reaction, but, not surprisingly based on prior results,[16] none of the desired product was obtained. The failure of primary amines may be because they are relatively poor nucleophiles compared with secondary amines (entry 3).

The results with other non-conjugated dienes proved rather disappointing. Compared with 1,5-hexadiene, the longer chain diene 1,9-decadiene gave a much lower yield of the desired product (entry 4). Only a very small amount of the coupling product was obtained from the branched diene 2,5-dimethyl-1,5-hexadiene (entry 5), and the product was contaminated with a 43% yield of a side product 2′-deoxyuridine (HdU=**11**) in which the iodine moiety of the starting material **1** had been reduced off. While 1,4-cyclohexadiene afforded a 30% yield of the desired coupling product, HdU (**11**) was also obtained in a 40% yield (entry 6).

Besides IdU, two other nucleosides, AcIdU and 5-iodouridine (**12**) have also been examined in the model reaction in the presence of $ZnCl_2$. As shown in Eq. 3, a 65% yield of the desired product **4** was obtained from AcIdU. However, **12** produced a somewhat lower yield of 44%, and the product **13** was contaminated with morpholine, which was recovered in 46% yield (Eq. 4).

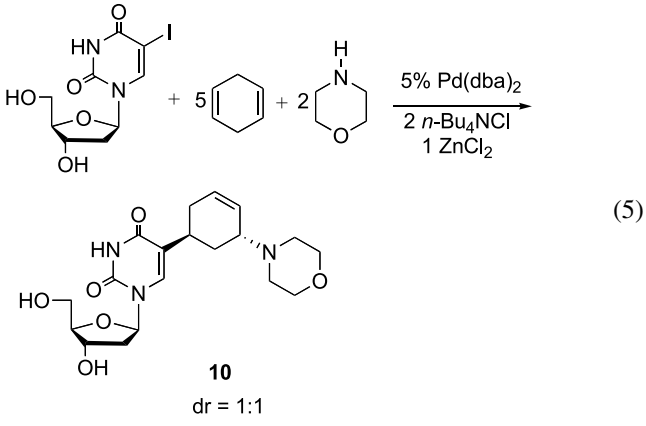


(3)



(4)

Finally, a wide variety of metal salts were examined in the coupling of IdU, 1,5-hexadiene, and morpholine. The percent yield for each of the reagents follow: $CuCl_2 \cdot 2H_2O$ (trace), $NiCl_2$ (26%), $FeCl_3 \cdot 6H_2O$ (35%), CuCl (37%), $CoCl_2 \cdot 6H_2O$ (46%), $BaCl_2 \cdot 2H_2O$ (60%), $CdCl_2$ (63%), ZnO (64%), $Zn(OAc)_2 \cdot 2H_2O$ (68%), $ZnCl_2$ (61%). The Lewis acids $BF_3 \cdot Et_2O$, $AlCl_3$, $SnCl_4 \cdot 5H_2O$, $SnCl_2 \cdot 2H_2O$, $HgCl_2$, $MgCl_2$, and $CrCl_2$ provided none of the anticipated product. Among all of the reagents examined, the Zn, Cd, and Ba reagents provided the best yields. Quite surprising is the observation that even zinc acetate and zinc oxide were very effective reagents, perhaps suggesting that it is not so much the Lewis acid nature of these reagents as some other feature of these particular metals that make them effective additives.



(5)

Further optimization of this process was performed using the reaction of IdU, 1,4-cyclohexadiene and morpholine as a model system (Eq. 5). Investigation of this system revealed the importance of the solvent on the yield of the product **10**, whose stereochemistry is assigned by analogy to compounds we have reported previously.[16,17] When the reaction was run under our previous best conditions [100 °C, 2 days, MeCN as solvent], the coupling product **10** was obtained in only a 30% yield. Switching to DMSO as the solvent at 100 °C afforded a 55% yield. Lowering the temperature to 80 °C for 2 days still gave a 53% yield, which could be raised to 70% by running the reaction for 4 days. The use of DMF as the solvent at 80 °C for 4 days gave a 59% yield. These results led to the development of the following general reaction procedure: 1 equiv of **1**, 5 equiv of diene, 2 equiv of amine, 5 mol% of $Pd(dba)_2$, 2 equiv of n-Bu_4NCl, 1 equiv of $ZnCl_2$ in DMSO at 80 °C.

Using this 'optimal' procedure, we have determined the scope and limitations of this methodology by using other amines and dienes. The results are summarized in Table 6. When coupled with IdU and 1,5-hexadiene, benzylmethylamine provided a 67% yield of the desired product (Table 6, entry 1). This is almost as good as the analogous reaction of morpholine. Di-*n*-propylamine and piperidine, however, gave somewhat lower yields of 42 and 53%, respectively, (entries 2 and 3). Although the primary amine aniline gave a 12% yield of the desired coupling product (entry 4), t-$BuNH_2$ and 3-aminopyridine failed to provide any of the anticipated products.

Several branched and longer chain dienes have also been coupled with morpholine and IdU. The branched dienes 2-methyl-1,5-hexadiene and 2,5-dimethyl-1,5-hexadiene behaved quite differently from linear dienes, and only yielded very small amounts of coupled products (entries 5 and 6). The longer chain dienes 1,9-decadiene and 1,13-tetradecadiene also provided much lower yields than 1,5-hexadiene (entries 7 and 8). The yield appears to drop with the length of the carbon chain. In all of these reactions, a significant amount of the reduced product HdU (**11**) was also observed.

The proposed mechanism for the formation of the reduced product is summarized in Scheme 1. The first step is oxidative addition of IdU (**1**) to Pd(0), the same first step as the coupling reaction. The resulting dUPdI then oxidizes an alcohol present in another molecule of substrate to the corresponding aldehyde or ketone. The resulting palladium hydride complex subsequently undergoes reductive elimination to afford HdU. Thus, it appears that coupling and reduction are two competing reactions. If organopalladium addition to the C–C double bond of the diene is slow, the reduced compound may become the major product. Therefore, protection of the 3′- and 5′- hydroxyl groups of IdU would appear to be required to avoid reduction.

Thus, the hydroxyl groups were once again protected as acetoxy groups and the product examined in the Pd cross-coupling process. AcIdU (**3**) was first employed in the coupling with 2-methyl-1,5-hexadiene. It provided coupled product **18** in 61% yield (Table 6, entry 9). The uridine group is observed to add cleanly to the less-substituted C–C double bond and the amine adds to the terminal carbon of the more substituted double bond. Only the *E*-isomer is observed. 2,5-Dimethyl-1,5-hexadiene, however, did not afford very good results under the same conditions (entry 10). Adding five equiv of morpholine raised the yield to only 28% (entry 11). Like the results with 1,5-hexadiene, only the *E*-isomer was obtained in these reactions and no internal addition of the uridine to the C–C double bond was observed.

Long chain dienes also afforded higher yields when coupled with protected AcIdU, but about one third of the product resulted from addition of the uridine moiety to the internal carbon of the C–C double bond (entries 12 and 13). Once again we have found that the yields decrease when the

Table 6. Palladium-catalyzed coupling of iodouridines, dienes and amines[a]

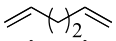
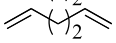
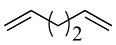
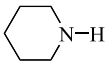
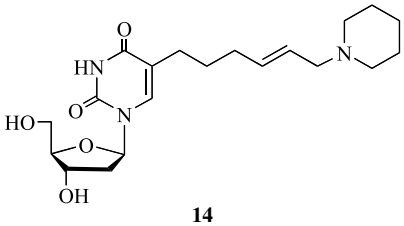
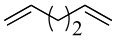
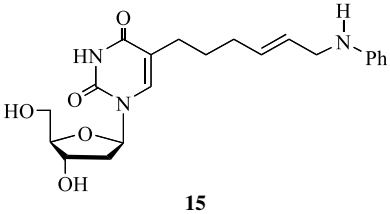
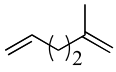
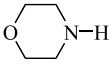
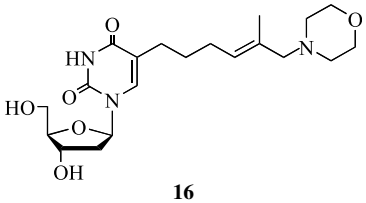
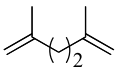
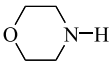
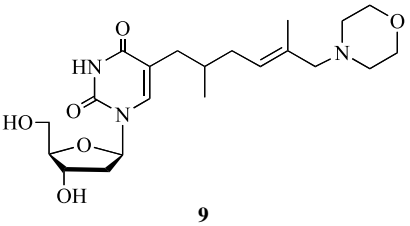
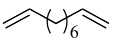
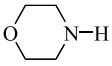
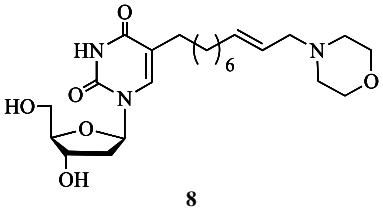
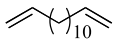
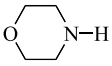
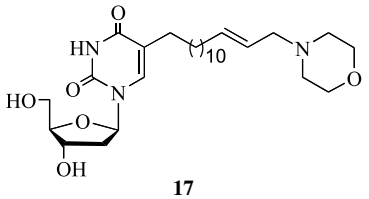
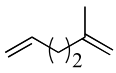
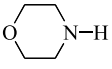
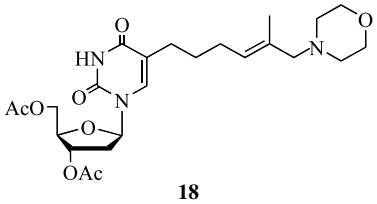
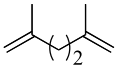
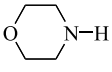
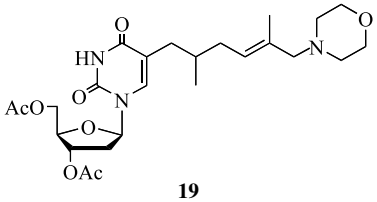
Entry	Iodouridine	Diene	Amine	Time (days)	Product(s)	Isolated yield (%)
1	IdU	5 	2 CH_3NHCH_2Ph	2	**5**	67
2	IdU	5 	2 *n*-Pr_2NH	2	**6**	42
3	IdU	5 	2 	4	 **14**	53
4	IdU	5 	2 $PhNH_2$	4	 **15**	12
5	IdU	5 	2 	4	 **16**	8
6	IdU	5 	2 	4	 **9**	8
7	IdU	5 	2 	4	 **8**	27
8	IdU	5 	2 	4	 **17**	16
9	AcIdU	5 	5 	4	 **18**	61
10	AcIdU	5 	2 	4	 **19**	17

Table 6 (*continued*)

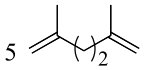
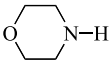
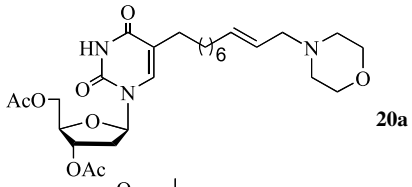
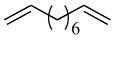
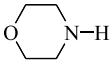
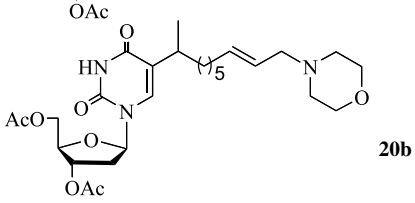
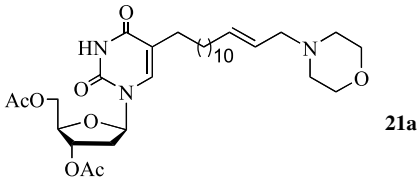
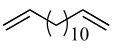
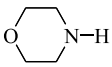
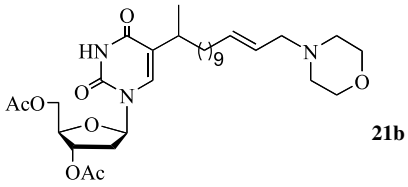
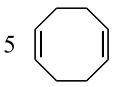
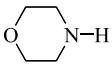
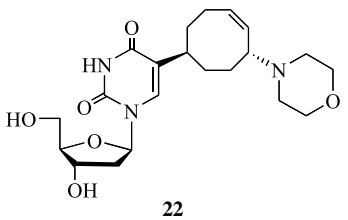
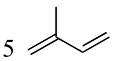
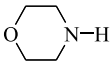
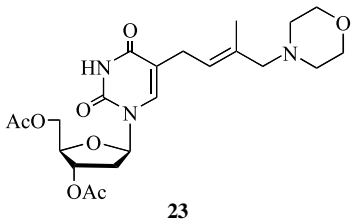
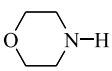
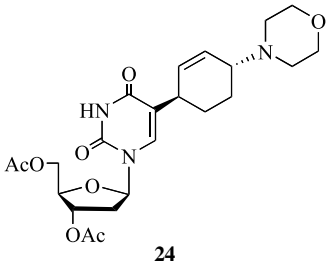
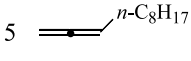
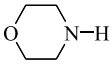
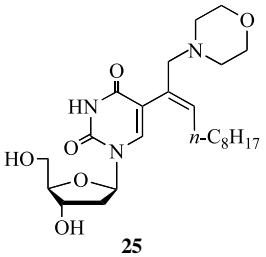
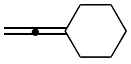
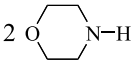
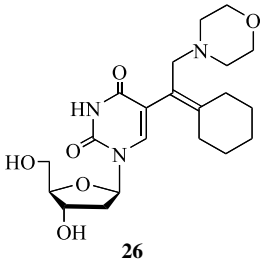
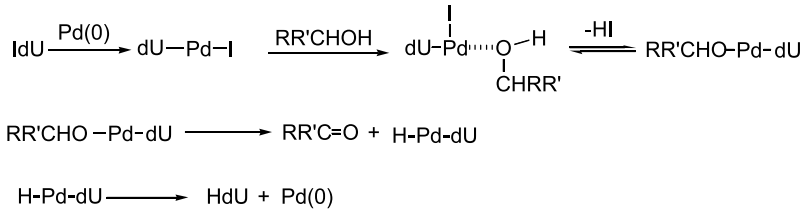
Entry	Iodouridine	Diene	Amine	Time (days)	Product(s)	Isolated yield (%)
11	AcIdU			4	**19**  **20a**	28
12	AcIdU			4	 **20b**	51 (67:33)
					 **21a**	
13	AcIdU			4	 **21b**	34 (66:34)
14	IdU			4	 **22**	63 (dr=1:1)
15	AcIdU			4	 **23**	73
16	AcIdU			4	 **24**	65 (dr=1:1)
17	IdU			2	 **25**	62

Table 6 (*continued*)

Entry	Iodouridine	Diene	Amine	Time (days)	Product(s)	Isolated yield (%)
18	IdU	5 	2 	2	 **26**	65

[a] All reactions were run using 1 equiv of the iodouridine, 5 equiv of diene, 2 equiv of the amine, 1 equiv of $ZnCl_2$, 2 equiv of n-Bu_4NCl and 5% $Pd(dba)_2$ in DMSO at 80 °C unless otherwise specified.



Scheme 1.

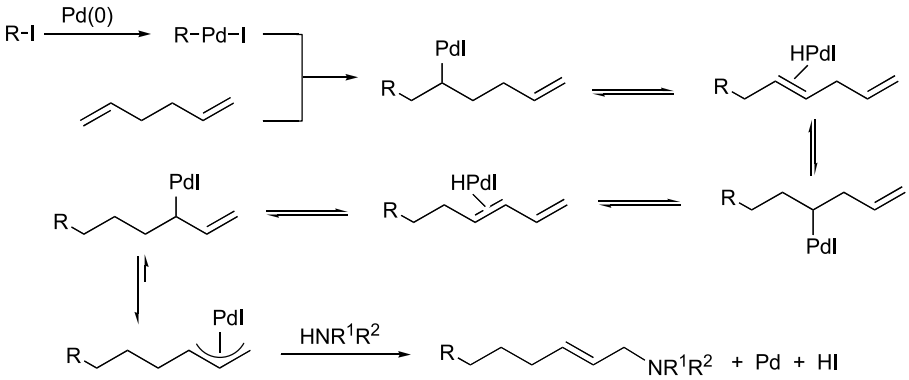
length of the carbon chain increases. In both of these reactions only the *E*-isomers were observed.

In contrast, non-conjugated cyclic dienes provide fairly good yields without protection of the hydroxyl groups. Both 1,4-cyclohexadiene (Eq. 5) and 1,5-cyclooctadiene (Table 6, entry 14) afford a single allylic amine in which organopalladium addition has taken place on one face of the diene and the amine is introduced from the opposite side of the ring. This is consistent with a process involving *syn* addition of an organopalladium species to the double bond, followed by a series of *syn* β-hydride eliminations and additions to form a π-allylpalladium intermediate in which the uridine moiety and the palladium are still on the same side of the ring, and subsequent backside displacement of palladium from the less hindered face of the resulting π-allylpalladium intermediate.

The coupling process for non-conjugated dienes presumably proceeds by a process involving (1) oxidative addition of the iodouridine to Pd(0) to form a vinylic palladium intermediate; (2) vinylic palladium addition to the less hindered C–C double bond of the diene so that the organic moiety adds exclusively to the terminal end of the double bond; (3) palladium migration by a series of palladium hydride β-elimination and readdition reactions to form a π-allylpalladium intermediate; and (4) nucleophilic displacement of the palladium by the amine with simultaneous regeneration of the Pd(0) catalyst (Scheme 2).

2.2. 1,3-Dienes

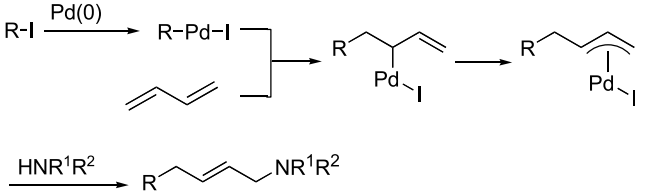
The palladium-catalyzed three component coupling of 1,3-dienes with amines and vinylic halides[19] or aryl halides[20] has been reported to afford low yields of the corresponding addition products. Products from attack of the amine on both ends of the π-allylpalladium intermediate are observed. We have, therefore, examined the palladium-catalyzed coupling of iodouridines, 1,3-dienes and amines as a potentially valuable way to introduce important functionality into the 5 position of nucleosides.



Scheme 2.

When isoprene and 1,3-cyclohexadiene were employed in the coupling with IdU (**1**), neither diene afforded any of the desired product. Good results can be obtained, however, by employing the acetyl protected uridine **3** (Table 6, entries 15 and 16). The stereochemistry of the C–C double bond of the acyclic allylic amine **22** produced by this process has been found to be exclusively *E* and only the terminal allylic amine product is formed. The cyclic 1,3-diene affords a single isomer **23** bearing the uridine moiety and the morpholine unit trans and 1,4 to one another on the cyclohexene ring.

The 1,3-diene reactions can be explained by the following mechanism (Scheme 3). Insertion of the conjugated 1,3-diene into the initially formed organopalladium species gives a π-allylpalladium complex as an intermediate, which subsequently reacts further with the amine nucleophile to form exclusively the 1,4-addition product.



Scheme 3.

2.3. 1,2-Dienes

The palladium-catalyzed coupling of 1,2-dienes, aryl or vinylic halides, and secondary amines provides a convenient synthesis of allylic amines.[21] Numerous intramolecular examples of this chemistry have been reported using aminoallenes as starting materials.[22]

We have also briefly examined the reaction of 1,2-dienes in our coupling process. The reaction of IdU (**1**) with both 1,2-undecadiene and vinylidene cyclohexane afforded good results without protection of the hydroxyl groups (Table 6, entries 17 and 18). The stereochemistry of compound **25** has been assigned using a NOESY experiment. Methoxy allene failed to gave any coupled product. All products consisted of a single regio- and stereoisomer. The products in all cases arise by uridine addition to the central carbon of the 1,2-diene to produce a sigma allylic palladium intermediate, which collapses to a π-allylpalladium complex; substitution of the palladium by the amine subsequently occurs at the less substituted carbon (Scheme 4). Apparently due to the steric hindrance of the uridine moiety, the π-allylpalladium intermediate formed reacts exclusively in the *anti* form affording the indicated stereoisomers.

3. Conclusion

The palladium-catalyzed coupling of C-5 iodopyrimidine nucleosides with a wide variety of dienes and amines in the presence of a Lewis acid, such as $ZnCl_2$, provides a novel and efficient method for the preparation of a wide variety of C-5 aminoalkyl-substituted nucleosides, which may exhibit potent antiviral activities and/or be valuable in oligonucleotide labeling studies. Simple non-conjugated dienes afford good yields of products by a palladium migration mechanism, but the yields drop as the carbon chain of the diene is lengthened or branching is introduced on the carbon–carbon double bond. The yields of the longer or branched dienes can be substantially improved if the hydroxyl groups of the 5-iodo-2′-deoxyuridine are protected as acetyl derivatives. Secondary amines afford higher yields than primary amines. The protected iodouridines and acyclic or cyclic 1,3-dienes undergo the same coupling process in good yields. Good yields of coupled products can also be obtained when using the unprotected iodouridines and 1,2-dienes.

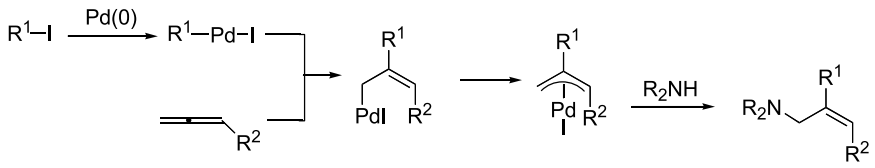
4. Experimental

4.1. Equipment

All ^1H and ^{13}C NMR spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz, respectively. All IR spectra were recorded on a Digilab FTS-7 spectrometer. High resolution mass spectral analyses were performed on a Kratos or MS-50 high resolution mass spectrometer. Gas chromatographic analyses were performed on an HP 5890 chromatograph equipped with an HP-1 Megabore column. Flash chromatography was carried out on 230–400 mesh silica gel. Thin-layer chromatography was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F). Visualization was effected with short wavelength UV light (254 nm) or basic $KMnO_4$ solution (3 g $KMnO_4$+20 g K_2CO_3+5 ml 5% NaOH+300 ml H_2O).

4.2. Reagents

$Pd(dba)_2$ was donated by Kawaken Fine Chemicals Co., Ltd *n*-Bu_4NCl was purchased from Lancaster Synthesis Inc. (+)-5-Iodo-2′-deoxyuridine, 5-iodouridine, 1,5-hexadiene, 1,4-cyclohexadiene, 1,9-decadiene, di-*n*-propylamine, *t*-butylamine, $BF_3\cdot Et_2O$, and $CrCl_2$ were purchased from Aldrich Chemical Company, Inc. Morpholine, dimethyl sulfoxide, *N*,*N*-dimethylformamide, acetonitrile, methanol, acetic anhydride, LiCl, $ZnCl_2$, $CoCl_2\cdot 6H_2O$, $HgCl_2$, and $AlCl_3$ were purchased from Fisher Scientific Company.



Scheme 4.

$Zn(OAc)_2 \cdot 2H_2O$, $BaCl_2 \cdot 2H_2O$, CuCl, $CdCl_2$, $MgCl_2$, $FeCl_3 \cdot 6H_2O$ and $SnCl_2 \cdot 2H_2O$ were purchased from J. T. Baker Chemical Co. ZnO, $CuCl_2 \cdot 2H_2O$, and $SnCl_4 \cdot 5H_2O$ were purchased from Mallinckrodt Chemical Works. $NiCl_2$ was purchased from Research Organic/Inorganic Chemical Corpn. Benzylmethylamine was purchased from Eastman Kodak Co.

4.2.1. Preparation of acetyl 5-iodo-2′-deoxyuridine (3).[23] To a solution of 5-iodo-2′-deoxyuridine (3.0 g, 8.5 mmol) in 30 ml of pyridine was slowly added 8.0 ml (85 mmol) of acetic anhydride at 0 °C. The resulting mixture was stirred at room temperature for 3 h, then poured into 200 ml of cold 2 N HCl and extracted with ethyl acetate three times. The organic layer was washed with satd $NaHCO_3$ and satd NaCl aqueous solutions, respectively, then dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the product was obtained as a white solid in a 93% yield; mp 161–162 °C (lit. mp 160.5–162 °C,[24] 158–160 °C[25]): ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.18 (m, 1H), 2.21 (s, 3H), 2.55 (ddd, J=14.1, 5.7, 2.1 Hz, 1H), 4.30 (m, 1H), 4.33 (dd, J=12.0, 2.7 Hz, 1H), 4.42 (dd, J=12.0, 3.0 Hz, 1H), 5.23 (dt, J=6.6, 1.8 Hz, 1H), 6.30 (dd, J=8.1, 5.7 Hz, 1H), 7.97 (s, 1H), 8.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.1, 38.3, 63.8, 68.9, 74.1, 82.6, 85.4, 143.7, 149.8, 159.6, 170.1, 170.3.

4.3. General procedure for the palladium-catalyzed coupling of C-5 iodopyrimidine nucleosides, nonconjugated dienes, and amines

To a 1 dram vial with a micromagnetic stirring bar were added 0.125 or 0.25 mmol of C-5 iodopyrimidine nucleoside; 0.625 or 1.25 mmol of diene; 0.25, 0.50, or 1.25 mmol of amine; 5 mol % of $Pd(dba)_2$, 0.25 or 0.50 mmol of n-Bu_4NCl; 0.125, 0.25, or 1.00 mmol of $ZnCl_2$; and 0.5 or 1 ml of CH_3CN or DMSO. The vial was capped with a screw-cap containing a teflon liner. The resulting mixture was stirred at 80 or 100 °C for 1–2 days. The mixture was then allowed to cool to room temperature. After removal of the solvent, the residue was purified by flash chromatography on a silica gel column using a mixture of hexanes and ethyl acetate as eluent.

4.3.1. Compound 2. Compound **2** was obtained as a light yellow wax in a 61% yield from the coupling of (+)-5-iodo-2′-deoxyuridine, 5 equiv of 1,5-hexadiene and 2 equiv of morpholine using the procedure above: ^{1}H NMR (CD_3SOCD_3) δ 1.47 (quintet, J=7.5 Hz, 2H), 1.97 (q, J=6.9 Hz, 2H), 2.07 (m, 2H), 2.16 (t, J=7.5 Hz, 2H), 2.29 (br s, 4H), 2.84 (d, J=6.0 Hz, 2H), 3.37 (m, 1H), 3.51–3.57 (m, 7H), 3.75 (dd, J=6.0, 3.0 Hz, 1H), 4.23 (m, 1H), 5.23 (m, 1H), 5.39 (dt, J=15.6, 6.3 Hz, 1H), 5.54 (dt, J=15.6, 6.3 Hz, 1H), 6.15 (t, J=6.6 Hz, 1H), 7.68 (s, 1H); ^{13}C NMR (CD_3SOCD_3) δ 25.9, 27.3, 31.3, 42.9, 52.2, 61.2, 63.4, 65.3, 70.4, 83.9, 87.3, 113.3, 124.2, 135.8, 136.3, 150.3, 163.3; IR (neat) 3402, 3196, 2934, 2860, 1704, 1669, 1462, 1278, 1110 cm^{-1}; HRMS for $C_{19}H_{29}N_3O_6$: calcd 395.2056, found 395.2051.

4.3.2. Compound 4. Compound **4** was obtained as a light yellow solid in a 65% yield from the coupling of acetyl 5-iodo-2′-deoxyuridine (**3**), 5 equiv of 1,5-hexadiene and 2 equiv of morpholine using the procedure above: ^{1}H NMR ($CDCl_3$) δ 1.59 (quintet, J=7.5 Hz, 2H), 2.08 (m, 2H), 2.11 (s, 3H), 2.12 (s, 3H), 2.16 (m, 1H), 2.31 (m, 2H), 2.45 (t, J=4.5 Hz, 4H), 2.50 (m, 1H), 2.94 (d, J=6.0 Hz, 2H), 3.72 (t, J=4.5 Hz, 4H), 4.25 (m, 1H), 4.33 (dd, J=12.3, 3.3 Hz, 1H), 4.39 (dd, J=12.3, 4.5 Hz, 1H), 5.21 (dt, J=6.6, 1.8 Hz, 1H), 5.49 (dt, J=15.3, 6.3 Hz, 1H), 5.60 (dt, J=15.3, 6.3 Hz, 1H), 6.31 (dd, J=8.7, 5.7 Hz, 1H), 7.22 (s, 1H), the peak for NH was not observed; ^{13}C NMR ($CDCl_3$) δ 20.8 (two carbon peaks), 26.8, 31.9, 37.4, 40.8, 53.3, 61.0, 63.8, 66.8, 74.1, 82.0, 84.8, 115.5, 126.3, 133.9, 134.3, 150.2, 163.2, 170.0, 170.3; IR (neat) 3181, 2958, 2933, 2857, 1745, 1709, 1685, 1458, 1236, 1116 cm^{-1}; HRMS for $C_{23}H_{33}N_3O_8$: calcd 479.2268, found 479.2275. The compound was not stable enough to measure its melting point.

4.3.3. Compound 5. Compound **5** was obtained as a light yellow wax in a 67% yield from the coupling of (+)-5-iodo-2′-deoxyuridine, 5 equiv of 1,5-hexadiene and 2 equiv of benzylmethylamine using the standard procedure: ^{1}H NMR (CD_3OD) δ 1.64 (quintet, J=7.5 Hz, 2H), 2.15 (q, J=6.6 Hz, 2H), 2.22 (m, 2H), 2.32 (t, J=7.5 Hz, 2H), 2.70 (s, 3H), 3.54 (d, J=6.9 Hz, 2H), 3.76 (m, 2H), 3.92 (dd, J=6.0, 3.0 Hz, 1H), 4.18 (s, 2H), 4.42 (m, 1H), 5.65 (dt, J=15.3, 7.2 Hz, 1H), 5.97 (dt, J=15.6, 6.9 Hz, 1H), 6.27 (t, J=6.3 Hz, 1H), 7.41–7.52 (m, 5H), 7.88 (s, 1H), the OH and NH peaks overlapped with the water peak at δ 4.94; ^{13}C NMR (CD_3OD) δ 27.1, 28.5, 33.2, 41.3, 53.6, 59.1, 60.6, 62.7, 72.2, 86.3, 88.8, 115.3, 121.7, 130.0, 130.2, 130.8, 131.7, 133.1, 142.1, 152.1, 165.8; IR (neat) 3370, 3026, 2925, 2500, 1686, 1669, 1459, 1277, 1097 cm^{-1}; HRMS for $C_{23}H_{31}N_3O_5$: calcd 429.2264, found 429.2264.

4.3.4. Compound 6. Compound **6** was obtained as a yellow wax in a 42% yield from the coupling of (+)-5-iodo-2′-deoxyuridine, 5 equiv of 1,5-hexadiene and 2 equiv of di-n-propylamine using the standard procedure: ^{1}H NMR (CD_3SOCD_3) δ 0.86 (t, J=7.5 Hz, 6H), 1.51 (m, 2H), 1.64 (sextet, J=7.5 Hz, 4H), 2.06 (m, 4H), 2.18 (t, J=7.5 Hz, 2H), 2.75 (t, J=7.5 Hz, 4H), 2.86 (m, 2H), 3.40 (br s, 2H), 3.58 (m, 3H), 3.76 (m, 1H), 4.26 (m, 1H), 5.33 (m, 1H), 5.61 (dt, J=15.0, 6.6 Hz, 1H), 5.94 (dt, J=15.0, 6.6 Hz, 1H), 6.15 (t, J=6.6 Hz, 1H), 7.75 (s, 1H); ^{13}C NMR (CD_3SOCD_3) δ 15.7, 25.9, 27.3, 31.3, 42.8, 59.5, 61.2, 63.4, 65.3, 83.9, 87.3, 113.3, 124.8, 135.8, 136.3, 150.3, 163.3; IR (neat) 3350, 3023, 2943, 2568, 1702, 1676, 1433, 1260, 1087 cm^{-1}.

4.3.5. Compound 8. Compound **8** was obtained as a yellow wax in a 31% yield from the coupling of (+)-5-iodo-2′-deoxyuridine, 5 equiv of 1,9-decadiene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR (CD_3OD) δ 1.31–1.40 (m, 8H), 1.48 (m, 2H), 2.08 (m, 2H), 2.24 (m, 2H), 2.28 (t, J=7.2 Hz, 2H), 2.84 (br s, 4H), 3.33 (m, 2H), 3.78 (br s, 6H), 3.92 (s, 1H), 4.42 (s, 1H), 5.53 (dt, J=15.6, 6.9 Hz, 1H), 5.85 (dt, J=15.6, 6.3 Hz, 1H), 6.15 (m, 1H), 7.82 (s, 1H), the OH and NH peaks overlapped with the water peak at δ 4.87; IR (neat) 3452, 2928, 2856, 2542, 1693, 1668, 1462, 1279 cm^{-1}. Other spectra were not taken because of a lack of material.

4.3.6. Compounds 10a and 10b. Compounds **10a** and **10b**

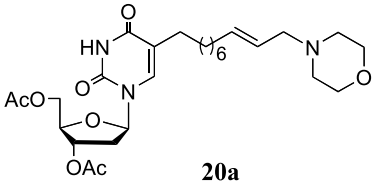
were obtained as a light yellow waxy, inseparable 50:50 mixture of diastereomers in a 70% combined yield from the coupling of (+)-5-iodo-2′-deoxyuridine, 5 equiv of 1,4-cyclohexadiene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR (CD_3OD) δ 1.85 (m, 1H), 2.22–2.42 (m, 4H), 3.00 (m, 1H), 3.10–3.21 (m, 4H), 3.56 (m, 1H), 3.74 (dd, J=12.0, 3.3 Hz, 1H), 3.80 (dd, J=12.0, 2.7 Hz, 1H), 3.85 (t, J=4.8 Hz, 4H), 3.93 (m, 1H), 4.41 (m, 1H), 5.88 (m, 1H), 6.25 (m, 1H), 6.30 (t, J=6.6 Hz, 1H), 6.31 (t, J=6.6 Hz, 1H), 7.86 (s, 1H), 7.89 (s, 1H), the OH and NH peaks overlapped with the water peak at δ 4.93; ^{13}C NMR (CD_3OD) δ 27.7, 28.0, 29.5, 29.6, 40.1, 48.7, 49.7, 58.2, 61.3, 61.5, 66.7, 70.9, 71.0, 85.0, 85.2, 87.5, 87.6, 117.6, 117.8, 126.3, 126.4, 130.3, 135.8, 135.9, 151.3, 164.9, 165.0; IR (neat) 3402, 3196, 2928, 2855, 1708, 1666, 1465, 1276, 1110 cm^{-1}; HRMS for $C_{19}H_{27}N_3O_6$: calcd 393.1899, found 393.1890.

4.3.7. Compound 13. Compound **13** was obtained as a yellow wax in a 44% yield from the coupling of 5-iodouridine, 5 equiv of 1,5-hexadiene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR (CD_3OD) δ 1.57 (quintet, J=7.2 Hz, 2H), 2.06 (q, J=6.6 Hz, 2H), 2.27 (t, J=7.2 Hz, 2H), 2.67 (br s, 4H), 3.19 (m, 2H), 3.71–3.79 (m, 6H), 3.99 (m, 1H), 4.15–4.21 (m, 2H), 5.50 (dt, J=15.3, 6.9 Hz, 1H), 5.77 (dt, J=15.3, 6.6 Hz, 1H), 5.89 (d, J=4.2 Hz, 1H), 7.86 (s, 1H), the OH and NH peaks overlapped with the water peak at δ 4.96; ^{13}C NMR (CD_3OD) δ 27.1, 28.5, 32.6, 53.7, 61.3, 62.2, 66.7, 71.4, 75.6, 86.5, 90.1, 115.4, 124.1, 138.5, 139.1, 152.5, 165.8; IR (neat) 3325, 3180, 2933, 2866, 2479, 1703, 1668, 1457, 1271, 1107 cm^{-1}; HRMS for $C_{19}H_{29}N_3O_7$: calcd 411.2006, found 411.2003.

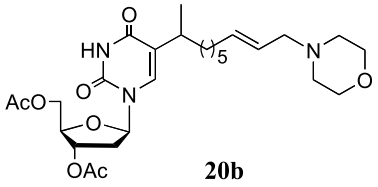
4.3.8. Compound 14. Compound **14** was obtained as a yellow wax in a 53% yield from the coupling of (+)-5-iodo-2′-deoxyuridine, 5 equiv of 1,5-hexadiene and 2 equiv of piperidine using the standard procedure: ^{1}H NMR (CD_3OD) δ 1.73–1.77 (m, 2H), 1.80–2.11 (m, 6H), 2.20 (q, J=6.9 Hz, 2H), 2.29 (m, 2H), 2.35–2.40 (m, 6H), 3.18 (d, J=6.0 Hz, 2H), 3.61–3.67 (m, 3H), 3.96 (dd, J=6.3, 3.0 Hz, 1H), 4.46 (m, 1H), 5.66 (dt, J=15.3, 7.2 Hz, 1H), 6.09 (dt, J=15.3, 7.2 Hz, 1H), 6.33 (t, J=6.9 Hz, 1H), 7.92 (s, 1H), the OH and NH peaks overlapped with the water peak at δ 4.94; ^{13}C NMR (CD_3OD) δ 23.4, 24.7, 25.8, 27.4, 31.3, 40.0, 53.5, 60.6, 61.4, 70.9, 85.0, 87.5, 114.1, 124.6, 136.8, 137.1, 151.0, 162.5; IR (neat) 3400, 3042, 2933, 2500, 1702, 1665, 1446, 1277, 1098 cm^{-1}; HRMS for $C_{20}H_{29}N_3O_5$: calcd 393.2834, found 393.2838.

4.3.9. Compound 18. Compound **18** was obtained as a light yellow solid in a 61% yield from the coupling of diacetyl 5-iodo-2′-deoxyuridine, 5 equiv of 2-methyl-1,5-hexadiene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR ($CDCl_3$) δ 1.56 (quintet, J=7.5 Hz, 2H), 1.63 (s, 3H), 2.07 (q, J=7.5 Hz, 2H), 2.119 (s, 3H), 2.123 (s, 3H), 2.18 (m, 1H), 2.33 (m, 6H), 2.48 (m, 1H), 2.82 (s, 2H), 3.70 (t, J=7.5 Hz, 4H), 4.25 (m, 1H), 4.37 (m, 2H), 5.21 (dt, J=6.6, 1.8 Hz, 1H), 5.31 (t, J=7.5 Hz, 1H), 6.33 (dd, J=8.7, 5.7 Hz, 1H), 7.23 (s, 1H), 9.53 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.10, 20.82, 20.92, 27.00, 27.48, 28.52, 37.55, 53.53, 63.91, 67.08, 67.73, 74.16, 82.14, 84.93, 115.82, 127.40, 132.66, 134.30, 150.25, 163.10, 170.13, 170.43; IR (neat) 3174, 2967, 2943, 2863, 1740, 1709, 1677, 1459, 1245, 1124 cm^{-1}; HRMS for $C_{24}H_{35}N_3O_8$: calcd 493.2424, found 493.2429. This compound was not stable enough to measure its melting point.

4.3.10. Compounds 20a and 20b. Compounds **20a** and **20b** were obtained as a yellow wax and an inseparable 67:33 mixture of isomers in a 51% combined yield from the coupling of diacetyl 5-iodo-2′-deoxyuridine, 5 equiv of 1,9-decadiene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR (CD_3COCD_3) δ 1.15 (d, J=6.9 Hz, 3H, **20b**), 1.23–1.70 (m, 10H), 1.99–2.07 (m, 4H), 2.08 (s, 3H), 2.11 (s, 3H), 2.28–2.51 (br m, 7H), 2.90 (d, J=6.3 Hz, 1H), 3.59 (t, J=4.8 Hz, 4H), 4.22–2.31 (m, 2H), 4.37 (m, 1H), 5.28 (m, 1H), 5.43 (m, 1H), 5.60 (m, 1H), 6.30 (dd, J=8.4, 6.0 Hz, 1H), 7.38 (s, 1H, **20b**), 7.49 (s, 1H), 9.69 (br s, 1H); ^{13}C NMR (CD_3COCD_3) δ 19.0, 19.3, 20.1, 20.13, 20.2, 26.9, 27.1, 31.4, 32.2, 35.3, 36.5, 36.6, 53.4, 53.6, 61.0, 63.9, 64.0, 66.5, 66.6, 74.5, 74.6, 82.1, 82.2, 84.8, 85.2, 114.9, 119.4, 126.5, 134.2, 134.5, 135.4, 150.1, 150.4, 162.8, 163.1, 169.9, 170.0; IR (neat) 3188, 2956, 2928, 2860, 1741, 1698, 1680, 1455, 1234, 1109 cm^{-1}; HRMS for $C_{27}H_{41}N_3O_8$: calcd 535.2894, found 535.2900.

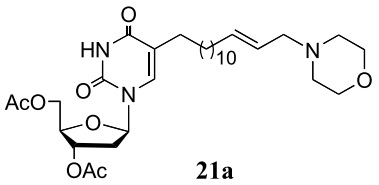


20a

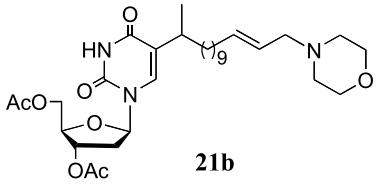


20b

4.3.11. Compounds 21a and 21b. Compounds **21a** and **21b** were obtained as a yellow wax as an inseparable 66:34 mixture of isomers in a 34% combined yield from the coupling of diacetyl 5-iodo-2′-deoxyuridine, 5 equiv of 1,13-tridecadiene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR (CD_3COCD_3) δ 1.10 (d, J=6.9 Hz, 3H, **21b**), 1.15–1.49 (m, 17H), 1.99–2.05 (m, 4H), 2.07 (s, 3H), 2.09 (s, 3H), 2.69–2.88 (br m, 7H), 2.87 (d, J=6.3 Hz), 3.58 (t, J=4.8 Hz, 4H), 4.25–4.37 (m, 3H), 5.25 (m, 1H), 5.47 (m, 1H), 5.62 (m, 1H), 6.30 (dd, J=8.4, 6.0 Hz, 1H), 7.37 (s, 1H, **21b**), 7.48 (s, 1H), 9.69 (br s, 1H); ^{13}C NMR (CD_3COCD_3) δ 20.1, 20.8, 20.9, 27.7, 33.0, 36.1, 37.3, 37.4, 54.2, 61.8, 64.6, 64.7, 67.3, 69.2, 69.3, 75.3, 75.4, 115.7, 120.2, 127.3, 134.9, 135.3, 136.1, 150.9, 151.1, 163.5, 163.8, 170.7, 170.8; IR (neat) 3177, 2950, 2913, 2830, 1723, 1698, 1676, 1434, 1230, 1098 cm^{-1}; HRMS for $C_{31}H_{49}N_3O_8$: calcd 591.3520, found 591.3515.



21a



21b

4.3.12. Compound 22. Compound **22** was obtained as a yellow solid in a 63% yield from the coupling of (+) 5-iodo-2′-deoxyuridine, 5 equiv of 1,5-cyclooctadiene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR (CD_3OD) δ 1.55 (m, 2H), 1.77–1.95 (m, 4H), 2.07–2.35 (m, 7H), 2.63 (br s, 4H), 2.80 (m, 1H), 3.73 (t, J=7.5 Hz, 5H), 3.95 (m, 1H), 4.30 (m, 1H), 5.63–5.84 (m, 2H), 6.34 (t, J=6.6 Hz, 1H), 7.84 (s, 0.5H), 7.85 (s, 0.5H), the OH and NH peaks overlapped with the water peak at δ 4.94; ^{13}C NMR (CD_3OD) δ 24.6, 24.7, 30.6, 30.7, 31.6, 31.7, 32.2, 32.5, 34.6, 34.7, 40.1, 61.3, 61.4, 62.5, 63.7, 66.5, 70.9, 85.1, 87.4, 87.5, 121.2, 121.4, 128.8, 130.7, 135.3, 142.9, 151.7, 165.5; IR (neat) 3365, 3054, 2932, 2498, 1689, 1663, 1443, 1286, 1116 cm^{-1}; HRMS for $C_{21}H_{31}N_3O_6$: calcd 421.2213, found 421.2206. This compound was not stable enough to measure its melting point.

4.3.13. Compound 23. Compound **23** was obtained as a yellow wax in a 73% yield from the coupling of diacetyl 5-iodo-2′-deoxyuridine, 5 equiv of isoprene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 2.18 (m, 1H), 2.35 (t, J=4.5 Hz, 4H), 2.50 (m, 1H), 2.85 (s, 2H), 3.08 (d, J=6.9 Hz, 2H), 3.70 (t, J=4.8 Hz, 4H), 4.26 (m, 1H), 4.32 (m, 2H), 5.20 (dt, J=6.6, 1.8 Hz, 1H), 5.36 (t, J=6.6 Hz, 1H), 6.28 (dd, J=8.7, 5.7 Hz, 1H), 7.20 (s, 1H), 9.69 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.1, 20.7, 20.8, 25.8, 37.4, 53.4, 63.8, 66.9, 67.2, 74.1, 82.1, 85.2, 114.6, 123.4, 134.5, 135.0, 150.4, 163.2, 170.1, 170.3; IR (neat) 3180, 2977, 2956, 2860, 1749, 1699, 1670, 1457, 1253, 1118 cm^{-1}; HRMS for $C_{22}H_{31}N_3O_8$: calcd 466.2111, found 465.2113.

4.3.14. Compound 24. Compound **24** was obtained as a yellow solid in a 65% yield from the coupling of diacetyl 5-iodo-2′-deoxyuridine, 5 equiv of 1,3-cyclohexadiene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR ($CDCl_3$) δ 1.36 (m, 2H), 1.65–1.84 (m, 2H), 2.11 (s, 3H), 2.12 (s, 3H), 2.18 (m, 1H), 2.50 (m, 1H), 2.62 (br s, 4H), 3.26 (br s, 1H), 3.48 (br s, 1H), 3.74 (t, J=4.5 Hz, 4H), 4.25 (m, 1H), 4.33 (m, 2H), 5.22 (m, 1H), 5.68 (m, 1H), 5.85 (m, 1H), 6.30 (m, 1H), 7.16 (s, 1H), 9.66 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.83, 20.91, 22.52, 22.79, 28.79, 29.33, 33.52, 33.76, 37.47, 37.54, 49.00, 60.16, 60.38, 63.92, 67.31, 74.29, 82.13, 82.19, 85.21, 119.14, 119.27, 131.03, 131.08, 131.50, 134.19, 134.31, 150.12, 150.14, 162.85, 170.14, 170.40; IR (neat) 3156, 2987, 2933, 2854, 1747, 1695, 1677, 1454, 1240, 1122 cm^{-1}; HRMS for $C_{23}H_{31}N_3O_8$: calcd 477.2111, found 477.2113. This compound was not stable enough to measure its melting point.

4.3.15. Compound 25. Compound **25** was obtained as a yellow solid in a 62% yield from the coupling of (+) 5-iodo-2′-deoxyuridine, 5 equiv of 1,2-undecadiene and 2 equiv of morpholine using the standard procedure: ^{1}H NMR (CD_3OD) δ 0.89 (t, J=6.9 Hz, 3H), 1.27 (m, 12H), 2.00 (m, 2H), 2.26 (m, 2H), 2.43 (br s, 4H), 3.11 (d, J=12.3 Hz, 2H), 3.24 (d, J=12.3 Hz, 1H), 3.64 (t, J=4.8 Hz, 4H), 3.72 (t, J=2.7 Hz, 2H), 3.94 (dd, J=6.0, 3.0 Hz, 1H), 4.40 (dt, J=6.0, 3.0 Hz, 1H), 5.75 (t, J=7.2 Hz, 1H), 6.32 (t, J=6.6 Hz, 1H), 7.95 (s, 1H), the OH and NH peaks overlapped with the water peak at δ 4.87; ^{13}C NMR (CD_3OD) δ 13.1, 22.4, 28.8, 29.0, 29.1, 31.7, 40.6, 43.8, 52.6, 61.4, 64.2, 64.3, 65.5, 71.0, 85.4, 87.9, 114.4, 126.8, 140.1, 150.7, 164.0, 175.7; IR (neat) 3409, 3186, 2928, 2846, 1689, 1657, 1460, 1279, 1118 cm^{-1}; HRMS for $C_{21}H_{39}N_3O_6$: calcd 465.2839, found 465.2837. This compound was not stable enough to measure its melting point.

4.3.16. Compound 26. Compound **26** was obtained as a yellow wax in a 65% yield from the coupling of (+) 5-iodo-2′-deoxyuridine, 5 equiv of vinylidenecyclohexane and 2 equiv of morpholine using the standard procedure: ^{1}H NMR (CD_3OD) δ 1.57–1.62 (m, 6H), 2.02–2.48 (m, 10H), 3.18 (br s, 2H), 3.62–3.94 (m, 6H), 3.93 (br t, J=10.5 Hz, 1H), 4.41 (dt, J=6.0, 3.0 Hz, 1H), 4.89 (br s, 1H), 6.33 (m, 1H), 7.85 (s, 1H), the OH and NH peaks overlapped with the water peak at δ 4.87; ^{13}C NMR (CD_3OD) δ 26.5, 27.6, 27.9, 28.0, 30.2, 32.7, 40.4, 53.2, 57.7, 57.9, 61.4, 61.6, 66.6, 71.0, 71.1, 85.1, 87.7, 114.6, 115.0, 119.1, 119.5, 139.0, 139.2, 145.5, 145.7, 151.0, 151.1, 264.1; IR (neat) 3389, 3167, 2956, 2855, 1700, 1637, 1465, 1270, 1123 cm^{-1}; HRMS for $C_{21}H_{31}N_3O_6$: calcd 421.2213, found 421.2212.

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Nickel-catalyzed couplings and cyclizations involving allenes, aldehydes, and organozincs

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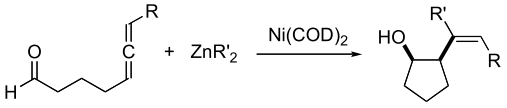
Abstract—Cyclizations of allenyl aldehydes and intermolecular couplings of allenes and aldehydes provide a direct procedure for the preparation of homoallylic alcohols. The couplings and cyclizations involve the use of diorganozinc reagents as reducing agents and $Ni(COD)_2$ as the catalyst.

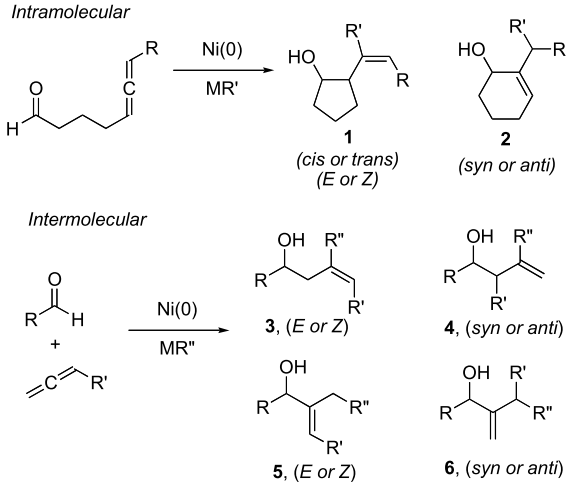
1. Introduction

Homoallylic alcohols are versatile building blocks typically prepared by the addition of allylmetals to aldehydes,[1] the addition of vinyl organometallics to epoxides,[2] or carbonyl ene reactions.[3] In addition to these well-established methods, an alternate preparative method for homoallylic alcohol synthesis involves the coupling of aldehydes and allenes. The earliest reports of allene/aldehyde cyclizations, in reports from Pattenden and Crandall, involved single electron transfer pathways.[4] Those studies demonstrated that carbonyl-derived radical anions undergo efficient cyclizations with allenes to generate allylic or homoallylic alcohols depending on the substrate structure and tether length. Studies from Grigg developed complementary allene/aldehyde couplings by involving a third aryl iodide component in a novel palladium-catalyzed procedure.[5] In order to expand the scope of allene/aldehyde addition reactions, we envisioned that the nickel-catalyzed coupling of allenes, aldehydes, and organozincs would afford a useful entry to homoallylic alcohols, and our group, concurrently with Kang, recently reported the first examples of nickel-catalyzed reductive and alkylative cyclizations of allenyl aldehydes (Eq. 1).[6] Additional approaches to nickel- and palladium-catalyzed aldehyde/allene couplings have recently appeared,[7,8] and other attractive nickel-catalyzed approaches to homoallylic alcohols have been reported.[9–11]



(1)

Exocyclizations of allenyl aldehydes may potentially proceed with selectivity toward either the proximal or distal π-system of the allene to generate the two constitutional isomers **1** or **2** (Scheme 1). Additions to the proximal π-system could be complicated by unselective formation of the trisubstituted alkene or of the two stereogenic centers, whereas addition to the distal π-system could be complicated by unselective formation of the two stereogenic centers. The corresponding intermolecular couplings are inherently more complex than cyclizations since they may proceed to generate four different constitutional isomers **3**–**6**



Scheme 1. Possible addition modes in aldehyde/allene couplings.

Keywords: Cyclizations; Couplings; π-System.
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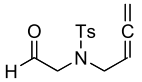
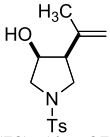
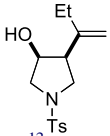
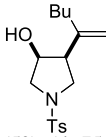
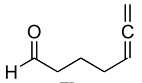
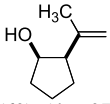
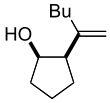
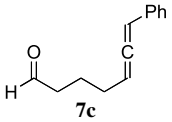
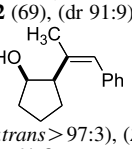
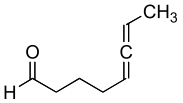
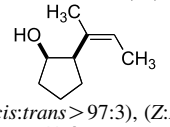
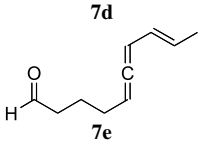
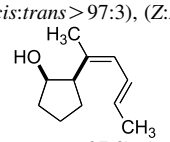
depending on the allene orientation (Scheme 1). Further complexities in the intermolecular couplings would result from lack of stereocontrol in the formation of trisubstituted alkenes or of the two stereogenic centers. Despite these potential hurdles, we set out to gain an understanding of the scope and efficiency of nickel-catalyzed additions of aldehydes and allenes. We describe in this paper, a more complete report of our previously communicated studies of nickel-catalyzed allenyl aldehyde cyclizations and provide the first examples of the corresponding fully intermolecular alkylative couplings of aldehydes, allenes, and organozincs.

2. Results

Our studies began with an examination of cyclizations of allenyl aldehydes that possess monosubstituted allenes in the presence of simple diorganozincs (Table 1, entries 1–5). Both heterocyclic (entries 1–3)[12] and carbocyclic (entries 4–5) frameworks could be prepared, and organozincs that either lacked (entries 1 and 4) or possessed (entries 2, 3, and 5) β-hydrogens were tolerated. Commercial organozincs could be directly used, or the organozinc may be prepared in situ by transmetalation of an organolithium reagent with zinc chloride. Diastereoselectivities in favor of the cis isomer were generally excellent, although cyclizations with $BuLi/ZnCl_2$ as the transmetalating component were less selective than the corresponding cyclizations with dimethylzinc or diethylzinc.

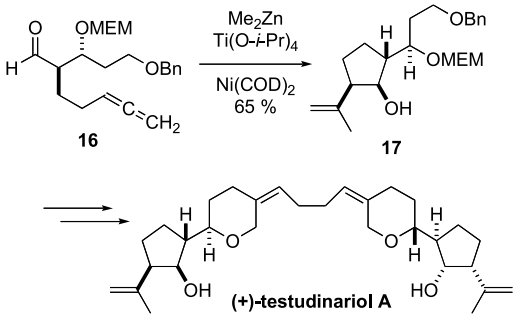
Following these initial studies, we next examined cyclizations of allenyl aldehydes that possess a 1,3-disubstituted allene. In all cases, the cis relationship of the contiguous

Table 1. Allenyl aldehyde cyclizations

Entry	Allenyl aldehyde	Organozinc	Product (%yield)
1	 **7a**	$ZnMe_2$	 **8** (70), (dr>97:3)
2	**7a**	$ZnEt_2$	 **9** (64),[12] (dr>97:3)
3	**7a**	$BuLi/ZnCl_2$	 **10** (52), (dr 75:25)
4	 **7b**	$MeLi/ZnCl_2$	 **11** (69), (dr>97:3)[a]
5	**7b**	$BuLi/ZnCl_2$	 **12** (69), (dr 91:9)
6[b]	 **7c**	$MeLi/ZnCl_2$	 **13** (71), (*cis*:*trans*>97:3), (*Z*:*E*>97:3)
7[b]	 **7d**	$MeLi/ZnCl_2$	 **14** (77), (*cis*:*trans*>97:3), (*Z*:*E*=77:23)
8[b]	 **7e**	$MeLi/ZnCl_2$	 **15** (68), (*cis*:*trans*>97:3), (*Z*:*E*=84:16)

[a] Isolated as the benzoate ester; two-step yield (cyclization and protection) is reported.
[b] Racemic allenes were used.

stereocenters was favored. Upon introducing aryl (Table 1, entry 6), alkyl (entry 7), or alkenyl (entry 8) functionality at the allene terminus, cis/trans selectivities of the newly formed contiguous stereocenters were outstanding, and *Z*/*E* selectivities of the trisubstituted alkene ranged from good to excellent. Homoallylic alcohols **14** and **15** were obtained as inseparable mixtures of *Z* and *E* isomers, and the identity of the minor isomer in both cases was confirmed by Swern oxidation of the mixture to an *E*:*Z* mixture of ketones of the identical isomeric composition as the starting alcohols. As an additional, more complex example, the $Ni(COD)_2$-catalyzed addition of dimethylzinc to allenyl aldehyde **16** proceeded in 65% yield (Eq. 2). Optimization of this particular example revealed that $Ti(O\text{-}i\text{-}Pr)_4$ was a convenient additive that resulted in slightly higher yields and improved diastereoselectivities relative to reactions carried out in its absence. The preparation of functionalized cyclopentanol **17** was a key step in our recent synthesis of (+)-testudinariol A.[6a]



(2)

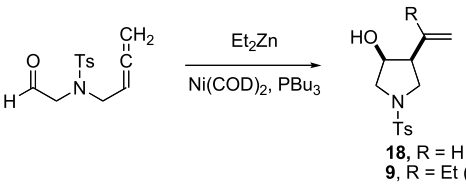
Ligand effects were not extensively studied, but an interesting effect that was noted is the role of basic phosphines. In analogy to observations made in ynal cyclizations,[13] pretreatment of $Ni(COD)_2$ with PBu_3 allowed reductive cyclizations with diethylzinc, in which H atom transfer predominantly occurred along with small amounts of ethyl transfer (Eq. 3). Yields and selectivities were lower with PPh_3 or $P(OMe)_3$ in place of PBu_3. It

Table 2. Intermolecular allene, aldehyde, organozinc couplings

Entry	Allene	Aldehyde	Organozinc	Products (%yield)
1	**19**		$ZnMe_2$	**20** (60, 7:3 dr)[a]; **21** (21)
2	**22**		$ZnMe_2$	**23** (67)
3	**24**		$ZnMe_2$	**25** (39)
4	**26**		$ZnMe_2$	**27** (36, 4:1 dr)[a]; **28** (35)
5	**29**		$ZnMe_2$	**30** (66, 19:1 dr)
6	**22**		$ZnMe_2$	**31** (61)
7	**22**		$ZnMe_2$	**32** (67)
8	**22**		$ZnMe_2$	**33** (21)
9	**22**		*n*-BuLi, $ZnCl_2$	**34** (48)

[a] Stereochemical relationship of the two diastereomers was not determined in this instance.

should be noted that selective ethyl transfer occurred in the absence of a phosphine ligand (Table 1, entry 2). Secondary and tertiary organozinc reagents were not examined, although their use led to increased substrate dimerization in related cyclizations of alkynyl enones.[14]



(3)

18, R = H (66 %)
9, R = Et (11%)

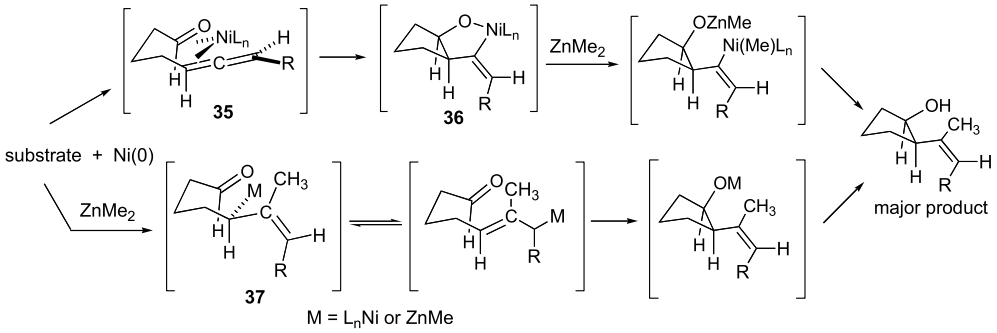
We next focused on a brief examination of intermolecular allene/aldehyde couplings. Representative mono-, di-, and trisubstituted allenes were examined in couplings with benzaldehyde (Table 2, entries 1–5). Using aromatic allene **19** as a representative monosubstituted allene, $Ni(COD)_2$-catalyzed coupling with benzaldehyde and dimethylzinc afforded product **20** as a 7:3 mixture of diastereomers in 60% yield along with the *Z* -isomer of **21** in 21% yield. Three different 1,1-disubstituted allenes **22**, **24**, and **26** were next examined. With doubly aliphatic substitution as in allenes **22** and **24**, selective addition to the unsubstituted allene terminus was observed in the production of compounds **23** and **25**. However, with allene **26**, which possesses both aromatic and aliphatic substituents at the allene terminus, a 1:1 mixture of products **27** and **28** was obtained, with product **27** being generated as a 4:1 ratio of diastereomers. 1,1,3-Trisubstituted allene **29** was also examined, and the less-substituted terminus, which possessed a carbomethoxy substituent, underwent coupling to benzaldehyde to generate product **30** in 66% yield as a 19:1 ratio of diastereomers. The relative stereochemistry of the major product was determined to be *syn* by ester reduction with lithium aluminum hydride followed by acetonide formation with dimethoxypropane to afford the easily characterized cyclic acetonide, which displayed a geminal coupling constant of 10.4 Hz between the two methine protons.

Using allene **22** as a test case, we then examined the efficiency of couplings with various aldehyde structures. *p*-Methoxy benzaldehyde and 2-furaldehyde were efficient coupling partners (entries 6 and 7), whereas heptaldehyde underwent coupling in low yield (entry 8). Finally, coupling of benzaldehyde and allene **22** with dibutylzinc generated in situ from butyl lithium and zinc chloride afforded the expected coupled product **34** in 48% yield via coupling at the unsubstituted allene terminus (entry 9).

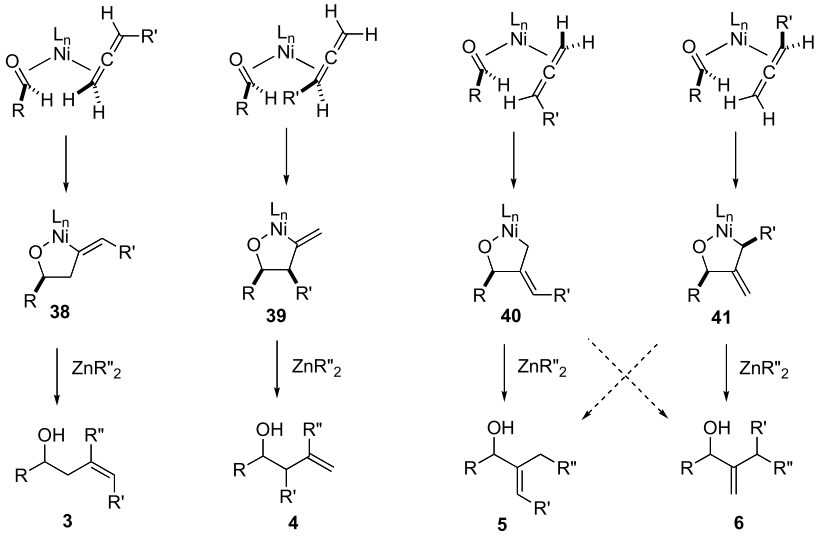
3. Discussion

The mechanism of the alkylative cyclizations could proceed by several potential pathways. The mechanism that we and others have generally favored in three-component nickel-catalyzed reductive couplings centers around the formation of nickel metallacycles, and an in-depth discussion of this general mechanism was provided in a recent combined experimental/computational study from our group in collaboration with Schlegel.[15] In analogy to this commonly invoked mechanistic pathway, the allenyl aldehyde cyclizations could proceed by oxidative cyclization of a Ni(0) π-complex **35** to the corresponding nickel metallacycle **36** (Scheme 2). Nickel complexation to the proximal allene π-system opposite the terminal allene substituent (R) is consistent with the observed products. Transmetallation of the organozinc, followed by reductive elimination would afford the observed products. This analysis correctly predicts the observed selectivity in the construction of trisubstituted alkenes. An alternate pathway could involve a carbonickelation pathway or a nickel-catalyzed carbozincation pathway to generate intermediate **37**, followed by addition of the resulting allyl metal species to the aldehyde.[5,8] Although simple allenes lacking an aldehyde undergo rapid oligomerization when exposed to $Ni(COD)_2$, no evidence for allene carbometallation was noted when simple allenes were treated with organozincs and $Ni(COD)_2$ under the standard conditions. The metallacycle-based mechanism is perhaps more consistent with this observation, although no firm insights into this question have been gained.

The intermolecular couplings are subject to the same questions, with the added complexity of allene orientation further complicating the analysis.[16] If a metallacycle-based mechanism is operative,[17] then four constitutional isomers **38–41** of the metallacycle may be obtained using a monosubstituted allene as a representative example (Scheme 3). Since homoallylic alcohols **3** and **4**, derived from addition to a terminal sp^2-hybridized carbon of the allene, are always obtained by this procedure, this suggests that metallacycles **38** and **39** could lead to the products obtained. Interestingly, the procedures recently reported by Mori[7b–c] (using DBU as the ligand) and by Jamison[7a] (using an *N*-heterocyclic carbene as the ligand) are consistent with the involvement of metallacycles analogous to **40** and **41**. Given that we demonstrated that Ni(0) complexes of phosphines catalyze the reductive coupling of aldehydes and alkynes by a mechanism that is entirely distinct from the



Scheme 2. Possible mechanisms of allenyl aldehyde cyclizations.



Scheme 3. Possible metallacycles in three-component couplings.

corresponding mechanism involved in reactions catalyzed by Ni(0) complexes of *N*-heterocyclic carbenes,[18] it is clearly possible that entirely different mechanisms could also be involved in the various procedures for nickel-catalyzed couplings of allenes and aldehydes. It would also not be surprising for the very different ligand structures involved to impart diverging selectivities between the two allene orthogonal π-systems even if a common mechanism were involved. A detailed evaluation of these intriguing questions awaits further study.

4. Conclusion

A procedure for the intramolecular and intermolecular coupling of allenes, aldehydes, and organozincs has been developed. In all instances, addition of a terminal position of the allene to the aldehyde is the preferred mode of addition, and the organozinc substituent is introduced at the central carbon of the allene. The reaction scope of cyclizations includes monosubstituted and 1,3-disubstituted allenes, and the scope in intermolecular examples includes mono-substituted, 1,1-disubstituted, 1,3-disubstituted, and 1,1,3-trisubstituted allenes. The efficiency of this method is highlighted as a key step in the total synthesis of the marine natural product (+)-testudinariol A.

5. Experimental

5.1. General

All reagents were used as received unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone ketyl or purified by filtration on an Innovative Technologies solvent purification system. All organolithium reagents were freshly titrated with 2,5-dimethoxybenzyl alcohol. Zinc chloride was dried at 150 °C at 0.1 mmHg overnight, thoroughly grounded by mortar and pestle in an inert atmosphere glove box, then dried again overnight at 150 °C at 0.1 mmHg and weighed in an inert atmosphere glove box. $Ni(COD)_2$ was stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under an argon atmosphere.

5.2. General procedure A for the $Ni(COD)_2$ catalyzed cyclization of dienals

A 0.5 M solution of $ZnCl_2$ (3.0 equiv) in Et_2O was stirred at 0 °C, and the organolithium (4.5 equiv) was added dropwise at 0 °C by syringe followed by stirring for 10–15 min at 0 °C. A 0.04 M THF solution of $Ni(COD)_2$ (0.1 equiv) was added, and the resulting mixture was immediately transferred to a 0.4 M solution of dienal in Et_2O at 0 °C. After consumption of starting material as judged by TLC analysis (typically 15–30 min at 0 °C), the reaction mixture was quenched with pH 8 NH_4Cl/NH_4OH buffer at 0 °C and was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by column chromatography on silica gel.

5.3. General procedure B for the $Ni(COD)_2$ catalyzed cyclization of dienals

Dialkylzinc (3.5 equiv) was added dropwise to a 0.1 M solution of $Ni(COD)_2$ (0.2 equiv) in THF at 0 °C. The resulting mixture was immediately transferred to a 0.05 M solution of dienal in THF at 0 °C. After consumption of starting material as judged by TLC analysis (typically 15–30 min at 0 °C), the reaction mixture was quenched with pH 8 NH_4Cl/NH_4OH buffer at 0 °C and was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated, and the residue was purified by column chromatography on silica gel.

5.3.1. 4-Isopropenyl-1-(toluene-4-sulfonyl)-pyrrolidin-3-ol (8). Following general procedure B, *N*-buta-2,3-dienyl-4-methyl-*N*-(2-*oxo*-ethyl)-benzenesulfonamide (51 mg, 0.19 mmol), Me_2Zn (33 μL, 0.67 mmol of 2.0 M toluene solution), and $Ni(COD)_2$ (11 mg, 0.038 mmol) were employed to provide, after flash chromatography (35%

EtOAc/Hexane), 37 mg (70%) of product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (br s, 1H), 1.75 (s, 3H), 2.42 (s, 3H), 2.62 (m, 1H), 3.30 (dd, J=9.6, 11.2 Hz, 1H), 3.43 (d, J=11.2 Hz, 1H), 3.50–3.567 (m, 2H), 4.26 (m, 1H), 4.72 (s, 1H), 5.02 (s, 1H), 7.31 (d, J=8.0 Hz, 2H), 7.72 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz) δ 21.8, 23.2, 48.0, 50.8, 56.2, 70.5, 114.2, 127.7, 129.9, 134.2, 139.8, 143.7; IR (film) 3510, 1643, 1596 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{14}H_{19}O_3NS$ 281.10857, found 281.10884 (M^+). Upon irradiation of the C-2 proton at δ 4.26, a positive was observed on the C-3 proton at δ 2.62 (5.8%), confirming the cis relationship between the C-2 proton and the C-3 proton.

5.3.2. 4-(1-Ethyl-vinyl)-1-(toluene-4-sulfonyl)-pyrrolidin-3-ol (9). Following general procedure B, *N*-buta-2,3-dienyl-4-methyl-*N*-(2-*oxo*-ethyl)-benzenesulfonamide (140 mg, 0.528 mmol), Et_2Zn (19 μL, 1.85 mmol neat solution), and $Ni(COD)_2$ (29 mg, 0.11 mmol) were employed to provide, after flash chromatography (1% MeOH/CH_2Cl_2), 99 mg (64%) of product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, J=7.5 Hz, 3H), 1.48 (br s, 1H), 1.94–2.10 (m, 2H), 2.41 (s, 3H), 2.67 (m, 1H), 3.29 (dd, J=9.5, 11.5 Hz, 1H), 3.43 (d, J=11.0 Hz, 1H), 3.51–3.56 (m, 2H), 4.22 (t, J=3.5 Hz, 1H), 4.76 (s, 1H), 5.03 (s, 1H), 7.31 (d, J=8.0 Hz, 2H), 7.73 (d, J=8.5 Hz, 2H); ^{13}C NMR (125 MHz) δ 12.3, 21.8, 29.3, 48.2, 49.8, 56.1, 70.3, 112.1, 127.7, 129.9, 134.3, 143.7, 145.3; IR (film) 3510, 1649, 1596 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{15}H_{21}O_3NS$ 295.1242, found 295.1243 (M^+). Upon irradiation of the C-2 proton at δ 4.22, positive NOE was observed on the C-3 proton at δ 2.67 (6.1%), confirming the cis relationship between the C-2 proton and the C-3 proton.

5.3.3. 4-(1-Butyl-vinyl)-1-(toluene-4-sulfonyl)-pyrrolidin-3-ol (10). Following general procedure A, *N*-buta-2,3-dienyl-4-methyl-*N*-(2-*oxo*-ethyl)-benzenesulfonamide (140 mg, 0.528 mmol), *n*-BuLi (1.5 mL, 2.38 mmol of 1.6 M hexane solution), $ZnCl_2$ (215 mg, 1.58 mmol), and $Ni(COD)_2$ (15 mg, 0.053 mmol) were employed to provide, after flash chromatography (20% EtOAc/Hexane), 88 mg (52%) of product as a colorless oil, a 3:1 inseparable mixture of cis and trans diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J=7.2 Hz, 3H), 1.22–1.40 (m, 4H), 1.61 (br s, 1H), 1.90–2.05 (m, 2H), 2.40 (s, 3H), 2.62 (br s, 1H), 3.27 (m, 1H), 3.41 (d, J=11.6 Hz, 1H), 3.51 (m, 2H), 4.20 (t, J=3.6 Hz, 1H), 4.74 (s, 1H), 5.0 (s, 1H), 7.30 (m, 2H), 7.7 (m, 2H); the following diagnostic peaks were noted for the trans isomer: 2.53 (q, J=6.4 Hz, 1H), 3.13 (dd, J=4.8, 10.4 Hz, 1H), 4.06 (q, J=5.6 Hz, 1H), 4.68 (s, 1H), 4.78 (s, 1H); ^{13}C NMR (100 MHz) δ 14.1, 21.8, 22.5, 30.1, 36.3, 48.3, 49.5, 56.2, 70.3, 113.0, 127.8, 130.0, 134.2, 143.7, 143.9; the following diagnostic peaks were noted for the trans isomer: 14.2, 22.6, 30.3, 35.0, 50.7, 52.2, 54.3, 73.8, 110.8, 127.8, 129.9, 133.8, 143.8, 146.9; IR (film) 3504, 1649, 1596 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{17}H_{25}O_3NS$ 323.1555, found 323.1557 (M^+). Upon irradiation of the C-2 proton at δ 4.20, a positive NOE was observed on the C-3 proton at δ 2.62 (6.8%), confirming the cis relationship between the C-1 proton and the C-2 proton.

5.3.4. 2-(Isopropenyl)cyclopentyl benzoate (benzoate ester of 11). Following general procedure A, hepta-5,6-dienal (110 mg, 1.0 mmol), MeLi (2.8 mL, 4.5 mmol of 1.6 M ether solution), $ZnCl_2$ (408 mg, 3.0 mmol), and $Ni(COD)_2$ (28 mg, 0.10 mmol) were employed, and after workup the crude product was treated with benzoyl chloride (466 μL, 4.0 mmol) and pyridine (970 μL, 12.0 mmol) in CH_2Cl_2 (10 mL) for 10 h at rt. The reaction mixture was quenched with satd $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic layers were washed with water, brine, and dried over $MgSO_4$, filtered, concentrated, to provide, after flash chromatography (5% Et_2O/Hexane), 158 mg (69%) of product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64–1.74 (m, 1H), 1.80 (s, 3H), 1.86–1.94 (m, 3H), 1.96–2.04 (m, 1H), 2.12–2.18 (m, 1H), 2.51 (m, 1H), 4.84 (s, 1H), 4.85 (s, 1H), 5.55 (t, J=4.8 Hz, 1H), 7.41 (m, 2H), 7.53 (m, 1H), 7.99 (m, 2H); ^{13}C NMR (100 MHz) δ 22.3, 23.3, 27.6, 32.9, 51.7, 77.4, 111.5, 128.5, 129.7, 131.2, 132.9, 143.7, 166.3; IR (film) 1719, 1649 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1308 (M^+). Upon irradiation of the C-1 proton at δ 5.55, a positive NOE was observed on the C-2 proton at δ 2.51 (4.0%), confirming the cis relationship between the C-1 proton and the C-2 proton.

5.3.5. 2-(1-Butyl-vinyl)-cyclopentanol (12). Following general procedure A, hepta-5,6-dienal (101 mg, 0.92 mmol), *n*-BuLi (2.6 mL, 4.1 mmol of 1.6 M ether solution), $ZnCl_2$ (313 mg, 2.3 mmol), and $Ni(COD)_2$ (25 mg, 0.092 mmol) were employed to produce, after flash chromatography (20% Et_2O/Hexane), 107 mg (69%) of product as a colorless oil, as a separable 10:1 ratio of cis and trans isomers. *Data for cis isomer*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J=7.0 Hz, 3H), 1.30–1.70 (m, 7H), 1.81 (m, 4H), 2.07 (m, 2H), 2.37 (br s, 1H), 4.12 (br s, 1H), 4.89 (s, 1H), 5.0 (s, 1H); ^{13}C NMR (100 MHz) δ 14.2, 22.0, 22.7, 26.4, 30.4, 33.8, 37.1, 52.3, 72.6, 111.3, 148.4; IR (film) 3451, 1643 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{11}H_{20}O$ 168.1514, found 168.1511 (M^+). Upon irradiation of the C-1 proton at δ 4.12, a positive NOE was observed on the C-2 proton at δ 2.37 (2.55%), confirming the cis relationship between the C-1 proton and the C-2 proton. *Data for trans isomer*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J=7.5, 3 Hz), 1.32 (quintet, J=6.0 Hz, 2H), 1.40–1.78 (m, 7H), 1.87–1.94 (m, 1H), 1.95–1.99 (m, 1H), 2.01 (t, J=7.5 Hz, 2H), 2.31 (q, J=1.30 Hz, 1H), 4.04 (q, J=7.0 Hz, 1H), 4.79 (q, J=2.5–3.0 Hz, 1H), 4.81 (s, 1H); ^{13}C NMR (125 MHz) δ 14.2, 21.6, 22.8, 29.7, 30.6, 34.0, 34.6, 55.1, 77.0, 108.6, 151.1. No NOE was observed between the C-1 proton at δ 4.04 and the C-2 proton at δ 2.31. Upon irradiation of the C-1 proton at δ 4.04, a positive NOE was observed on the C-7 methylene proton at δ 4.80 (0.8%).

5.3.6. 2-(1-Methyl-*Z*-2-phenyl-vinyl)-cyclopentanol (13). Following general procedure A, 7-phenylhepta-5,6-dienal (65 mg, 0.35 mmol), MeLi (1.7 mL, 0.98 mmol of 1.6 M ether solution), $ZnCl_2$ (143 mg, 1.05 mmol), and $Ni(COD)_2$ (10 mg, 0.035 mmol) were employed to provide, after flash chromatography (20% Et_2O/Hexane), 50 mg (71%) of product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 1H), 1.56 (br s, 1H), 1.62 (m, 2H), 1.84 (m, 1H), 1.94 (m, 2H), 2.00 (s, 3H), 2.98 (m, 1H), 4.27 (dt, J=3.2, 5.6 Hz, 1H), 6.54 (s, 1H), 7.21 (m, 3H), 7.32 (m, 2H); ^{13}C NMR (100 MHz) δ 23.1, 24.0, 27.8, 35.2, 46.9, 77.2, 126.4, 128.4, 128.7, 128.74, 138.6, 138.9; IR (film) 3417, 1637 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{14}H_{18}O$ 202.1358,

found 202.1359 (M^+). Upon irradiation of the C-1 proton at δ 4.27, a positive NOE was observed on the C-2 proton at δ 2.98 (2.9%), confirming the cis relationship between the C-1 proton and the C-2 proton. Upon irradiation of the C-7 proton at δ 6.54, a positive NOE was observed on the C-6 methyl group at δ 2.00 (4.5%) and the C-7 phenyl group at δ 7.21 (2.4%), confirming the *Z* geometry of the olefin.

5.3.7. 2-(1-Methyl-*Z*-propenyl)-cyclopentanol (14). Following general procedure A, octa-5,6-dienal (110 mg, 0.887 mmol), MeLi (2.5 mL, 4.0 mmol of 1.6 M ether solution), $ZnCl_2$ (302 mg, 2.22 mmol), and $Ni(COD)_2$ (25 mg, 0.09 mmol) were employed to provide, after flash chromatography (20% Et_2O/Hexane), 96 mg (77%) of product as a colorless oil, as an inseparable 3.4:1 ratio of *Z* and *E* isomers. ^1H NMR (500 MHz, $CDCl_3$) δ 1.45–1.70 (m, 7H), 1.74 (d, $J=1.0$ Hz, 3H), 1.81–1.89 (m, 2H), 1.93–2.0 (m, 1H), 2.735 (m, 1H), 4.28 (dt, $J=2.5$, 5.8 Hz, 1H), 5.47 (qq, $J=1.5$, 6.8 Hz, 1H); the following diagnostic peaks were noted for the (*E*)-isomer: 2.3 (m, 1H), 4.15 (m, 1H), 5.38 (m, 1H); ^{13}C NMR (125 MHz) δ 13.5, 23.3, 23.9, 27.0, 34.3, 47.1, 75.2, 122.3, 135.3; the following diagnostic peaks were noted for the (*E*)-isomer: 13.6, 17.2, 22.1, 25.6, 33.6, 54.8, 72.7, 120.9, 134.0; IR (film) 3446, 1655 cm^{-1}; HRMS (EI) *m/e* calcd for $C_9H_{16}O$ 140.1201, found 140.1199 (M^+). Upon irradiation of the C-1 proton at δ 4.280, a positive NOE was observed on the C-2 proton at δ 2.735 (2.3%), confirming the cis relationship between the C-1 proton and the C-2 proton. Upon irradiation of the C-7 proton at δ 5.47, positive NOEs were observed on the C-6 methyl group at δ 1.74 (1.5%) and the C-7 methyl group at δ 1.60 (2.5%), confirming the *Z* geometry of the olefin.

5.3.8. 2-(1-Methyl-penta-*Z*,*E*-1,3-dienyl)-cyclopentanol (15). Following general procedure A, deca-5,6,8-trienal (112 mg, 0.747 mmol), MeLi (2.1 mL, 3.4 mmol of 1.6 M ether solution), $ZnCl_2$ (305 mg, 2.24 mmol), and $Ni(COD)_2$ (21 mg, 0.075 mmol) were employed to provide, after flash chromatography (10% Et_2O/Hexane), 84 mg (68%) of product as a colorless oil, as an inseparable 5.3:1 ratio of *Z* and *E* isomers. ^1H NMR (400 MHz, $CDCl_3$) δ 1.45–1.54 (m, 2H), 1.57–1.70 (m, 2H), 1.75 (d, $J=7.2$ Hz, 3H), 1.82 (s, 3H), 1.84–1.92 (m, 2H), 1.99–2.05 (m, 1H), 2.86 (m, 1H), 4.30 (dt, $J=2.4$, 5.6 Hz, 1H), 5.60 (m, 1H), 6.00 (d, $J=11.6$ Hz, 1H), 6.26 (m, 1H); the following diagnostic peaks were noted for the *E* isomer: 2.35 (m, 1H), 4.20 (m, 1H), 5.68 (m, 1H), 6.32 (m, 1H), 5.94 (d, $J=10.4$ Hz, 1H); ^{13}C NMR (100 MHz) δ 18.6, 23.4, 24.0, 27.1, 34.3, 47.7, 76.4, 127.4, 128.0, 128.2, 135.0; the following diagnostic peaks were noted for the *E* isomer: 17.9, 22.2, 25.7, 33.8, 55.1, 73.3, 126.5, 127.7, 128.8, 133.42; IR (film) 3434, 1614 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{11}H_{18}O$ 166.1358, found 166.1357 (M^+). Upon irradiation of the C-1 proton at δ 4.30, a positive NOE was observed on the C-2 proton at δ 2.86 (2.6%), confirming the cis relationship between the C-1 proton and the C-2 proton. Upon irradiation of the C-7 proton at δ 6.0, positive NOEs were observed on the C-6 methyl group at δ 1.82 (3.5%) and the C-9 proton at δ 5.6 (3.7%), confirming the *Z* and *E* geometry of the olefins.

5.3.9. (3*S*,4*S*)-1-tosyl-4-vinylpyrrolidin-3-ol (18). To a 0.01 M solution of $Ni(COD)_2$ (12 mg, 0.045 mmol, 0.2 equiv) in THF was added dropwise PBu_3 (45 μL, 0.18 mmol, 0.8 equiv) at rt followed by stirring for 5–10 min. To the resulting mixture was added a 0.5 M solution of Et_2Zn (81 μL, 0.793 mmol, 3.5 equiv) in THF at 0 °C, and was quickly transferred to a 0.075 M solution of dienal (60 mg, 0.23 mmol) in THF at 0 °C. After consumption of starting material as judged by TLC analysis (20–30 min at 0 °C), the reaction mixture was subjected to an extractive work-up (pH 8 NH_4Cl/NHOH buffer/Et_2O). After flash chromatography (35% EtOAc/Hexane), 40 mg (0.15 mmol, 66%) of reductive product and 7 mg (0.025 mmol, 11%) of product **9** was obtained as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (br s, 1H), 2.42 (s, 3H), 2.71 (m, 1H), 3.22 (t, $J=9.6$ Hz, 1H), 3.34 (dd, $J=1.6$, 11.2 Hz, 1H), 3.51 (m, 2H), 4.20 (dt, $J=1.6$, 4.0 Hz, 1H), 5.14 (d, $J=17.2$ Hz, 1H), 5.23 (d, $J=10.8$ Hz, 1H), 5.74 (ddd, $J=10.6$, 6.8, 17.4 Hz, 1H), 7.31 (d, $J=8.0$ Hz, 2H), 7.72 (d, $J=8.0$ Hz, 2H); ^{13}C NMR (100 MHz) δ 21.8, 48.1, 49.4, 56.0, 72.7, 119.7, 127.7, 129.9, 132.7, 134.1, 143.8; IR (film) 3498, 1639, 1595 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{13}H_{17}O_3NS$ 267.09292, found 267.09301 (M^+). Upon irradiation of the C-2 proton at δ 4.20, NOEs were observed on the C-3 proton at δ 2.71 (5.4%), confirming the cis relationship between the C-2 proton and the C-3 proton. Spectral data for product **9** was identical to that prepared as described in Table 1, entry 2.

5.4. General experimental procedure for the $Ni(COD)_2$ catalyzed intermolecular coupling reactions

A 0.6 M solution of $ZnCl_2$ (3.0 equiv) in THF was stirred at 0 °C, and the MeLi (5.4 equiv) was added dropwise at 0 °C by syringe followed by stirring for 10–15 min at 0 °C. A 0.04 M solution of $Ni(COD)_2$ (0.2 equiv) in THF was added by cannula, and a 0.024 M (based on the allene) solution containing the aldehyde (3.0 equiv) and the allene (1.0 equiv) in THF was added by syringe pump for 4 h at 0 °C. After consumption of the allene as judged by TLC analysis (typically 15 min at 0 °C), the reaction mixture was quenched with pH 8 NH_4Cl/NH_4OH buffer at 0 °C and was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel.

5.4.1. 3-Methyl-1,2-diphenyl-but-3-en-1-ol (20). Following the general procedure, phenyl allene (50 mg, 0.43 mmol), benzaldehyde (137 mg, 1.29 mmol), MeLi (1.46 mL, 2.33 mmol of 1.6 M ether solution), $ZnCl_2$ (176 mg, 1.29 mmol), and $Ni(COD)_2$ (24 mg, 0.086 mmol) were employed to produce, after flash chromatography (10% EtOAc/Hexane), 83 mg (81%) of product as a colorless oil, a separable 3:1 ratio of regioisomers **20** and **21** (major isomer **20** as a 7:3 ratio of inseparable diastereomers A and B). *Diastereomer A*. ^1H NMR (500 MHz, $CDCl_3$) δ 1.76 (s, 3H), 2.56 (d, $J=2.0$ Hz, 1H), 3.55 (d, $J=10.5$ Hz, 1H), 5.07 (dd, $J=1.8$, 10.3 Hz, 1H), 5.16 (m, 1H), 5.29 (s, 1H), 7.0 (m, 2H), 7.13–7.18 (m, 4H), 7.32–7.37 (m, 4H); ^{13}C NMR (125 MHz) δ 22.6, 62.3, 75.6, 112.5, 126.8, 127.3, 127.7, 128.2, 128.3, 128.8, 139.5, 142.0, 146.3; *Diastereomer B*. ^1H NMR (500 MHz, $CDCl_3$) δ 1.56 (s, 3H), 1.87 (m, 1H), 3.65 (d, $J=8.5$ Hz, 1H), 4.78 (quintet, $J=1.5$ Hz, 1H), 4.89 (s, 1H), 5.21 (dd, $J=3.0$, 9.5 Hz, 1H), 7.08–7.13 (m, 5H), 7.26–7.30 (m, 5H); ^{13}C NMR (125 MHz) δ 22.5, 61.1, 75.4, 113.4, 127.2, 127.3,

128.0, 128.5, 129.1, 139.8, 142.8, 145.2; IR (film) 3427, 1644 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{17}H_{18}O$ 238.13576, found 220.12497 (M^+-H_2O). *3-Methyl-1,4-diphenyl-but-3-en-1-ol (**21**)*. ^1H NMR (500 MHz, $CDCl_3$) δ 1.90 (d, J=3.0 Hz, 1H), 1.97 (d, J=1.5 Hz, 3H), 2.45 (dd, J=4.5, 13.5 Hz, 1H), 2.93 (dd, J=9.5, 14.3 Hz, 1H), 4.94 (m, 1H), 6.5 (s, 1H), 7.24–7.34 (m, 10H); ^{13}C NMR (125 MHz) δ 24.5, 42.5, 72.6, 126.0, 126.5, 127.8, 128.4, 128.7, 129.0, 129.5, 135.3, 138.1, 144.5; IR (film) 3380, 1648 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{17}H_{18}O$ 238.13577, found 238.13547 (M^+). Upon irradiation of the C-4 proton at δ 6.50, a positive NOE was observed in the C-3 methyl at δ 1.97 (3.5%), confirming the *Z* geometry of the olefin.

5.4.2. 3,4-Dimethyl-1-phenyl-pent-3-en-1-ol (23). Following the general procedure, 3-methyl-buta-1,2-diene (50 mg, 0.734 mmol), benzaldehyde (134 mg, 2.2 mmol), MeLi (2.5 mL, 4.0 mmol of 1.6 M ether solution), $ZnCl_2$ (234 mg, 2.2 mmol), and $Ni(COD)_2$ (40 mg, 0.15 mmol) were employed to produce, after flash chromatography (10% EtOAc/Hexane), 93 mg (67%) of product as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 3H), 1.72 (s, 6H), 2.14 (br s, 1H), 2.30 (dd, J=5.0, 13.5 Hz, 1H), 2.68 (dd, J=9.0, 13.5 Hz, 1H), 4.78 (dd, J=5.0, 9.0 Hz, 1H), 7.28 (m, 1H), 7.33–7.40 (m, 4H); ^{13}C NMR (125 MHz) δ 18.9, 20.8, 21.1, 45.3, 72.7, 124.1, 126.0, 127.5, 128.5, 129.2, 144.8; IR (film) 3385, 1603 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{13}H_{18}O$ 190.13577, found 190.13587 (M^+).

5.4.3. 3-Cyclohexylidene-1-phenyl-butan-1-ol (25). Following the general procedure, vinylidene–cyclohexane (50 mg, 0.46 mmol), benzaldehyde (147 mg, 1.39 mmol), MeLi (1.6 mL, 2.5 mmol of 1.6 M ether solution), $ZnCl_2$ (189 mg, 1.389 mmol), and $Ni(COD)_2$ (26 mg, 0.093 mmol) were employed to produce, after flash chromatography (10% EtOAc/Hexane), 41 mg (39%) of product as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 1.35–1.59 (m, 6H), 1.70 (s, 3H), 2.03 (br s, 1H), 2.12–2.23 (m, 4H), 2.29 (dd, J=4.8, 13.3 Hz, 1H), 2.69 (dd, J=9.0, 13.0 Hz, 1H), 4.75 (dd, J=5.0, 9.0 Hz, 1H), 7.26 (m, 1H), 7.32–7.39 (m, 4H); ^{13}C NMR (125 MHz) δ 18.5, 27.0, 28.3, 28.6, 30.8, 31.1, 44.7, 72.6, 120.7, 126.0, 127.5, 128.5, 138.0, 144.7; IR (film) 3362, 1603 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{16}H_{22}O$ 230.16707, found 230.16697 (M^+).

5.4.4. 2,3-Dimethyl-1,2-diphenyl-but-3-en-1-ol (27). Following the general procedure, (1-methyl-propa-1,2-dienyl)-benzene (50 mg, 0.385 mmol), benzaldehyde (123 mg, 1.154 mmol), MeLi (1.3 mL, 2.08 mmol of 1.6 M ether solution), $ZnCl_2$ (157 mg, 1.154 mmol), and $Ni(COD)_2$ (21 mg, 0.077 mmol) were employed to produce, after flash chromatography (10% EtOAc/Heaxane), 69 mg (71%) of product as a colorless oil, as a separable 1:1 ratio of regioisomers **27** and **28** (**27** as 4:1 ratio of diastereomers). *Major isomer of* **27**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.65 (s, 3H), 2.52 (s, 1H), 5.28 (s, 1H), 5.31 (s, 1H), 5.36 (s, 1H), 6.82 (m, 2H), 7.05–7.30 (m, 8H); ^{13}C NMR (100 MHz) δ 16.8, 22.0, 53.8, 78.6, 111.8, 126.7, 127.1, 127.14, 127.6, 128.1, 128.3, 140.4, 143.1, 150.2; IR (film) 3452, 1636 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{18}H_{20}O$ 252.15141, found 235.14825 (M^+-OH); *Minor isomer of* **27**. ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 2.22 (d, J=3.2 Hz, 1H), 5.08 (s, 1H), 5.15 (s, 1H), 6.86 (m, 2H); ^{13}C NMR (100 MHz) δ 21.6, 22.5, 53.5, 78.2, 112.7, 126.7, 127.4, 127.7, 128.6, 129.4, 141.2, 141.7, 150.3. *3-Methyl-1,4-diphenyl-pent-3-en-1-ol (**28**)*. ^1H NMR (400 MHz, $CDCl_3$) δ 1.79 (br s, 1H), 1.90 (s, 3H), 2.0 (s, 3H), 2.27 (dd, J=4.0, 14.0 Hz, 1H), 2.51 (dd, J=9.0, 13.8 Hz, 1H), 4.78 (dd, J=5.0, 9.8 Hz, 1H), 7.03 (m, 2H), 7.15 (m, 2H), 7.19–7.31 (m, 6H); ^{13}C NMR (100 MHz) δ 18.5, 21.9, 45.5, 72.9, 125.9, 126.3, 127.3, 127.5, 128.4, 128.5, 128.6, 135.4, 144.7, 144.8; IR (film) 3399, 1599 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{18}H_{20}O$ 252.15141, found 234.14050 (M^+-H_2O). Upon irradiation of the C-4 methyl at δ 2.0, a positive NOE was observed on the C-3 methyl at δ 1.9 (3.1%), confirming the *Z* geometry of the olefin.

5.4.5. 2-(Hydroxy-phenyl-methyl)-3,4-dimethyl-pent-3-enoic acid ethyl ester (30). Following the general procedure, 4-methyl-penta-2,3-dienoic acid ethyl ester (50 mg, 0.357 mmol), benzaldehyde (114 mg, 1.07 mmol), MeLi (1.2 mL, 1.9 mmol of 1.6 M ether solution), $ZnCl_2$ (146 mg, 1.07 mmol), and $Ni(COD)_2$ (20 mg, 0.071 mmol) were employed to produce, after flash chromatography (10% EtOAc/Hexane), 62 mg (66%) of product as a colorless oil, a separable 95:5 ratio of *syn* and *anti* diastereomers. *Syn isomer*. ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J=7.3 Hz, 3H), 1.28 (d, J=1.5 Hz, 3H), 1.46 (s, 3H), 1.58 (s, 3H), 3.29 (br s, 1H), 3.81 (d, J=9.5 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 5.03 (d, J=9.5 Hz, 1H), 7.21–7.28 (m, 5H); ^{13}C NMR (125 MHz) δ 14.5, 15.5, 20.5, 21.0, 56.9, 61.1, 73.7, 121.3, 126.8, 127.9, 128.1, 131.2, 141.3, 174.8; IR (film) 3471, 1713, 1494 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{16}H_{22}O_3$ 262.15688, found 245.15399 (M^+-OH). *Anti isomer*. ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (t, J=7.3 Hz, 3H), 1.67 (d, J=1.0 Hz, 3H), 1.75 (s, 3H), 1.81 (t, J=1.3 Hz, 3H), 2.37 (d, J=2.0 Hz, 1H), 3.88 (d, J=8.5 Hz, 1H), 3.98 (dq, J=1.5, 7.0 Hz, 2H), 5.10 (dd, J=2.0, 8.5 Hz, 1H), 7.24–7.33 (m, 3H), 7.39 (m, 2H); ^{13}C NMR (125 MHz) δ 14.2, 14.8, 20.9, 21.6, 56.6, 60.6, 73.1, 121.9, 127.3, 128.1, 128.4, 133.4, 142.0, 172.3.

5.4.6. 1-(4-Methoxy-phenyl)-3,4-dimethyl-pent-3-en-1-ol (31). Following the general procedure, 3-methyl-buta-1,2-diene (30 mg, 0.44 mmol), *p*-anisaldehyde (180 mg, 1.32 mmol), MeLi (1.5 mL, 2.4 mmol of 1.6 M ether solution), $ZnCl_2$ (180 mg, 1.32 mmol), and $Ni(COD)_2$ (24 mg, 0.088 mmol) were employed to produce, after flash chromatography (10% Et_2O/Hexane), 59 mg (61%) of product as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (s, 3H), 1.68 (s, 3H), 1.69 (m, 3H), 2.05 (s, 1H), 2.25 (dd, J=5.0, 13.8 Hz, 1H), 2.66 (dd, J=9.4, 13.8 Hz, 1H), 3.80 (s, 3H), 4.73 (dd, J=4.8, 8.8 Hz, 1H), 6.88 (m, 2H), 7.29 (m, 2H); ^{13}C NMR (100 MHz) δ 18.9, 20.8, 21.1, 45.2, 55.5, 72.3, 113.9, 124.2, 127.2, 129.0, 136.9, 159.1; IR (film) 3415, 1612 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{14}H_{20}O_2$ 220.14633, found 220.14613 (M^+).

5.4.7. 1-Furan-2-yl-3,4-dimethyl-pent-3-en-1-ol (32). Following the general procedure, 3-(methyl)buta-1,2-diene (40 mg, 0.59 mmol), 2-furaldehyde (169 mg, 1.76 mmol), MeLi (2.0 mL, 3.2 mmol of 1.6 M ether solution), $ZnCl_2$ (240 mg, 1.76 mmol), and $Ni(COD)_2$ (32 mg, 0.12 mmol) were employed to produce, after flash chromatography (20% Et_2O/Hexane), 70 mg (67%) of product as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 1.64 (s, 3H), 1.69 (s, 6H),

2.08 (br s, 1H), 2.46 (dd, J=4.8, 13.3 Hz, 1H), 2.76 (dd, J=8.5, 13.0 Hz, 1H), 4.78 (dd, J=5.5, 9.0 Hz, 1H), 6.23 (d, J=3.5 Hz, 1H), 6.32 (m, 1H), 7.37 (m, 1H); ^{13}C NMR (125 MHz) δ 18.7, 20.8, 21.1, 41.0, 66.5, 106.1, 110.4, 123.3, 129.2, 142.0, 156.6; IR (film) 3387, 1597 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{11}H_{16}O_2$ 180.11503, found 180.11506 (M^+).

5.4.8. 2,3-Dimethyl-undec-2-en-5-ol (33). Following the general procedure, 3-methyl-buta-1,2-diene (30 mg, 0.44 mmol), heptaldehyde (151 mg, 1.32 mmol), MeLi (1.5 mL, 2.4 mmol of 1.6 M ether solution), $ZnCl_2$ (180 mg, 1.32 mmol), and $Ni(COD)_2$ (24 mg, 0.088 mmol) were employed to produce, after flash chromatography (5% Et_2O/Hexane), 18 mg (21%) of product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.24–1.36 (m, 8H), 1.47 (m, 2H), 1.57 (br s, 1H), 1.67 (s, 3H), 1.69 (s, 3H), 1.70 (s, 3H), 2.04 (dd, J=3.8, 13.8 Hz, 1H), 2.34 (dd, J=9.3, 13.8 Hz, 1H), 3.69 (m, 1H); ^{13}C NMR (125 MHz) δ 14.3, 18.9, 20.9, 21.1, 22.9, 26.1, 29.7, 32.1, 37.4, 42.8, 70.2, 124.6, 128.5; IR (film) 3356, 1458 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{13}H_{26}O$ 198.19837, found 198.19862 (M^+).

5.4.9. 3-Butyl-4-methyl-1-phenyl-pent-3-en-1-ol (34). Following the general procedure, 3-methyl-buta-1,2-diene (30 mg, 0.44 mmol), benzaldehyde (140 mg, 1.32 mmol), and MeLi (1.5 mL, 2.4 mmol of 1.6 M ether solution), $ZnCl_2$ (180 mg, 1.32 mmol), $Ni(COD)_2$ (24 mg, 0.088 mmol) were employed to produce, after flash chromatography (10% Et_2O/Hexane), 49 mg (48%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J=6.6 Hz, 3H), 1.26–1.4 (m, 4H), 1.68 (s, 3H), 1.72 (s, 3H), 1.96 (m, 1H), 2.05 (br s, 1H), 2.15 (m, 1H), 2.30 (dd, J=4.0, 12.8 Hz, 1H), 2.61 (dd, J=9.2, 13.2 Hz, 1H), 4.75 (dd, J=4.8, 9.8 Hz, 1H), 7.25–7.39 (m, 4H); ^{13}C NMR (100 MHz) δ 14.3, 20.8, 21.0, 23.2, 31.2, 32.2, 43.0, 72.9, 126.0, 127.5, 128.5, 129.1, 129.7, 144.7; IR (film) 3378, 1603 cm^{-1}; HRMS (EI) *m/e* calcd for $C_{16}H_{24}O$ 234.19836, found 214.17189 ($M^+ - OH$).

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Three-component synthesis of polysubstituted benzene derivatives via Diels–Alder reaction of cyclopentadienone acetal with alkyne

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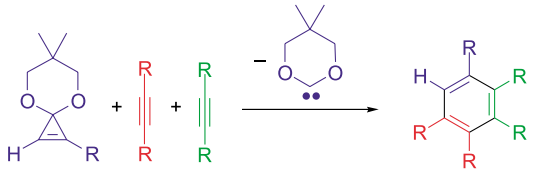
Abstract—An efficient and regioselective synthesis of polysubstituted benzene derivatives was achieved via multicomponent reaction of a substituted cyclopropenone acetal and two alkyne molecules. The synthesis utilizes cyclopentadienone acetal as an intermediate and enables regioselective [2+2+2] assembly of the three-components into a benzene ring. A variety of polysubstituted benzene derivatives of synthetic and structural interest have been synthesized.

1. Introduction

Polysubstituted benzene is an important class of compounds in organic chemistry, natural product chemistry, and materials science. Multicomponent construction of benzene ring is an intriguing possibility in benzene synthesis. For instance, a [2+2+2] synthesis has been achieved by transition metal catalyzed reactions,[1–3] and a [4+2] synthesis either by transition metal catalyzed reactions or by thermal reactions.[1,4,5] These examples largely dealt with intramolecular reactions, and regioselective synthesis by intermolecular reactions has remained to be a challenge for synthetic chemists. We herein report an example of regioselective [2+2+2] synthesis of polysubstituted benzenes by a thermal intermolecular reaction (Scheme 1). The synthesis involves cyclopentadienone acetal (CPDA)[6] as a transient or an isolated intermediate. The stepwise synthesis with isolated CPDA comprises a [2+2+2] assembly of three different components into a benzene ring. We have previously reported an example of the transformation[6] and describe here the scope of the three-component synthesis.



Scheme 1.

Keywords: Polysubstituted benzene; Three-component [2+2+2] synthesis; Diels–Alder reaction; Cyclopropene; Cyclopentadiene.
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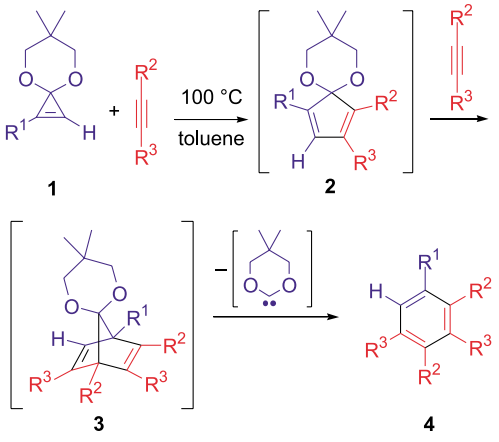
2. Results and discussion

2.1. One-pot three-component synthesis of polysubstituted benzene derivatives. Thermal reaction of CPA and alkynes

During the investigation of the synthesis of CPDA derivatives,[6] we noticed that a thermal reaction of a cyclopropenone acetal (CPA **1**)[7] with an alkyne gives a small amount of polysubstituted benzene. For instance, when equimolar amounts of phenyl CPA **1a** and dimethyl acetylene dicarboxylate (DMAD) was heated in toluene for 1 h, we obtained a polysubstituted benzene **4a** in 9% yield along with CPDA **2a** in 40% yield (Eq. 1; Table 1, entry 1). The observation suggested occurrence of three successive reactions shown in Eq. 1, that is, [3+2] cycloaddition, Diels–Alder reaction, and cheletropic extrusion of dialkoxycarbene (vide infra). The net result is the one-pot assembly of one molecule of CPA and two molecules of an alkyne into a polysubstituted benzene in a [2+2+2] manner.



(1)

Table 1. One-pot three-component synthesis of polysubstituted benzene derivatives by the reaction shown in Eq. 1

Entry	Alkyne (equiv)	Yield of **4** (%)		Substituents of **4**
1[a]	1.0	9	**4a**	R^1=Ph, R^2=CO_2Me, R^3=CO_2Me
2[b]	4.0	59		
3[b]	4.0	63	**4b**	R^1=4-$MeOC_6H_4$, R^2=CO_2Me, R^3=CO_2Me
4[b]	2.0	76	**4c**	R^1=1-naphthyl, R^2=CO_2Me, R^3=CO_2Me
5[b]	2.0	31	**4d**	R^1=Ph, R^2=Ph, R^3=SO_2CF_3

[a] CPDA **2a** (R^1=Ph, R^2=R^3=CO_2Me) was obtained in 40% yield.
[b] CPDA **2** was not obtained.

The new benzene synthesis was found to have considerable generality as a method to synthesize a variety of polysubstituted benzene derivatives. Thus, when phenyl CPA **1a**, anisyl CPA **1b**, or 1-naphthyl CPA **1c** was allowed to react with 2–4 equiv of DMAD or an unsymmetric alkyne, the corresponding benzene derivatives **4a**, **4b**, **4c**, and **4d** were obtained in 59, 63, 76, and 31% yield, respectively.

Crystallographic analysis of the highly substituted benzene **4d** revealed that the molecule is significantly distorted owing to steric interactions among substituents (Fig. 1). The torsion angle between *ortho*-substituents measures as much as 27.7° at S^1–C^1–C^2–C^7 (Fig. 1b) and that of the benzene ring reaches 12.3° at C^1–C^2–C^3–C^4. Nonplanar benzene rings have been observed rarely and only for symmetric benzene derivatives.[8]

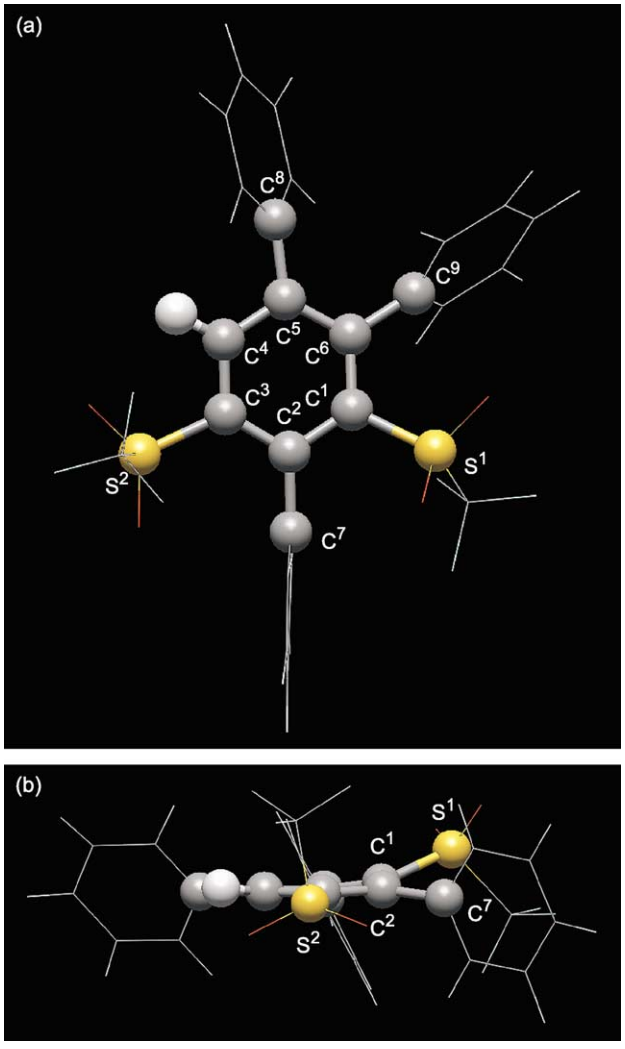
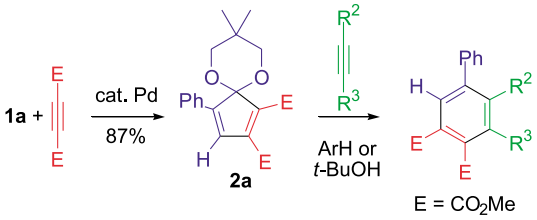


Figure 1. X-ray crystallographic structure of disulfonyl benzene **4d**. The key atoms are shown in a ball and stick model. (a) Top view; (b) side view shown along the C^4–C^5 bond. Color codes of atoms: C, gray; H, white; O, red; S, yellow; F, blue.

2.2. Stepwise three-component synthesis of polysubstituted benzene derivatives. Thermal Diels–Alder reaction of CPDA and alkynes

The reaction described above incorporates two identical alkynes into a benzene ring. Two different alkynes can be incorporated when CPDA is synthesized first and then allowed to react with the second alkyne (Eq. 2).[9] A variety of CPDA **2** can be synthesized by the Pd-catalyzed method that we reported.[6] The Diels–Alder reaction of the substituted CPDA with the second alkyne enables the assembly of three different components into a benzene ring in a controlled manner.

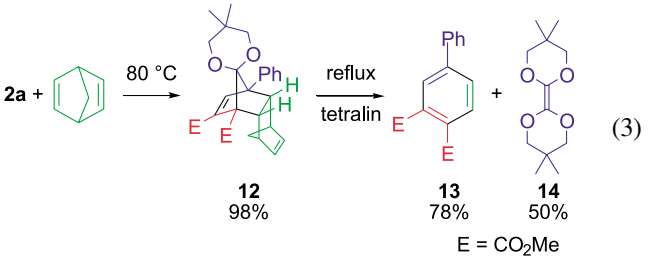


(2)

The reaction of CPDA **2a** with alkynes proceeded in one-pot to afford a variety of polysubstituted benzene derivatives in moderate to high yield (Table 2). CPDA **2a** was first prepared by the Pd-catalyzed [3+2] synthesis[6] and then allowed to react with an equimolar amount of a aryl alkyne to give the corresponding benzene derivative as a single regioisomer (Table 2, entry 1 and 2). The reaction with an enyne proceeded regioselectively and chemoselectively at the C–C triple bond. The yield of the benzene derivative **7** was not high in the reaction without solvent, but dramatic improvement to 75% yield was observed when we carried out the reaction in an alcohol to capture the extruded dialkoxycarbene (entry 3). The benzene derivative was obtained as a mixture of regioisomer in the reaction with propargyl ether (entry 4). A synthetically useful arylboronate **9**[10] was obtained in 68% yield when we used ethynyl boronate as a dienophile (entry 5).[11] The high regioselectivity in the reaction with monosubstituted alkynes results from the selectivity in the Diels–Alder cycloaddition, and the origin of the selectivity will be the subject of future theoretical study. The reaction with a disubstituted alkyne such as tolane was not as efficient as monosubstituted ones, giving the benzene derivative **10** in 39% yield (entry 6).

The use of acetylene (gas) in the present synthesis is difficult, because the reaction requires high temperature. However, the

use of its surrogate, norbornadiene, allowed the incorporation of an acetylene unit into a benzene ring.[6] Norbornadiene was first allowed to react with CPDA **2a** to obtain the Diels–Alder adduct **12** in 98% yield. The adduct **12** was then converted to the benzene derivative **13** in 78% yield by thermolytic extrusion of dialkoxycarbene and cyclopentadiene (Eq. 3). Dialkoxycarbene generated by the cheletropic extrusion was identified by isolation of its dimer, tetraalkoxyethylene **14**.



3. Conclusion

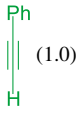
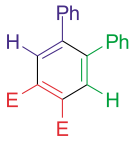
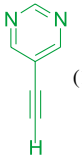
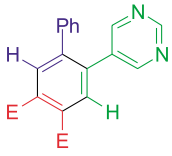
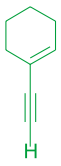
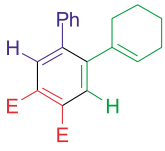
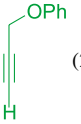
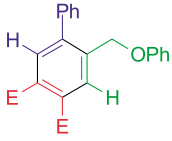
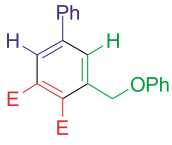
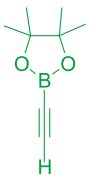
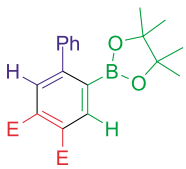
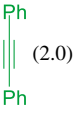
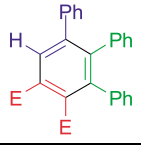
In summary, we have developed a method for the synthesis of polysubstituted benzene derivatives. The present [2+2+2] synthesis is highly regioselective and chemoselective and tolerates a variety of functional groups including a sulfonyl and a boryl groups. Such synthesis of unsymmetric polysubstituted benzene derivatives has been rarely achieved by transition metal catalyzed reactions and will find applications in the synthesis of polycyclic aromatic compounds.[10,12]

4. Experimental

4.1. General

IR spectra were obtained on an ASI Applied Systems REACT IR1000 equipped with an attenuated total reflection

Table 2. Stepwise synthesis of polysubstituted benzene derivatives by the reaction of CPDA **2a** and alkyne (Eq. 2)

Entry	Alkyne (equiv)	Conditions	Product[a]
1	 (1.0)	Toluene, 100 °C, 110 h	 **5**, 97%
2	 (1.0)	PhCl, reflux, 24 h	 **6**, 88%
3	 (35)	*t*-BuOH, 150 °C, 21 h	 **7**, 75%[b]
4	 (2.4)	1,2,4-$Cl_3C_6H_3$, 150 °C, 8 days	 **8**, 76%
			 **9**, 15%
5	 (2.0)	PhCl, 120 °C, 42 h	 **10**, 68%
6	 (2.0)	Ph_2O, reflux, 12 h	 **11**, 39%

[a] E=CO_2Me.
[b] The reaction in the absence of solvent gave **7** in 22% yield.

(ATR) instrument. NMR spectra were obtained on JEOL EX-270, AL-300, ECX-400, ECA-500, and Bruker AV-500 spectrometers. ^{1}H NMR spectra in $CDCl_3$ were referenced internally to tetramethylsilane as a standard. ^{13}C NMR spectra in $CDCl_3$ were referenced to the solvent resonance, and methyl, methylene, and methyne signals were assigned by DEPT spectra. ^{19}F NMR spectra in $CDCl_3$ were referenced externally to trifluoroacetic acid at −76.5 ppm. Mass spectra were obtained on JEOL JMS-T100LC (AccuTOF; APCI/ESI-TOF MS). Gel permeation column chromatography was performed on a Japan Analytical Industry LC-908 (eluent: chloroform) with JAIGEL 1H and 2H columns.

4.2. Materials

Commercially available alkynes were purchased and purified by distillation or recrystallization before reactions. Phenyl(trifluoromethanesulfonyl)acetylene was synthesized as reported.[13] All solvents were purified by distillation and dried on molecular sieves 4 Å. All new compounds were determined to be >98% pure by ^{1}H NMR spectroscopy.

4.3. Synthetic procedure and physical properties

4.3.1. Biphenyl-2,3,4,5-tetracarboxylic acid tetramethyl ester 4a[3] Phenyl CPA **1a** (649 mg, 3.50 mmol) and DMAD (1.48 mL, 12.0 mmol) were dissolved in 0.75 mL of toluene and heated at 100 °C for 1 h. The solvent was removed in vacuo to give crude materials. Purification by silica gel column chromatography (eluent: 20% ethyl acetate/hexane) afforded the title compound **4a** as a white solid in 59% yield (684 mg, 1.77 mmol). IR and NMR spectra matched with those reported in the literature.

4.3.2. 4′-Methoxybiphenyl-2,3,4,5-tetracarboxylic acid tetramethyl ester 4b. Anisyl CPA **1b** (61.6 mg, 0.250 mmol) and DMAD (123 μL, 1.00 mmol) were dissolved in 0.25 mL of toluene and heated at 100 °C for 1 h. The solvent was removed in vacuo to give crude materials. Purification by silica gel column chromatography (eluent: 40% ethyl acetate/hexane) afforded the title compound **4b** as a white solid in 63% yield (66.0 mg, 0.159 mmol). IR (powder) 2952, 2840, 1731, 1721, 1607, 1594, 1559, 1515, 1443, 1432, 1391, 1341, 1277, 1246, 1227, 1179, 1160, 1113, 1102, 1025, 1005, 994, 957, 917, 874, 847, 828, 805, 797, 785, 758, 749, 727, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 6.95 (d, J=8.4 Hz, 2H), 7.27 (d, J=8.4 Hz, 2H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.61 (CH_3), 52.95 (CH_3), 52.98 (CH_3), 53.18 (CH_3), 55.28 (CH_3), 114.04 (CH), 129.46 (CH), 129.98, 130.16, 130.33, 133.49, 134.08 (CH), 136.52, 141.78, 159.88, 164.98, 165.70, 167.50, 167.64. Anal. Calcd for $C_{21}H_{20}O_9$: C, 60.58; H, 4.84. Found: C, 60.48; H, 4.90.

4.3.3. 5-Naphthalen-1-yl-benzene-1,2,3,4-tetracarboxylic acid tetramethyl ester 4c. 1-Naphthyl CPA **1c** (200 mg, 0.750 mmol) and DMAD (184 μL, 1.50 mmol) were dissolved in 0.38 mL of toluene and heated at 100 °C for 31 h. The solvent was removed in vacuo to give crude materials. Purification by silica gel column chromatography (eluent: 50% ethyl acetate/hexane) afforded the title compound **4c** as a viscous liquid in 71% yield (232 mg, 0.532 mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.89 (s, 3H×2), 4.00 (s, 3H), 7.31 (dd, J=1.2, 7.2 Hz, 1H), 7.5 (m, 4H), 7.89 (d, J=4.4 Hz, 2H), 8.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.23 (CH_3), 52.89 (CH_3), 53.01 (CH_3), 53.13 (CH_3), 124.79 (CH), 125.32 (CH), 126.09 (CH), 126.50 (CH), 126.84 (CH), 128.17 (CH), 128.92 (CH), 129.74, 130.08, 131.30, 133.28, 134.39, 135.05, 135.14 (CH), 137.87, 140.89, 164.77, 165.57, 166.70, 167.39; HR-APCI-MS calcd for $C_{24}H_{20}O_8$ ($[M+H]^+$) 437.1236, found 437.1227.

4.3.4. Disulfonyl benzene 4d. Phenyl CPA **1a** (921 mg, 3.93 mmol) and phenyl(trifluoromethanesulfonyl)acetylene (1869 mg, 7.98 mmol) were dissolved in 5.5 mL of toluene and heated at 100 °C for 4 h. The solvent was removed in vacuo to give crude materials. Purification by silica gel column chromatography (eluent: 4% ethyl acetate/hexane) afforded the title compound **4d** as a white solid in 31% yield (695 mg, 1.22 mmol). IR (powder) 3062, 2962, 2921, 2852, 1445, 1426, 1389, 1374, 1260, 1212, 1138, 1109, 1050, 1025, 857, 803, 782, 758, 729, 700, 677, 634, 625, 614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (m, 2H), 7.06 (m, 2H), 7.21 (m, 6H), 7.4 (m, 4H), 7.5 (m, 1H), 8.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.47 (q, J=326 Hz, CF_3), 119.53 (q, J=326 Hz, CF_3), 126.67 (CH), 127.13 (CH), 128.11 (CH), 128.13 (CH), 128.48 (CH), 129.29 (CH), 129.54 (CH), 129.86 (CH), 130.75 (CH), 130.90, 134.07, 134.09, 135.27, 137.40, 139.86 (CH), 146.81, 148.04, 152.86; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.26 (s), −72.14 (s); HR-ESI-MS calcd for $C_{26}H_{16}F_6O_4S_2Na$ ($[M+Na]^+$) 593.0292, found 593.0296.

4.3.5. [1,1′;2′,1″]Terphenyl-4′,5′-dicarboxylic acid dimethyl ester 5.[14] CPDA **2a** (17.9 mg, 50.0 μmol) and phenylacetylene (36.6 μL, 0.300 μmol) were dissolved in 0.60 mL of toluene and heated at 100 °C for 110 h. Purification by silica gel column chromatography (eluent: 20% ethyl acetate/hexane) afforded the title compound **5** as a white solid in 97% yield (100 mg, 0.290 mmol). IR (powder) 3058, 3025, 3014, 2956, 1721, 1611, 1602, 1495, 1437, 1391, 1324, 1275, 1245, 1227, 1194, 1138, 1079, 1054, 1030, 963, 915, 886, 824, 782, 772, 754, 739, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 6H), 7.13 (m, 4H), 7.23 (m, 6H), 7.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.62 (CH_3), 127.33 (CH), 128.07 (CH), 129.52 (CH), 130.66, 131.16 (CH), 139.45, 143.32, 167.73. Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.05; H, 5.23.

4.3.6. 6-Pyrimidin-5-yl-biphenyl-3,4-dicarboxylic acid dimethyl ester 6. CPDA **2a** (89.6 mg, 0.250 mmol) and 5-ethynylpyrimidine (26.0 mg, 0.250 mmol) were dissolved in 0.50 mL of chlorobenzene and refluxed for 24 h. The solvent was removed in vacuo to give crude materials. Purification by silica gel column chromatography (eluent: 40% ethyl acetate/hexane) afforded the title compound **6** as a white solid in 88% yield (77.0 mg, 0.221 mmol). IR (powder) 2955, 1726, 1607, 1579, 1557, 1543, 1445, 1438, 1428, 1416, 1382, 1354, 1319, 1283, 1270, 1250, 1188, 1133, 1075, 1054, 1033, 960, 933, 911, 888, 828, 793, 780, 769, 741, 730, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H×2), 7.12 (m, 2H), 7.30 (m, 3H), 7.82 (s, 1H),

7.84 (s, 1H), 8.52 (s, 2H), 9.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.90 ($CH_3\times2$), 128.31 (CH), 128.80 (CH), 129.62 (CH), 130.91 (CH), 131.13, 131.45 (CH), 132.73, 133.45, 135.76, 138.04, 144.20, 156.75 (CH), 157.40 (CH), 167.03, 167.42. Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 69.23; H, 4.75; N, 7.92.

4.3.7. 6-Cyclohex-1-enyl-biphenyl-3,4-dicarboxylic acid dimethyl ester 7. CPDA **2a** (179 mg, 0.500 mmol) and 1-ethynylcyclohexene (2.06 mL, 17.5 mmol) were dissolved in 0.95 mL of *t*-butanol and heated at 150 °C for 21 h in a sealed tube. The solvent was removed in vacuo to give crude materials. Purification by silica gel column chromatography (eluent: 15% ethyl acetate/hexane) afforded the title compound **7** as a white solid in 75% yield (131 mg, 0.375 mmol). IR (KBr) 3445, 2931, 1730, 1436, 1308, 1246, 1130, 1075, 968, 910, 772, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43–1.48 (m, 2H), 1.49–1.54 (m, 2H), 1.75–1.79 (m, 2H), 2.07–2.12 (m, 2H), 3.90 (s, 3H), 3.93 (s, 3H), 5.75 (m, 1H), 7.32–7.43 (m, 5H), 7.59 (s, 1H), 7.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.70 (CH_2), 22.67 (CH_2), 25.59 (CH_2), 28.76 (CH_2), 52.56 (CH_2), 52.60 (CH_2), 127.56 (CH), 128.12 (CH), 128.62 (CH), 129.29 (CH), 129.83, 129.97 (CH), 130.57, 130.70 (CH), 138.05, 140.21, 142.43, 146.49, 167.85, 168.14. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.28; H, 6.37.

4.3.8. 6-Phenoxymethyl-biphenyl-3,4-dicarboxylic acid dimethyl ester 8. CPDA **2a** (17.9 mg, 50.0 μmol) and phenylprop-2-yl ether (15.4 μL, 120 μmol) were dissolved in 0.30 mL of 1,2,4-trichlorobenzene and stirred at 150 °C for 8 days. Purification by silica gel column chromatography (eluent: 20% ethyl acetate/hexane) afforded the 5:1 mixture of regioisomers **8** and **9** in 91% yield (17.2 mg, 45.7 μmol). Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.28; H, 5.51. Purification by gel permeation column chromatography afforded the title compound **8** as a viscous liquid in 76% yield (14.3 mg, 38.0 μmol) and minor product **9** as a viscous liquid in 15% yield (2.8 mg, 7.4 μmol).

Compound **8**. IR (KBr) 3059, 3029, 2951, 1730, 1599, 1587, 1496, 1435, 1393, 1313, 1242, 1193, 1170, 1133, 1072, 1031, 966, 912, 848, 793, 756, 704, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.93 (s, 3H), 4.96 (s, 2H), 6.85 (m, 2H), 6.94 (m, 1H), 7.25 (m, 2H), 7.34–7.45 (m, 5H), 7.68 (s, 1H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.68 ($CH_3\times2$), 67.06 (CH_2), 114.78 (CH), 121.27 (CH), 128.23 (CH), 128.56 (CH), 128.76 (CH), 129.46 (CH), 129.48 (CH), 130.51, 130.78, 131.40 (CH), 137.68, 138.42, 144.28, 158.15, 167.67, 167.78. We observed $^3J_{CH}$ HMBC correlations between methyne protons and carbonyl carbons and determined the positions of substituents as shown in Table 2.

Compound **9**. IR (KBr) 2951, 2919, 2858, 1730, 1599, 1496, 1456, 1434, 1382, 1331, 1242, 1159, 1107, 1068, 1033, 986, 755, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.94 (s, 3H), 5.19 (s, 2H), 6.97 (m, 3H), 7.29 (m, 2H), 7.41 (m, 1H), 7.47 (m, 2H), 7.60 (s, 2H), 7.97 (m, 1H), 8.14 (d, J=1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.69 (CH_3), 52.77 (CH_3), 67.13 (CH_2), 114.84 (CH), 121.39 (CH), 127.24 (CH), 128.04 (CH), 128.35 (CH), 129.01 (CH), 129.57 (CH), 130.37 (CH), 130.56, 132.13, 136.02, 139.06, 142.80, 158.29, 166.31, 168.80. The coupling constant of two protons on benzene ring measured J= 1.8 Hz, which indicate their *meta*-relationship.

4.3.9. 6-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-biphenyl-3,4-dicarboxylic acid dimethyl ester 10. CPDA **2a** (358 mg, 1.00 mmol), ethynylboronate ester (304 mg, 2.00 mmol), and dodecane (113 μL, 0.500 mmol, internal standard) were dissolved in 0.50 mL of chlorobenzene and heated at 120 °C. Complete consumption of alkyne was confirmed after 42 h by GC analysis. The solvent was removed in vacuo to give crude materials. Purification by silica gel column chromatography (eluent: 3% ethyl acetate/toluene) afforded the title compound **10** as a viscous liquid in 68% yield (269 mg, 0.679 mmol). IR (liquid) 2979, 2952, 2111, 2092, 1727, 1546, 1509, 1486, 1436, 1389, 1324, 1285, 1247, 1131, 1096, 1067, 1028, 963, 895, 853, 828, 768, 739, 702, 689, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 12H), 3.91 (s, 3H), 3.92 (s, 3H), 7.38 (m, 5H), 7.68 (s, 1H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.56 (CH_3), 52.59 (CH_3), 52.70 (CH_3), 84.29, 127.81 (CH), 128.00 (CH), 128.87, 128.93 (CH), 129.05 (CH), 132.69 (br, CB), 133.54, 135.16 (CH), 141.18, 150.58, 167.85, 168.21. Anal. Calcd for $C_{22}H_{25}O_6B$: C, 66.69; H, 6.36. Found: C, 66.44; H, 6.50. We observed $^3J_{CH}$ HMBC correlations between methyne protons and carbonyl carbons and determined the positions of substituents as shown in Table 2.

4.3.10. 3,4,5-Triphenylphthalic acid dimethyl ester 11.[15] CPDA **2a** (17.9 mg, 50.0 μmol) and diphenylacetylene (17.8 mg, 100 μmol) were dissolved in 0.10 mL of diphenyl ether and refluxed for 12 h. Purification by silica gel column chromatography (eluent: 5% ethyl acetate/toluene) afforded the title compound **11** as a white solid in 39% yield (8.2 mg, 19 μmol). IR (powder) 3053, 3026, 2948, 1733, 1723, 1588, 1555, 1497, 1445, 1426, 1337, 1297, 1262, 1235, 1202, 1146, 1073, 1063, 1030, 965, 911, 849, 807, 766, 753, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (s, 3H), 3.92 (s, 3H), 6.76 (m, 2H), 6.93 (m, 3H), 7.06 (m, 4H), 7.12 (m, 3H), 7.16 (m, 3H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.15 (CH_3), 52.58 (CH_3), 126.13, 126.40 (CH), 126.89 (CH), 127.01 (CH), 127.15 (CH), 127.23 (CH), 127.76 (CH), 129.64 (CH), 130.19 (CH), 130.82 (CH), 131.02 (CH), 135.15, 137.59, 138.07, 140.29, 140.31, 142.76, 144.78, 165.88, 169.10. Anal. Calcd for $C_{22}H_{18}O_4$: C, 79.60; H, 5.25. Found: C, 79.50; H, 5.47.

4.3.11. Diels–Alder adduct of CPDA and 2,5-norbornadiene 12.[6] CPDA **2a** (143 mg, 0.400 mmol) was dissolved in 0.80 mL of 2,5-norbornadiene and stirred at 80 °C for 7 h, and the solvent was removed in vacuo to give the title compound **12** as a white solid in 98% yield (176 mg, 0.392 mmol). A single crystal was obtained by recrystallization from methylene chloride/pentane, and the structure was determined by X-ray diffraction study. IR (powder) 2962, 2946, 1740, 1717, 1600, 1465, 1447, 1434, 1362, 1312, 1299, 1275, 1264, 1250, 1233, 1221, 1210, 1191, 1177, 1158, 1127, 1113, 1094, 1073, 1059, 1032, 1003, 974, 965, 942, 924, 909, 895, 868, 853, 814, 801, 785, 770, 747, 720, 702, 687, 656, 621 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ

0.43 (s, 3H), 0.70 (s, 3H), 0.99 (d, $J=10$ Hz, 1H), 1.84 (d, $J=10$ Hz, 1H), 2.61 (d, $J=2$ Hz, 1H), 2.82 (d, $J=2$ Hz, 1H), 3.00 (d, $J=11$ Hz, 1H), 3.04 (d, $J=7$ Hz, 1H), 3.16 (d, $J=11$ Hz, 1H), 3.17 (d, $J=7$ Hz, 1H), 3.23 (d, $J=11$ Hz, 1H), 3.37 (d, $J=11$ Hz, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 6.30 (dd, $J=3$, 3 Hz, 1H), 6.38 (dd, $J=3$, 3 Hz, 1H), 7.06 (s, 1H), 7.35 (m, 3H), 7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.83 (CH_3), 23.09 (CH_3), 30.54, 41.44 (CH), 42.08 (CH_2), 42.44 (CH), 46.59 (CH), 47.25 (CH), 51.89 (CH_3), 51.96 (CH_3), 64.64, 65.11, 72.27 (CH_2),72.36 (CH_2), 121.05, 127.43 (CH), 128.12 (CH), 128.76 (CH), 135.62, 136.99, 140.19 (CH), 141.49 (CH), 147.80 (CH), 164.13, 171.55. Anal. Calcd for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.80; H, 6.75.

4.3.12. Dimethyl 4-phenylphtalate 13.[6] Diels–Alder adduct **12** (113 mg, 0.250 mmol) was dissolved in 2.0 mL of tetralin in a sealed tube. The reaction vessel was heated at 230 °C for 5 days. Purification by silica gel column chromatography (eluent: 5% ethyl acetate/toluene) afforded the title compound **13** as a white solid in 86% yield (58.4 mg, 0.216 mmol) and tetraalkoxyethylene **14**[16] (eluent: 40% ethyl acetate/hexane) as a white solid in 52% yield (14.6 mg, 0.0644 mmol).

Compound **13**. IR (powder) 3014, 2956, 1725, 1605, 1582, 1566, 1508, 1436, 1395, 1298, 1285, 1272, 1248, 1194, 1160, 1129, 1077, 1046, 1025, 1000, 959, 922, 897, 863, 824, 793, 780, 766, 746, 699, 675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.94 (s, 3H), 7.46 (m, 3H), 7.62 (m, 2H), 7.74 (dd, $J=2$, 8 Hz, 1H), 7.84 (d, $J=8$ Hz, 1H), 7.91 (d, $J=2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.56 (CH_3), 52.66 (CH_3), 127.12 (CH), 127.25 (CH), 128.38 (CH), 128.94 (CH), 129.21 (CH), 129.63 (CH), 129.78, 132.99, 138.86, 144.24, 167.55, 168.25. Anal. Calcd for $C_{23}H_{25}NO_6$: C, 71.10; H, 5.22. Found: C, 70.96; H, 5.16.

Compound **14**. IR (powder) 2956, 2925, 2873, 2856, 1725, 1602, 1472, 1447, 1436, 1401, 1376, 1260, 1233, 1169, 1115, 1094, 1073, 1061, 1034, 762, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 12H), 4.08 (s, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.12 (CH_3), 28.44, 77.47 (CH_2), 148.09. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.34; H, 8.73.

4.4. X-ray crystallographic study

Suitable crystals of **4a**, **4d**, and **12** were obtained by recrystallization from methylene chloride/pentane. X-ray diffraction study was carried out on a MacScience DIP2030 Imaging Plate diffractometer. Space group determination, structural solution, and refinement were performed using a maXus program. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 273014 (**4a**), 273015 (**4d**), and 244460 (**12**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.4.1. Selected X-ray crystallographic data for compound 4a. $C_{20}H_{18}O_8$, monoclinic, $P2_1/c$, $a=10.518(2)$ Å, $b=7.8120(4)$ Å, $c=23.596(2)$ Å, $\beta=101.878(5)°$, $V=1897.3(4)$ Å^3, $Z=4$, $D_{calcd}=1.353$ g cm^{-3}, $R=0.071$, $R_w=0.144$.

4.4.2. Selected X-ray crystallographic data for compound 4d. $C_{26}H_{16}F_6O_4S_2$, triclinic, P-1, $a=10.2070(9)$ Å, $b=11.1210(6)$ Å, $c=12.0070(9)$ Å, $\alpha=84.070(4)°$, $\beta=80.885(4)°$, $\gamma=66.172(4)°$, $V=1229.9(2)$ Å^3, $Z=2$, $D_{calcd}=1.541$ g cm^{-3}, $R=0.045$, $R_w=0.094$.

4.4.3. Selected X-ray crystallographic data for compound 12.[6] $C_{27}H_{30}O_6$, triclinic, P-1, $a=9.9730(5)$ Å, $b=11.3770(10)$ Å, $c=10.8700(10)$ Å, $\alpha=94.578(4)°$, $\beta=99.652(5)°$, $\gamma=104.643(5)°$, $V=1166.7(2)$ Å^3, $Z=2$, $D_{calcd}=1.282$ g cm^{-3}, $R=0.167$, $R_w=0.486$.

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Aqueous medium effects on multi-component reactions

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Abstract—The effect of aqueous media on many organic reactions has been studied, and often those reactions exhibiting pressure acceleration are also accelerated in water. Because some specific examples of the Ugi and Passerini reactions that are inefficient under conventional conditions have been accelerated by pressure, we examined Ugi and Passerini reactions in aqueous solutions, where significant increases in efficiency were observed. These effects were correlated to the cohesive energy density of aqueous solutions.

1. Introduction

Approaches to the acceleration of reactions are of the most fundamental interest to chemists. Some approaches such as increasing temperature are quite general; others, like catalysis, are less so. Still others are specific to particular reaction classes. Any reaction in which the molar volume of the transition state is significantly less than the reactants can be accelerated by high pressure. Many cycloaddition reactions exhibit pressure acceleration, including the Diels–Alder reaction. It often has a large free energy of activation, in part dictated by its large negative activation entropy (owing to its highly ordered transition state). It is also very responsive to high pressure, owing to its negative activation volume (which is to say that the transition state is more compact than the reactants). The definition of the volume of activation, $\Delta V^{\ddagger}$, for the reaction of A with B is the molar volume of the activated complex less the molar volumes of the reactants (Fig. 1, Eq. 1). A classic example of a preparatively useful high-pressure Diels–Alder reaction is found in Dauben's cantharadin synthesis (Scheme 1).[1] The volume of activation of a wide selection of chemical reactions has been determined since the initial demonstration of pressure acceleration in the 1930s.[2–6]

$$\Delta V^{\ddagger} = V_{AB*} - (V_A + V_B) \quad (1)$$

For example, the Diels–Alder reaction of maleic anhydride with cyclohexadiene has a $\Delta V^{\ddagger}$ of $-37\ \mathrm{cm}^3/\mathrm{mol}$ (Scheme 2). Properties of reactions that create volume contraction in the transition state (producing negative activation volumes) include cyclization, which reduces the molecular packing coefficient, and generation of charged species, which creates solvent electrostriction. In multi-step reactions, the $\Delta V^{\ddagger}$ is dependent on mechanistic detail such as the rate-determining step and presence or absence of reversible steps. For reactions in which only reversible step(s) precede an irreversible, rate-determining step, the overall $\Delta V^{\ddagger}$ is the sum of the $\Delta V^{\ddagger}$s of all reversible steps and the rate-determining step (Fig. 2, Eq. 2). An example of this behavior is the Baylis-Hillman reaction, which exhibits a

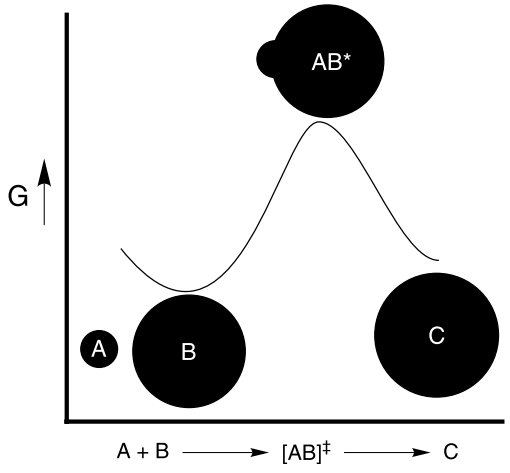

Figure 1. This figure depicts possible changes in the volumes of molecules along the reaction coordinate diagram. The volume of the activated complex AB* shown here is less than the sum of the volumes of molecules A and B.

Keywords: Ugi reaction; Passerini reaction; Cohesive energy density; Volume of activation; Combinatorial libraries; β-Lactams.
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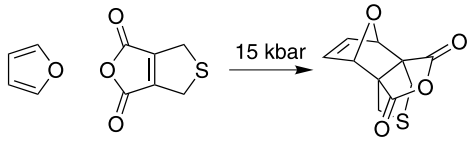
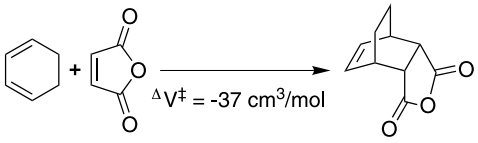


Scheme 1.

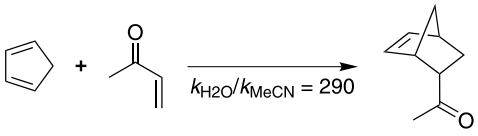


Scheme 2.

dramatic $-70\ \mathrm{cm}^3/\mathrm{mol}$ $\Delta V^{\ddagger}$. It is also significantly pressure-accelerated.[7]

$$\Delta V^{\ddagger} = \Delta V^{\ddagger}(1) + \Delta V^{\ddagger}(2) + \cdots + \Delta V^{\ddagger}(n) \tag{2}$$

Another influence on reactions like the Diels–Alder reaction that has been deeply investigated is aqueous solvent. Breslow originally demonstrated a 300-fold rate acceleration for the reaction of cyclopentadiene with methyl vinyl ketone in water compared to acetonitrile (Scheme 3).[8] Many explanations have been offered for this observation.[9,10,11] The simplest to understand is the classical hydrophobic effect. When non-polar solutes (organic compounds) that are immiscible with water are dissolved/suspended in it, a



Scheme 3.

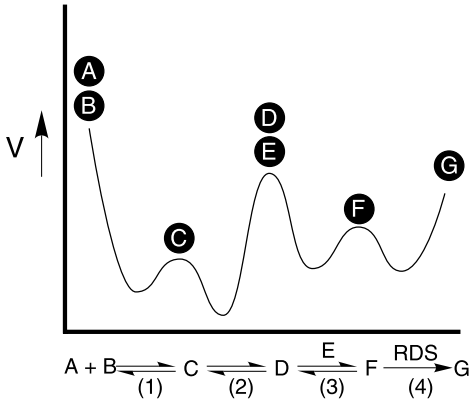


Figure 2. Note the change of the *y*-axis from free energy in Figure 1 to molar volume in this figure. This figure depicts the volumes of reactants along a putative multi-step reaction pathway. As A and B react, the volume goes through a minimum, but the product C has a larger volume than the transition state leading to it. This reaction process has the same essential features as that in Figure 1. C undergoes a unimolecular reaction that has a more compact transition state than C itself, giving D. Because D reacts with a new molecule E, their total volume is significantly larger than C. Their conversion to F also proceeds through a volume minimum. Finally, in the rate-determining and irreversible step in the process, F is converted to G, which has a larger molar volume than F, but it does so through a transition state that has a smaller molar volume than F. Each of the minima in this plot corresponds to the volume of an activated complex, thus each of the elemental steps in the overall process has a negative volume of activation.

cavity is created in the ordered structure of water, effectively assembling water molecules around the solute and creating what has been called a clathrate. This arrangement minimizes the surface area of contact between polar and non-polar molecules, and (obviously) has a favorable free energy. When multiple clathrates are present, their coalescence into fewer, larger clathrates is favorable because the surface area of contact between the non-polar solute and water is lower for larger volumes (Fig. 3). This effect can increase the local concentration of hydrophobic molecules and therefore the effective molarity of the reactants, explaining the rate acceleration.

A less appreciated property of solvents is their cohesive energy density (c.e.d.), the intermolecular force that gives liquids their cohesion.[12] The c.e.d. is the energy required to remove a molecule from its nearest neighbors in the bulk, leading to the creation of a cavity, factored by the volume of the molecule removed. One can readily see in this concept a relation between c.e.d. and the hydrophobic effect. In formula form, c.e.d. is defined as the ratio of the heat of vaporization (less *RT*) to the molar volume (Eq. 3). The c.e.d. has been measured for a wide number of pure liquids. Water has one of the largest c.e.d.'s at about 550 cal/cm^3. A large value is readily understandable because water has a very large heat of vaporization (the numerator) for its molecular weight and a very low molar volume (the denominator) because of its low molecular weight. Other solvents with large c.e.d.'s to which we will later refer include formamide (376 cal/cm^3) and methanol (209 cal/cm^3). It is noteworthy that the c.e.d. has units corresponding to a pressure, with the translation to more familiar pressure units being 23.8 cal/cm^3 = 1 kbar. Therefore, the cohesive energy of water corresponds to a pressure of about 20 kbar.

$$\text{c.e.d.} = \frac{\Delta H_{\text{vap}} - RT}{M/\rho} \tag{3}$$

M = molecular weight; ρ = density.

Aqueous solutions are well-known to exhibit differences in properties from pure water, such as colligative properties

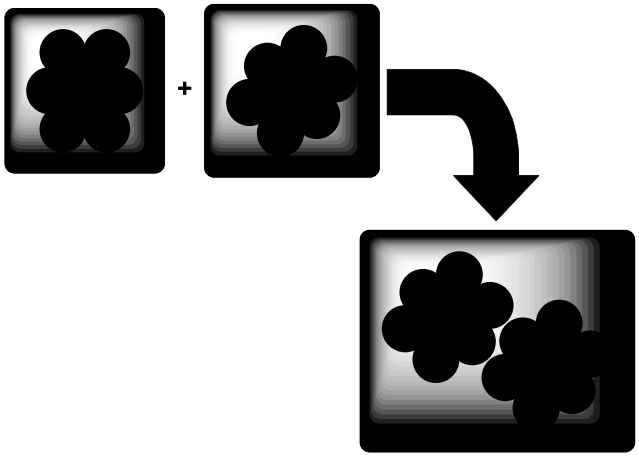


Figure 3. Hydrophobic molecules in aqueous solution are surrounded by a cage of water molecules. The condensation of individual molecules to form local domains consisting of multiple hydrophobes surrounded by water cages is favored by the minimization of the surface area of contact between the hydrophobic and hydrophilic domains.

like freezing point and boiling point. Well-solvated solutes can interact with water by hydrogen bonding, dipole–dipole interactions, or dipole–ion interactions, as in the case of a carbohydrate or a salt such as LiCl (Fig. 4). The enthalpic benefit derived from the bonding of solvation is countered by the loss of entropy as water is ordered around the solute to solubilize it.

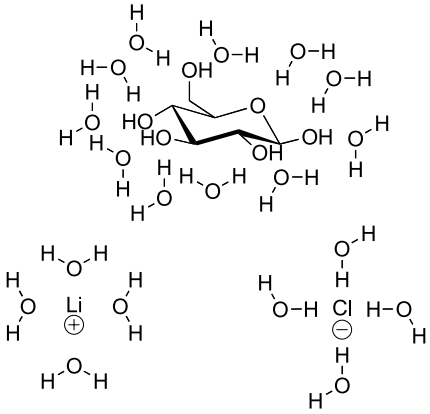
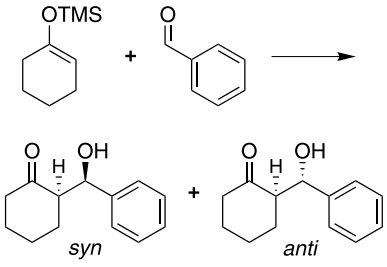


Figure 4. The solvation of hydrophilic or ionic molecules leads to the organization of water around the solute, increasing water's structure.

Reactions (other than the Diels–Alder reaction) have been conducted in aqueous solution for which effects similar to those of high pressure have been achieved. While it is not necessarily intuitive that water should have the same effect on a reaction as pressure, indeed this has been observed. For example,[13] the aldol condensation with benzaldehyde of the enol silane derived from cyclohexanone gives a 1:3 *syn*:*anti* ratio in organic solvent at STP when catalyzed by $TiCl_4$ (Scheme 4). When the reaction is instead conducted in organic solvent at 10 kbar, a 3:1 *syn*:*anti* ratio is observed. This turnover in diastereoselectivity is attributed to favoring of the more compact transition state leading to the *syn* isomer at the higher pressure (Fig. 5). The interesting result for the current discussion is that a 3:1 *syn*:*anti* ratio is also observed in an aqueous solvent mixture at STP.



Scheme 4.

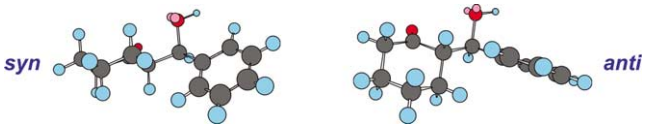
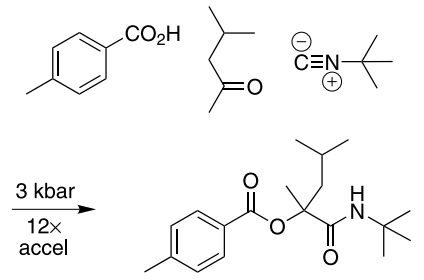
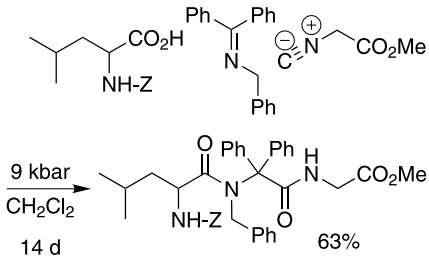


Figure 5. The transition state leading to the *syn* isomer on the left is more compact than that leading to the *anti* isomer on the right, explaining the reversal in stereoselectivity with pressure.

Multi-component reactions are of continuing interest in chemistry, which interest has been significantly enhanced by their application in combinatorial chemistry.[14] Means to promote, enhance, and accelerate multi-component reactions therefore have currency. Both the Passerini[15] and Ugi[16] reactions, when involving sterically hindered carbonyl components, have been shown to be accelerated at high pressure (Schemes 5 and 6), suggesting that these reactions have significant negative activation volumes. Given the combination of several molecular components into a single product in these reactions, it is reasonable that this is the case, but no measurements of activation volumes for any multi-component reaction have been reported. Given the proven ability to accelerate multi-component reactions with pressure and tantalizing indications that aqueous solutions can offer kinetic effects on reactions similar to pressure, we thought it worthwhile to examine the acceleration of multi-component reactions in water.

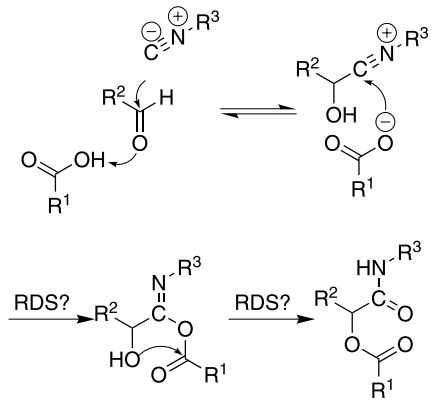


Scheme 5.



Scheme 6.

When contemplating tactics to accelerate a reaction, it is extremely helpful to know its rate-determining step. The kinetic mechanism of the Ugi reaction has not been determined, but the mechanism of the Passerini reaction has been studied.[17] The reaction is overall third order, and as shown in Scheme 7, the rate-determining step is either the addition of the carboxylate to the nitrilium ion or the rearrangement of the resulting adduct to the product. The addition step could certainly have a negative activation volume if it is the rate-determining step, or if the addition is reversible and rearrangement to the product is the rate-determining step, the overall reaction would still have a negative activation volume, as described above for the Baylis-Hillman reaction. Whatever the rate-determining step, demonstration of the pressure acceleration of the Passerini reaction creates strong suspicion that it would be accelerated in water. Likewise for the Ugi reaction. A recent report describes the use of water as a solvent for a three-component condensation reaction, though this work did not

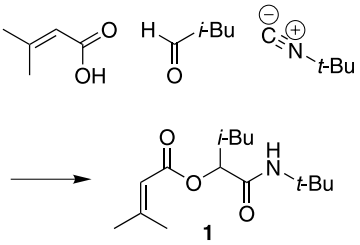


Scheme 7.

investigate reaction kinetics or comment upon rate acceleration.[18] This paper reports in full our recently communicated results[19] on the acceleration of multi-component reactions in aqueous solutions.

2. Results

Following preliminary experiments demonstrating that several Passerini reactions are significantly accelerated in water, the reaction in Scheme 8 was chosen for careful kinetic analysis. As described below, efficient mixing is crucial to obtaining the maximum accelerating effects of aqueous solutions. The most effective mixing used in this work was conducted in peptide synthesis vessels on a wrist-action shaker. To ensure that differential solubility of the three reactants and the product (almost insoluble) in water did not skew the data, samples were taken by extraction of the aqueous solution with organic solvent prior to gas chromatographic analysis. An internal standard of dinitrobenzene was used that has a significantly different retention time than reactants or product. Progress curves are given in Figure 6 for the reaction in Scheme 8 conducted in pure water and in dichloromethane. As is readily seen, the reaction goes to completion within about 3 h in water, whereas it is only 80% complete after 2 days in dichloromethane. Kinetic data were analyzed according to the integrated form of the third-order rate equation (Eq. 4) to obtain rate constants. Kinetic constants were determined in triplicate and their percent standard deviation was $<3\%$. This Passerini reaction has an 18-fold acceleration in water (Table 1). This positive result prompted examination of the Ugi reaction in Scheme 9 in water. Progress curves are given in Figure 7 for the reaction in Scheme 9 conducted in pure water and in methanol. Kinetic data for this reaction proved more difficult to analyze, but we estimated a 49-fold



Scheme 8.

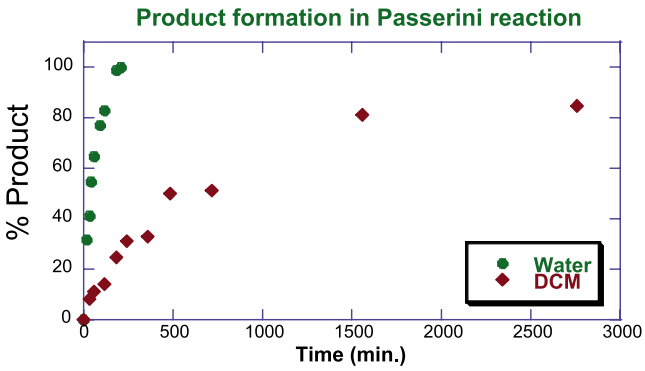


Figure 6. Reaction progress for the Passerini reaction in Scheme 8 in water (●) and dichloromethane (♦) solutions.

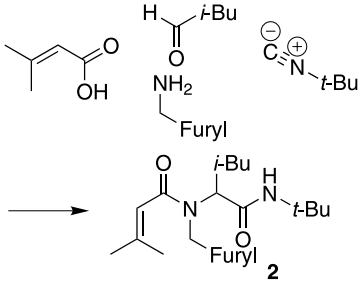
acceleration in water.

$$kt = \frac{1}{2}\left[\frac{1}{([\mathrm{RCO_2H}]^{t})^2} - \frac{1}{([\mathrm{RCO_2H}]^{t_0})^2}\right] = [\mathrm{P}] \qquad (4)$$

where $[\mathrm{RCO_2H}]^{t} = [\mathrm{RCO_2H}]^{t_0} - [\mathrm{P}]$.

An interesting aspect of reactions accelerated in aqueous solutions is that co-solutes can have a dramatic effect on observed rates.[20] These additives are variously described as chaotropic or *anti*-chaotropic, hydrophobic or *anti*-hydrophobic, or 'salting-in' or 'salting-out'. The latter concept is familiar from strategies to drive partially water-soluble organic compounds from the aqueous phase to the organic phase during solvent extractions. That is to say, salt (NaCl specifically) makes water more hydrophilic. Interestingly, other solutes that have the effect of 'organizing' water can exert a similar effect despite being non-ionic. The effect of two co-solutes, glucose (0.5 M) and LiCl (1 M) on the Passerini reaction in Scheme 8 was examined. The former provides a seven-fold acceleration over pure water, and the latter provides a 16-fold acceleration over pure water (Table 1). Compared to the same reaction in dichloromethane, aqueous LiCl provides an overall 288-fold rate acceleration. Practically, this means that the reaction in Scheme 8 is complete in 15 min when conducted in aqueous LiCl.

We next addressed the postulate that acceleration of the Passerini reaction in water is related not to hydrophobic effects but to more conventional aspects of water as a solvent, such as its hydrogen bond donor/acceptor capabilities or its very high dielectric constant. Comparison solvents were methanol (c.e.d. 209; ε 32) and formamide (c.e.d. 376; ε 109). Formamide in particular is an excellent solvent with



Scheme 9.

Table 1. Rates of the Passerini reaction in Scheme 8 to give **1** under various conditions

Solvent	Time (h)	Temperature (°C)	Conversion (%)	Yield (%)	Rate ($M^{-2}\,s^{-1}$)[a]
CH_2Cl_2	18	25	50	45	0.01
H_2O	3.5	25	100	95	0.18
2.5 M aqueous LiCl	0.3	25	100	95	ND
1.0 M aqueous LiCl	0.8	25	100	95	2.86
1.0 M aqueous glucose	0.8	25	100	95	ND
0.5 M aqueous glucose	2	25	100	94	1.29

ND-not determined.
[a] Percent standard deviations were 3–6%.

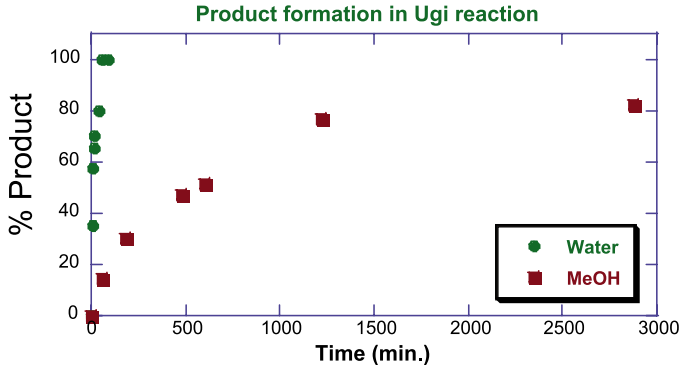


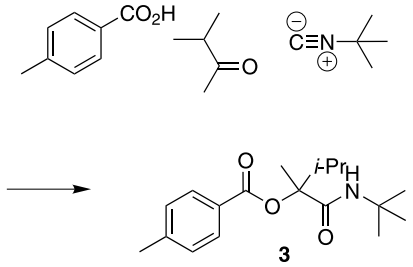
Figure 7. Reaction progress for the Ugi reaction in Scheme 9 in water (●) and methanol (■) solutions.

which to contrast water (c.e.d. 550; ε 78), as it has a higher dielectric constant but a significantly lower c.e.d. In the event, the Passerini reaction in Scheme 8 does not proceed at all in methanol (24 h), and in formamide the product **1** can be isolated in only 15% yield after 24 h.

A classical image of the hydrophobic effect relates to the formation of clathrates around a hydrophobic molecule in water, and the tendency of those hydrophobic droplets to merge so as to minimize the surface area of contact between hydrophobic molecules and water. Therefore, the acceleration of a reaction through the hydrophobic effect is expected to correlate with the hydrophobic surface area of the reactant(s). As discussed above, the influence of water on some reactions is very much like the influence of pressure, in which reactions that minimize volume along the reaction coordinate are accelerated. The c.e.d. also bears units of pressure and water's c.e.d. has a magnitude that is comparable to pressures known to exert significant rate effects on reactions. Of course, distinguishing between surface area-related effects and volume-related effects is difficult because molecular surface area and volume tend to co-vary, at least for roughly spherical molecules. One aspect of cohesive energy density that is potentially distinct from the hydrophobic effect is its temperature dependence. Because the density of water is temperature-dependent and is maximum at 4 °C, at this temperature the c.e.d. is maximum, and therefore reactions whose acceleration is related to c.e.d. effects should show the greatest rate acceleration at 4 °C. The Passerini reaction in Scheme 8 was therefore examined at 4 °C. The reaction rate speeds by 10% at the lower temperature. This inverse temperature dependence contravenes the conventional, $\Delta H^{\ddagger}$-based effect, faster reaction at higher temperature. This percentage change in reaction rate compares to a difference in c.e.d. of +0.75% at 4 °C versus rt.

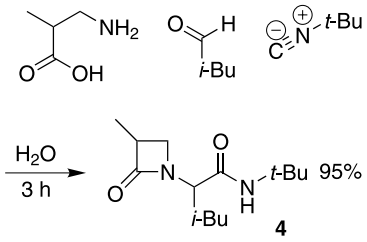
The successes discussed earlier in using pressure to promote difficult Ugi and Passerini reactions suggested that the influence of water on these specific reactions should be investigated. When the Passerini reaction in Scheme 10 is conducted in water at rt for 36 h, the product **3** is obtained in 44% yield, comparable to the 39% yield obtained in neat ketone at 3 kbar for 16 h. When the Ugi reaction in Scheme 6 is conducted in water at rt for 3 days, the product is obtained in 55% yield, comparable to the 61% yield obtained in dichloromethane at 9 kbar for 14 days. These results are certainly gratifying, as conducting reactions in water is far easier than using high pressure apparatus. Even better outcomes were obtained with aqueous salt solutions as solvent. When conducted in 2.5 M aqueous LiCl, the Ugi reaction gives 75% yield in 3 days, and the Passerini reaction gives 65% yield in 36 h.

The power to promote these otherwise recalcitrant transformations suggested that the effect of water as a solvent could be used to promote unprecedented multi-component reactions. Ring formation via the use of compounds bearing two of the functional groups needed for a multi-component reaction is known, but the creation of strained ring systems is more challenging. As mentioned



Scheme 10.

earlier, ring formation leads to volume contraction in the transition state and should mean a reaction that is responsive to pressure or aqueous solution. There is but a single report on the use of β-amino acids in an Ugi reaction to generate β-lactams.[21] When the reaction in Scheme 11 is conducted in water, the product **4** is obtained in essentially quantitative yield in 3 h. For comparison, the reported reaction in MeOH requires up to several days. These reactions create new stereogenic centers adjacent to nitrogen and, unsurprisingly, little influence from the pre-existing stereogenic centers is evident, as ~1:1 diastereoisomeric mixtures are seen in the product β-lactams.



Scheme 11.

The ability to quickly take reactions to completion is highly useful for processes in combinatorial chemistry, so the use of water as solvent for preparation of simple molecular libraries was investigated. For the Passerini products **6** in Figure 8, four acids, four aldehydes, and two isonitrile building blocks (listed in Table 2) were used to create a 32-member library. Reaction conditions were 3 h at rt in water. Yields were 72–93% (av 87%), and HPLC purities of crude reaction products were 72-100% (av 87%). Likewise, for the Ugi products **7**, four acids, three aldehydes, two amines, and two isonitrile building blocks (listed in Table 2) were used to create a 48-member library. Reaction conditions were 3–6 h at rt in water. Yields were 78–95% (av 86%), and HPLC purities of crude reaction products were 83–99% (av 95%). Likewise, for the β-lactam

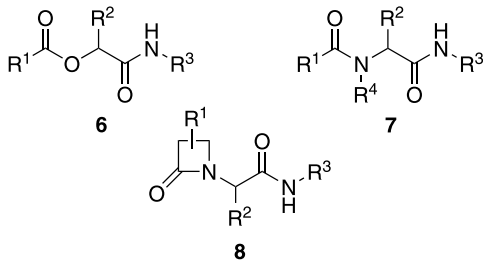


Figure 8. Passerini, Ugi, and β-lactam reaction products of parallel library synthesis.

producing Ugi process, four aldehydes, four β-amino acids, and two isonitrile building blocks (Table 3) were used to create a 32-member library of products **8**. Reaction conditions were 3 h at rt in water. Yields were 71–89% (av 84%), and HPLC purities of crude reaction products were 70–99% (av 89%). Ugi reactions of β-ketoacids to generate strained bicyclic β-lactams are detailed in another publication.[22] These processes require the use of 1 M aqueous glucose to promote reaction and have no counterpart in organic solvents.

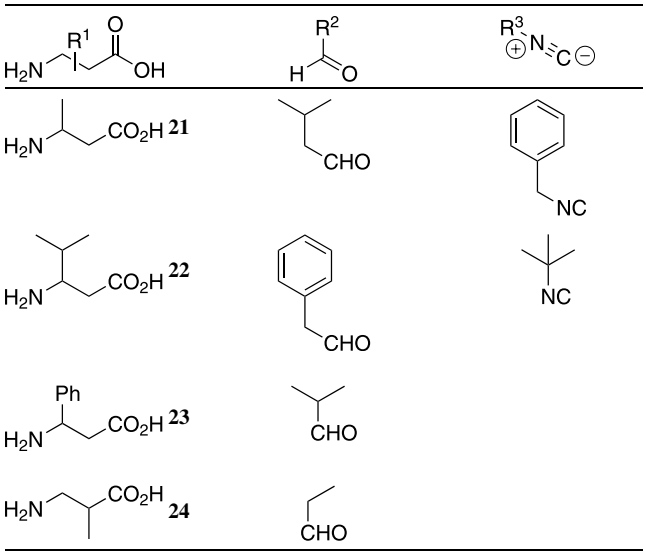
A particularly convenient operational aspect of all of these reactions should be mentioned. While some starting materials may have some solubility in water, the aggregation of a number of hydrophobic groups into a single molecule and the significant increase in molecular size means that the products of these reactions have very low solubility in water. Because these products are frequently solids, they can be isolated by simple filtration (or decantation) and washing with a small amount of aqueous bicarbonate solution. For the few liquid products, extraction with dichloromethane, washing with aqueous bicarbonate, and evaporation provides the crude product.

The reactants for these multi-component reactions are only marginally soluble in water, and the products are widely insoluble. Therefore, these are clearly heterogeneous

Table 2

R^1 acid	R^2 aldehyde	R^3 isonitrile	R^4 amine
9	**13**	**17**	**19**
10	**14**	**18**	**20**
11	**15**		
12	**16**		

Table 3



reactions. For any heterogeneous reaction, efficient mass transport between phases can be crucial for rapid reaction rates, and the method of mixing can strongly influence rate. Most of the reactions described so far were conduced in sealed peptide synthesis vessels on a wrist-action shaker. Results obtained with this method of mixing were superior to the use of a magnetic stirring bar and motor. The influence of mixing ferocity and method on reactions of organic compounds in water are subjects of our ongoing investigations.

In some cases, it is possible to enhance these reactions by the addition of a small amount (3–10% by volume) of $CHCl_3$ or toluene. The basis of this 'trick' is uncertain. One postulate is that organic solvents reduce the solute radius (or increase curvature of the droplets) and enhance the hydrophobic effect.[23] This 'trick' particularly applies when reactants are solids. In such cases, these highly water insoluble reactants may not mix well with other reactants. Therefore, another postulate is that these organic solvents can dissolve the solid organic reactant, enabling more efficient mixing with the aqueous phase.

Chemists have extensive experience with heterogeneous reactions, and many strategies to increase mass transport between phases are available. These are subjects for future investigation. While the need for efficient mixing is a less convenient aspect of conducting reactions in water, it is worth emphasis that the lack of miscibility of reactants with water is essential for the rate accelerating effect promoted by water. If the reactions were homogeneous, no hydrophobic effect should obtain, and no rate acceleration should be observed. That is, reactants need not be soluble in water to be successfully used in reactions that benefit from rate acceleration by water, and indeed, full water solubility is undesirable. There is clearly a limit beyond which a lack of solubility in water will preclude a reactant from reaching other reactants in the aqueous phase, and thereby preventing a reaction. The limits of water solubility and hydrophobicity are the subject of our ongoing investigations.

3. Discussion

Earlier studies have demonstrated the powerful effect of water on reactions for which negative activation volumes can be expected. Atom-transfer radical cyclizations of iodoacetates that generate lactones are far more efficient in water, including reactions that form large rings.[24] The yield enhancement in that work was specifically attributed to the large c.e.d. of water, consistent with a significant volume contraction in the transition state. This negative activation volume is related to the reduction of the molecular packing coefficient upon cyclization. Similar effects may be at work in the synthesis of β-lactams described here, even beyond the rate acceleration attributed to conduct of the multicomponent reaction in water. More detailed study would be required to establish this unambiguously, however. While the activation volumes of multicomponent reactions have never been measured, our results and the earlier studies of pressure acceleration suggest strongly that they have negative activation volumes.

A common misconception concerning reactions in water is that the reagents must be water-miscible. Not only is this not necessary, compounds that are completely miscible with water should not experience the hydrophobic and c.e.d. effects of water that have been suggested to play a major role in rate acceleration. Of course, some water solubility is essential to enable reagents to come into contact with one another.

The rate accelerations reported here might be attributed to a surfactant effect or 'micellar catalysis'.[25] The IUPAC definition of micellar catalysis[26] is:

> The acceleration of a chemical reaction in solution by the addition of a surfactant at a concentration higher than its critical micelle concentration so that the reaction can proceed in the environment of surfactant aggregates (micelles). (Rate enhancements may be due, for example, to higher concentration of the reactants in that environment, more favorable orientation and solvation of the species, or enhanced rate constants in the micellar pseudophase of the surfactant aggregate).

By strict application of this definition, none of these reactions can be ascribed to micellar catalysis because a surfactant has not been added above its CMC. The additives that were studied are not surfactants and do not form micelles. However, it might be imagined that the reactants themselves form micelles. Comparing this idea to the picture that was presented earlier in this paper, droplets of hydrophobic reactants surrounded by a clathrate of water molecules, this may be a distinction without a difference.

While some have attributed the hydrophobic effect to water's large cohesive energy, deeper considerations have suggested that the two phenomena are independent.[27] Thus, the ability to manipulate solvent hydrophobicity and c.e.d. independently, as in our small temperature study, shows that it may be possible to determine the individual contributions of these effects to a specific reaction. Clearly, other ways to

perturb slightly the c.e.d. and hydrophobicity of water, such as isotopic substitution, are also of interest.

While the principle that reactions in water can experience effects similar to reactions conducted under pressure is not new, having been well-examined in physical organic studies over the past two decades, it is likely under-appreciated in the synthetic community. A report has recently appeared concerning significant acceleration of reactions conducted 'on water'.[28] The concentration at which these preparative reactions were conducted, as compared to relatively low concentrations in earlier mechanistic studies, was offered as a factor of particular significance. The concentrations typically used for the reactions described in our work is 0.1 M. Our perspective on water's unique properties and heterogeneous reaction media, provided in this paper, readily explains the observations of Sharpless. Future work in our lab will investigate these issues in greater depth.

Water offers other virtues, such as being a 'green' solvent. The ability to speed reactions significantly and conduct reactions that have no counterpart when run in organic solvent should be a more recognized property of water as a solvent for synthetic organic reactions.

4. Experimental

4.1. General procedure for kinetic runs with Passerini reaction in Scheme 5

Solutions of aldehydes were prepared in water and added (0.5 mL) to neat acids and reaction solutions (water or 2× solutions of glucose or LiCl, 0.5 mL), creating 0.1 M reactions in replicate of the number of time points. Isonitrile was added neat, reaction mixtures were sealed in peptide synthesis vessels, and they were agitated with a wrist-action mechanical shaker. At time points, agitation was stopped and one reaction mixture was extracted with stock solution (1.0 mL) of ethyl acetate containing dinitrobenzene (DNB; 0.10 M) as an internal standard. The crude reaction mixture was analyzed by capillary gas chromatography with flame ionization detection using a DB-5 column (30 m, 0.25 mm ID) with the following temperature program: 150 °C, 1 min; +10 °C/min, 10 min; 300 °C, 2 min. The retention time of the product was 5.4 min, and of the standard was 2.0 min. The ratio of the integrated area of the product to DNB was used to calculate the percent conversion and therefore the concentration of product.

4.2. General procedure for kinetic runs with Ugi reaction in Scheme 6

The procedure for these experiments was similar to that above. Differences included the final reactant concentration (0.12 M) and therefore the scale (0.12 mmol/1 mL), and the use of magnetic stirring.

4.3. General procedure for the synthesis of libraries of Passerini reaction products 6

Isonitrile (0.3 mmol) was added to a suspension of acid (0.3–0.35 mmol) and aldehyde (0.3 mmol) in water (3 mL). The resulting mixture was stirred/shaken (by a wrist shaker) for 3–6 h at rt. For solids, the product was isolated by filtration. The residue was washed with 3×1 mL of 10% $NaHCO_3$ and 2×1 mL water and dried under high vacuum. For oily products, 2 mL dichloromethane was added to the reaction mixture. The aqueous layer was separated, and the organic layer was washed with 3×1 mL of 10% $NaHCO_3$ and 2 mL of brine. This solution was passed through a plug of anhyd Na_2SO_4 and concentrated under reduced pressure to give the desired product. *Acid*: (1) 2-cyclopentylacetic acid (**9**); (2) 3-methylbut-2-enoic acid (**10**); (3) 4-methylbenzoic acid (**11**); (4) 3,5-dimethoxybenzoic acid (**12**). *Aldehyde*: (1) isobutyraldehyde (**15**); (2) 3-methylbutanal (**13**); (3) propionaldehyde (**16**); (4) 2-phenylacetaldehyde (**14**). *Isonitrile*: (1) 1-(isocyanomethyl)benzene (**17**); (2) 2-isocyano-2-methylpropane (**18**).

4.3.1. 1-(Benzylamino)-3-methyl-1-oxobutan-2-yl 2-cyclopentylacetate 6{1,1,1}. ^{1}H NMR δ: 7.26 (m, 5H), 6.29 (br s, 1H), 5.11 (d, J=3.9 Hz, 1H), 4.44 (s, 2H), 2.40–2.15 (m, 4H), 1.77 (m, 2H), 1.55 (m, 4H), 1.11 (m, 2H), 0.94 (m, 6H). ^{13}C NMR δ: 172.3, 169.6, 138.1, 128.9, 127.9, 127.8, 78.1, 43.4, 40.6, 36.7, 32.7, 30.8, 25.2, 19.0, 17.24. LRMS (CI) *m/z*: 318 (MH^+). Yield: 87%. HPLC purity: 97%.

4.3.2. 1-(Benzylamino)-3-methyl-1-oxobutan-2-yl 3-methylbut-2-enoate 6{2,1,1}. ^{1}H NMR δ: 7.30 (m, 5H), 6.30 (br s, 1H), 5.74 (s, 1H), 5.20 (d, J=3.9 Hz, 1H), 4.54 (dd, J=14.1, 5.7 Hz, 1H), 4.43 (dd, J=15.0, 5.7 Hz, 1H), 2.39 (m, 1H), 2.18 (s, 3H), 1.92 (s, 3H), 0.97 (d, J=4.5 Hz, 3H), 0.95 (d, J=4.5 Hz, 3H). ^{13}C NMR δ: 170.0, 165.4, 159.8, 138.2, 128.9, 127.9, 127.7, 115.1, 77.2, 43.3, 30.9, 27.8, 20.7, 19.1, 17.2. LRMS (ESI^+) *m/z*: 290.1 (MH^+), 312.1 ($[M+Na]^+$). Yield: 90%. HPLC purity: >99%.

4.3.3. 1-(Benzylamino)-3-methyl-1-oxobutan-2-yl 4-methylbenzoate 6{3,1,1}. ^{1}H NMR δ: 7.94 (d, J=8.1 Hz, 2H), 7.28 (m, 2H), 6.32 (br s, 1H), 5.37 (d, J=4.2 Hz, 1H), 4.56 (dd, J=15.0, 5.7 Hz, 1H), 4.43 (dd, J=15.0, 5.4 Hz, 1H), 2.52 (m, 1H), 2.48 (s, 3H), 1.06 (d, J=7.2 Hz, 3H), 1.04 (J=7.2 Hz, 3H). ^{13}C NMR δ: 169.7, 165.8, 144.8, 130.0, 129.6, 129.0, 127.8, 78.7, 43.4, 31.1, 21.9, 19.2, 17.2. LRMS (FAB^+) *m/z*: 326.3 (MH^+). Yield: 85%. HPLC purity: 95%.

4.3.4. 1-(Benzylamino)-3-methyl-1-oxobutan-2-yl 3,5-dimethoxybenzoate 6{4,1,1}. ^{1}H NMR δ: 7.30 (m, 5H), 7.19 (d, J=2.4 Hz, 2H), 6.68 (t, J=2.4 Hz, 1H), 6.31 (br s, 1H), 5.36 (d, J=4.2 Hz, 1H), 4.55 (d, J=15.0, 6.0 Hz, 1H), 4.44 (dd, J=15.0, 5.7 Hz, 1H), 3.81 (s, 6H), 2.48 (m, 1H), 1.06 (d, J=4.8 Hz, 3H), 1.04 (d, J=5.1 Hz, 3H). ^{13}C NMR δ: 169.5, 165.5, 161.1, 131.3, 129.0, 127.8, 107.7, 106.0, 79.0, 55.8, 43.4, 31.1, 19.2, 17.2. LRMS (FAB^+) *m/z*: 372.3 (MH^+). Yield: 94%. HPLC purity: 79%.

4.3.5. 1-(Benzylamino)-4-methyl-1-oxopentan-2-yl 2-cyclopentylacetate 6{1,2,1}. ^{1}H NMR δ: 7.30 (m, 2H), 7.25 (m, 3H), 6.22 (br s, 1H), 5.24 (m, 1H), 4.44 (s, 2H), 2.34 (m, 2H), 2.19 (m, 1H), 1.80–1.65 (m, 5H), 1.53 (m, 4H), 1.10 (m, 2H), 0.92 (d, J=2.1 Hz, 6H). ^{13}C NMR δ: 172.4, 170.5, 138.0, 129.0, 127.9, 127.8, 72.8, 43.5, 41.1, 40.6, 36.6, 32.7, 25.2, 24.8, 23.4, 21.9. LRMS (CI) *m/z*: 332 (MH^+). Yield: 85%. HPLC purity: 76%.

4.3.6. 1-(Benzylamino)-4-methyl-1-oxopentan-2-yl 3-methylbut-2-enoate 6{2,2,1}. ^{1}H NMR δ: 7.39–7.21 (m, 5H), 6.32 (br s, 1H), 5.71 (s, 1H), 5.30 (t, J=5.4 Hz, 1H), 4.46 (m, 2H), 2.18 (s, 3H), 1.92 (s, 3H), 1.80–1.71 (m, 3H), 0.94 (d, J=5.4 Hz, 6H). ^{13}C NMR δ: 170.9, 165.3, 158.8, 136.0, 128.9, 127.8, 127.7, 115.13, 72.1, 43.3, 41.2, 27.8, 24.8, 23.4, 22.0, 20.7. LRMS (FAB$^+$) *m/z*: 304.3 (MH$^+$). Yield: 89%. HPLC purity: 91%.

4.3.7. 1-(Benzylamino)-4-methyl-1-oxopentan-2-yl 4-methylbenzoate 6{3,2,1}. ^{1}H NMR δ: 7.95 (d, J=9.0 Hz, 2H), 7.28 (m, 2H), 6.35 (br s, 1H), 5.51 (dd, J=9.0, 4.5 Hz, 1H), 4.53 (dd, J=15.0, 6.0 Hz, 1H), 4.43 (dd, J=15.0, 5.7 Hz, 1H), 2.42 (s, 3H), 1.91 (m, 2H), 1.79 (m, 1H), 0.98 (d, J=3.3 Hz, 3H), 0.96 (d, J=3.3 Hz, 3H). ^{13}C NMR δ: 170.7, 165.8, 144.7, 138.1, 130.1, 129.6, 129.0, 127.7, 126.7, 73.4, 43.4, 41.1, 25.0, 23.4, 22.0. LRMS (FAB$^+$) *m/z*: 340.3 (MH$^+$). Yield: 93%. HPLC purity: 88%.

4.3.8. 1-(Benzylamino)-4-methyl-1-oxopentan-2-yl 3,5-dimethoxybenzoate 6{4,2,1}. ^{1}H NMR δ: 7.31 (m, 5H), 7.18 (d, J=2.1 Hz, 2H), 6.67 (t, J=2.4 Hz, 1H), 6.66 (br s, 1H), 5.50 (dd, J=9.0, 4.8 Hz, 1H), 4.52 (dd, J=15.0, 6.0 Hz, 1H), 4.44 (dd, J=15.0, 6.0 Hz, 1H), 3.81 (s, 6H), 1.90 (m, 2H), 1.79 (m, 1H), 0.99 (d, J=2.7 Hz, 3H), 0.97 (d, J=2.4 Hz, 3H). ^{13}C NMR δ: 170.4, 165.6, 161.0, 131.3, 131.1, 129.0, 127.8, 107.7, 106.2, 73.8, 55.8, 43.4, 41.1, 25.0, 23.4, 22.0. LRMS (FAB$^+$) *m/z*: 386.3 (MH$^+$). Yield: 89%. HPLC purity: 97%.

4.3.9. 1-(Benzylamino)-1-oxobutan-2-yl 2-cyclopentylacetate 6{1,3,1}. ^{1}H NMR δ: 7.36–7.24 (m, 5H), 6.35 (br s, 1H), 5.21 (t, J=5.1 Hz, 1H), 4.46 (d, J=5.7 Hz, 2H), 2.37 (d, J=9.0 Hz, 2H), 2.23 (m, 1H), 1.93 (m, 2H), 1.77 (m, 2H), 1.53 (m, 4H), 1.12 (m, 2H), 0.93 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 172.2, 170.0, 138.1, 129.0, 128.0, 127.9, 75.0, 43,4, 40.6, 36.7, 32.7, 25.4, 25.2, 9.3. LRMS (CI) *m/z*: 304 (MH$^+$). Yield: 86%. HPLC purity: >99%.

4.3.10. 1-(Benzylamino)-1-oxobutan-2-yl 3-methylbut-2-enoate 6{2,3,1}. ^{1}H NMR δ: 7.37–7.25 (m, 5H), 6.39 (br s, 1H), 5.73 (s, 1H), 5.25 (dd, J=7.7, 4.5 Hz, 1H), 4.57 (dd, J=12.0, 6.3 Hz, 1H), 4.43 (dd, J=15.0, 5.7 Hz, 1H), 2.18 (s, 3H), 1.98 (m, 2H), 1.91 (s, 3H), 0.94 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 170.4, 165.3, 159.8, 138.0, 128.9, 127.9, 127.7, 115.2, 74.2, 43.3, 27.8, 25.5, 20.7, 9.3. LRMS (FAB$^+$) *m/z*: 276.3 (MH$^+$). Yield: 89%. HPLC purity: 97%.

4.3.11. 1-(Benzylamino)-1-oxobutan-2-yl 4-methylbenzoate 6{3,3,1}. ^{1}H NMR δ: 7.94 (d, J=8.4 Hz, 2H), 7.29 (m, 2H), 6.41 (br s, 1H), 5.46 (t, J=5.1 Hz, 1H), 4.55 (dd, J=15.0, 5.7 Hz, 1H), 4.45 (dd, J=16.5, 6.0 Hz, 1H), 2.43 (s, 3H), 2.07 (m, 2H), 1.03 (t, J=6.0 Hz, 3H). ^{13}C NMR δ: 170.1, 169.8, 144.7, 130.5, 130.0, 129.6, 129.4, 129.0, 127.8, 75.5, 43.4, 25.5, 21.9, 9.5. LRMS (FAB$^+$) *m/z*: 312.2 (MH$^+$). Yield: 92%. HPLC purity: 71%.

4.3.12. 1-(Benzylamino)-1-oxobutan-2-yl 3,5-dimethoxybenzoate 6{4,3,1}. ^{1}H NMR δ: 7.26 (m, 5H), 7.16 (d, J=2.4 Hz, 2H), 6.66 (br s, 1H), 6.44 (br s, 1H), 5.43 (m, 1H), 4.49 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2.06 (m, 2H), 1.02 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 170.0, 165.4, 161.0, 138.1, 131.3, 129.0, 127.8, 107.6, 106.1, 75.9, 55.8, 43.4, 25.5, 9.5. LRMS (FAB$^+$) *m/z*: 358.0 (MH$^+$). Yield: 85%. HPLC purity: 89%.

4.3.13. 1-(Benzylamino)-1-oxo-3-phenylpropan-2-yl 2-cyclopentylacetate 6{1,4,1}. ^{1}H NMR δ: 7.40–7.08 (m, 10H), 6.20 (br s, 1H), 5.45 (m, 1H), 4.38 (d, J=6.0 Hz, 2H), 3.20 (m, 2H), 2.29 (m, 2H), 2.11 (m, 1H), 1.67 (m, 2H), 1.51 (m, 4H), 1.03 (m, 2H). ^{13}C NMR δ: 172.0, 169.2, 137.8, 136.1, 129.9, 128.9, 128.6, 127.9, 127.8, 127.1, 74.3, 43.4, 40.4, 38.0, 36.5, 32.6, 25.1. LRMS (FAB$^+$) *m/z*: 366.3 (MH$^+$). Yield: 81%. HPLC purity: 95%.

4.3.14. 1-(Benzylamino)-1-oxo-3-phenylpropan-2-yl 3-methylbut-2-enoate 6{2,4,1}. ^{1}H NMR δ: 7.35–7.04 (m, 10H), 6.23 (br s, 1H), 5.67 (s, 1H), 5.49 (m, 1H), 2.43 (m, 1H), 4.30 (m, 1H), 3.23 (br s, 2H), 2.13 (s, 3H), 1.89 (s, 3H). ^{13}C NMR δ: 169.5, 164.9, 160.1, 137.9, 136.3, 130.3, 128.8, 128.5, 128.3, 127.8, 127.7, 127.0, 115.0, 73.6, 43.2, 37.9, 27.8, 20.7. LRMS (FAB$^+$) *m/z*: 338.3 (MH$^+$). Yield: 86%. HPLC purity: 83%.

4.3.15. 1-(Benzylamino)-1-oxo-3-phenylpropan-2-yl 4-methylbenzoate 6{3,4,1}. ^{1}H NMR δ: 7.87 (d, J=8.4 Hz, 2H), 7.30 (m, 10H), 1.08 (m, 2H), 6.28 (br s, 1H), 5.71 (t, J=5.7 Hz, 1H), 4.49 (dd, J=15.0, 6.3 Hz, 1H), 4.26 (dd, J=15.0, 5.7 Hz, 1H), 3.36 (d, J=5.7 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR δ: 169.3, 165.5, 144.8, 137.9, 136.1, 130.1, 129.6, 128.9, 128.7, 128.4, 127.7, 127.2, 126.6, 74.8, 43.3, 38.0, 22.0. LRMS (FAB$^+$) *m/z*: 374.3 (MH$^+$). Yield: 85%. HPLC purity: 92%.

4.3.16. 1-(Benzylamino)-1-oxo-3-phenylpropan-2-yl 3,5-dimethoxybenzoate 6{4,4,1}. ^{1}H NMR δ: 7.31–7.10 (m, 8H), 7.08 (d, J=2.4 Hz, 2H), 7.06 (m, 2H), 6.65 (t, J=2.4 Hz, 1H), 6.16 (br s, 1H), 5.68 (t, J=5.4 Hz, 1H), 4.48 (dd, J=15.0, 6.3 Hz, 1H), 4.36 (dd, J=15.0, 5.4 Hz, 1H), 3.78 (s, 6H), 3.35 (d, J=5.7 Hz, 2H). ^{13}C NMR δ: 169.1, 165.2, 161.0, 136.0, 131.2, 130.0, 128.9, 128.7, 127.7, 127.2, 107.5, 106.5, 75.1, 55.8, 43.4, 38.0. LRMS (FAB$^+$) *m/z*: 420.0 (MH$^+$). Yield: 90%. HPLC purity: 80%.

4.3.17. 1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl 2-cyclopentylacetate 6{1,1,2}. ^{1}H NMR δ: 5.74 (br s, 1H), 4.93 (d, J=3.0 Hz, 1H), 2.38 (m, 2H), 2.25 (m, 2H), 1.82 (m, 2H), 1.58 (m, 4H), 1.32 (s, 9H), 1.17 (m, 2H), 0.90 (m, 6H). ^{13}C NMR δ: 172.2, 168.7, 78.2, 51.4, 40.9, 36.8, 32.7, 30.7, 28.9, 25.2, 19.0, 17.1. LRMS (CI) *m/z*: 284 (MH$^+$). Yield: 85%. HPLC purity: 98%.

4.3.18. 1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl 3-methylbut-2-enoate 6{2,1,2}. ^{1}H NMR δ: 5.80 (br s, 1H), 5.76 (s, 1H), 5.01 (d, J=3.9 Hz, 1H), 2.33 (m, 1H), 2.20 (s, 3H), 1.95 (s, 3H), 1.35 (s, 9H), 0.94 (d, J=2.1 Hz, 3H), 0.92 (d, J=2.1 Hz, 3H). ^{13}C NMR δ: 169.1, 165.3, 159.8, 115.3, 78.0, 51.3, 30.8, 28.9, 27.8, 20.7, 19.0, 17.0. LRMS (FAB$^+$) *m/z*: 256.3 (MH$^+$), 257.3 ([M+2H]$^+$). Yield: 88%. HPLC purity: 84%.

4.3.19. 1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl 4-methylbenzoate 6{3,1,2}. ^{1}H NMR δ: 7.97 (d, J=8.4 Hz, 2H), 7.29 (d, J=7.8 Hz, 2H), 5.83 (br s, 1H), 5.20 (d, J=4.2 Hz, 1H), 2.47 (m, 1H), 2.43 (s, 3H), 1.33 (s, 9H),

1.03 (d, J=6.9 Hz, 3H), 1.00 (d, J=6.9 Hz, 3H). ^{13}C NMR δ: 168.7, 165.6, 144.6, 129.9, 129.6, 127.0, 78.7, 51.5, 30.9, 28.9, 21.9, 19.2, 17.1. LRMS (FAB$^+$) m/z: 292.2 (MH$^+$). Yield: 87%. HPLC purity: 93%.

4.3.20. 1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl 3,5-dimethoxybenzoate 6{4,1,2}. ^{1}H NMR δ: 7.21 (d, J=2.4 Hz, 2H), 6.70 (t, J=2.4 Hz, 1H), 5.81 (br s, 1H), 5.18 (d, J=3.9 Hz, 1H), 3.85 (s, 6H), 2.44 (m, 1H), 1.35 (s, 9H), 1.03 (d, J=7.5 Hz, 3H), 1.00 (d, J=7.2 Hz, 3H). ^{13}C NMR δ: 168.6, 165.4, 161.1, 131.5, 107.6, 105.9, 79.1, 55.8, 51.5, 30.9, 28.9, 19.2, 17.1. LRMS (EI$^+$) m/z: 337 (M$^+$). Yield: 85%. HPLC purity: 96%.

4.3.21. 1-(*tert*-Butylamino)-4-methyl-1-oxopentan-2-yl 2-cyclopentylacetate 6{1,2,2}. ^{1}H NMR δ: 5.76 (br s, 1H), 5.07 (m, 1H), 2.36 (m, 2H), 2.25 (m, 1H), 1.82 (m, 2H), 1.70–1.45 (m, 7H), 1.33 (s, 9H), 1.16 (m, 2H), 0.90 (m, 6H). ^{13}C NMR δ: 172.3, 169.7, 73.1, 51.3, 41.0, 40.7, 36.8, 32.7, 28.9, 25.2, 24.8, 23.3, 22.1. LRMS (CI) m/z: 298 (MH$^+$). Yield: 87%. HPLC purity: 86%.

4.3.22. 1-(*tert*-Butylamino)-4-methyl-1-oxopentan-2-yl 3-methylbut-2-enoate 6{2,2,2}. ^{1}H NMR δ: 5.82 (br s, 1H), 5.73 (s, 1H), 5.18 (m, 1H), 2.20 (s, 3H), 1.93 (s, 3H), 1.81 (m, 1H), 1.69 (m, 2H), 1.29 (s, 9H), 0.92 (m, 6H). ^{13}C NMR δ: 170.1, 165.3, 159.4, 115.3, 72.3, 51.2, 44.3, 41.3, 28.9, 24.8, 23.7, 22.1, 20.7. LRMS (FAB$^+$) m/z: 270.3 (MH$^+$). Yield: 86%. HPLC purity: 77%.

4.3.23. 1-(*tert*-Butylamino)-4-methyl-1-oxopentan-2-yl 4-methylbenzoate 6{3,2,2}. ^{1}H NMR δ: 7.94 (J=8.1 Hz, 2H), 7.28 (m, 2H), 5.88 (br s, 1H), 5.34 (m, 1H), 2.43 (s, 3H), 1.83 (m, 2H), 1.73 (m, 1H), 1.33 (s, 9H), 0.96 (d, J=3.0 Hz, 3H), 0.94 (J=2.8 Hz, 3H). ^{13}C NMR δ: 169.8, 165.2, 144.6, 130.5, 129.6, 129.4, 73.6, 51.4, 41.0, 34.4, 28.9, 24.9, 23.4, 21.9. LRMS (FAB$^+$) m/z: 306.3 (MH$^+$). Yield: 91%. HPLC purity: 82%.

4.3.24. 1-(*tert*-Butylamino)-4,4-dimethyl-1-oxohexan-2-yl 3,5-dimethoxybenzoate 6{4,2,2}. ^{1}H NMR δ: 7.20 (d, J=2.1 Hz, 2H), 6.69 (t, J=2.4 Hz, 1H), 5.83 (br s, 1H), 5.31 (dd, J=9.0, 3.6 Hz, 1H), 3.84 (s, 6H), 1.87–1.73 (m, 3H), 1.34 (s, 9H), 0.97 (d, J=2.4 Hz, 3H), 0.95 (d, J=2.1 Hz, 3H). ^{13}C NMR δ: 169.5, 165.4, 161.1, 131.5, 107.6, 106.1, 74.0, 55.8, 51.4, 41.0, 28.9, 24.9, 23.4, 22.1. LRMS (FAB$^+$) m/z: 352.0 (MH$^+$). Yield: 82%. HPLC purity: 94%.

4.3.25. 1-(*tert*-Butylamino)-1-oxobutan-2-yl 2-cyclopentylacetate 6{1,3,2}. ^{1}H NMR δ: 5.84 (br s, 1H), 5.04 (t, J=6.0 Hz, 1H), 2.40 (d, J=6.0 Hz, 2H), 2.26 (m, 1H), 1.86 (m, 4H), 1.60 (m, 4H), 1.31 (s, 9H), 1.19 (m, 2H), 0.91 (t, J=6.6 Hz, 3H). ^{13}C NMR δ: 172.1, 169.0, 75,1, 51.4, 40.7, 36.8, 32.8, 28.9, 27.9, 25.2, 9.1. LRMS (CI) m/z: 270 (MH$^+$). Yield: 72%. HPLC purity: 94%.

4.3.26. 1-(*tert*-Butylamino)-1-oxobutan-2-yl 3-methylbut-2-enoate 6{2,3,2}. ^{1}H NMR δ: 5.89 (br s, 1H), 5.74 (s, 1H), 5.07 (dd, J=6.0, 5.1 Hz, 1H), 2.19 (s, 3H), 1.93 (s, 3H), 1.86 (m, 2H), 1.33 (s, 9H), 0.90 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 169.4, 165.1, 159.3, 115.3, 74.3, 51.3, 28.9, 27.8, 25.3, 20.7, 9.1. LRMS (FAB$^+$) m/z: 242.3 (MH$^+$). Yield: 89%. HPLC purity: 79%.

4.3.27. 1-(*tert*-Butylamino)-1-oxobutan-2-yl 4-methylbenzoate 6{3,3,2}. ^{1}H NMR δ: 7.95 (J=8.1 Hz, 2H), 7.28 (d, J=8.4 Hz, 2H), 5.93 (br s, 1H), 5.28 (t, J=6.0 Hz, 1H), 2.43 (s, 3H), 1.99 (m, 2H), 1.34 (s, 9H), 0.99 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 169.1, 165.8, 144.6, 129.9, 129.6, 128.9, 75.6, 41.5, 28.9, 25.3, 21.9, 9.2. LRMS (FAB$^+$) m/z: 278.3 (MH$^+$). Yield: 87%. HPLC purity: 72%.

4.3.28. 1-(*tert*-Butylamino)-1-oxobutan-2-yl 3,5-dimethoxybenzoate 6{4,3,2}. ^{1}H NMR δ: 7.21 (d, J=2.4 Hz, 2H), 6.70 (t, J=2.4 Hz, 1H), 5.83 (br s, 1H), 5.39 (t, J=6.0 Hz, 1H), 3.81 (s, 6H), 1.99 (m, 2H), 1.34 (s, 9H), 0.99 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 169.5, 165.4, 161.1, 131.5, 107.6, 106.1, 74.9, 55.8, 51.4, 28.9, 24.9, 9.5. LRMS (FAB$^+$) m/z: 324.0 (MH$^+$). Yield: 82%. HPLC purity: 85%.

4.3.29. 1-(*tert*-Butylamino)-1-oxo-3-phenylpropan-2-yl 2-cyclopentylacetate 6{1,4,2}. ^{1}H NMR δ: 7.30–7.15 (m, 5H), 5.62 (br s, 1H), 5.24 (m, 1H), 3.12 (m, 1H), 2.29 (m, 2H), 2.14 (m, 1H), 1.73 (m, 2H), 1.55 (m, 4H), 1.25 (s, 9H), 1.06 (m, 2H). ^{13}C NMR δ: 171.9, 168.3, 136.3, 129.9, 128.5, 127.0, 74.5, 51.4, 40.5, 37.8, 36.6, 32.6, 28.7, 25.1. LRMS (FAB$^+$) m/z: 332.3 (MH$^+$). Yield: 88%. HPLC purity: 81%.

4.3.30. 1-(*tert*-Butylamino)-1-oxo-3-phenylpropan-2-yl 3-methylbut-2-enoate 6{2,4,2}. ^{1}H NMR δ: 7.30–7.16 (m, 5H), 5.69 (s, 1H), 5.64 (br s, 1H), 5.31 (t, J=5.4 Hz, 1H), 3.17 (d, J=5.4 Hz, 2H), 2.14 (s, 3H), 1.92 (s, 3H), 1.24 (s, 9H). ^{13}C NMR δ: 166.5, 164.9, 147.9, 136.4, 130.1, 128.4, 128.9, 115.2, 73.7, 51.3, 37.8, 28.8, 27.8, 20.7. LRMS (FAB$^+$) m/z: 304.3 (MH$^+$), 305.3 ([M+2H]$^+$). Yield: 88%. HPLC purity: 83%.

4.3.31. 1-(*tert*-Butylamino)-1-oxo-3-phenylpropan-2-yl 4-methylbenzoate 6{3,4,2}. ^{1}H NMR δ: 7.86 (d, J=8.4 Hz, 2H), 7.36 (m, 7H), 5.66 (br s, 1H), 5.52 (t, J=5.7 Hz, 1H), 3.29 (m, 2H), 2.42 (s, 3H), 1.25 (s, 9H). ^{13}C NMR δ: 168.3, 165.3, 144.6, 136.2, 130.1, 129.9, 129.6, 129.4, 128.5, 127.1, 74.9, 51.4, 37.9, 28.8, 21.9. LRMS (FAB$^+$) m/z: 340.3 (MH$^+$). Yield: 93%. HPLC purity: 73%.

4.3.32. 1-(*tert*-Butylamino)-1-oxo-3-phenylpropan-2-yl 3,5-dimethoxybenzoate 6{4,4,2}. ^{1}H NMR δ: 7.28 (m, 5H), 7.10 (d, J=2.1 Hz, 2H), 6.67 (t, J=2.4 Hz, 1H), 5.61 (br s, 1H), 5.48 (t, J=5.1 Hz, 1H), 3.82 (s, 6H), 3.28 (m, 2H), 1.25 (s, 9H). ^{13}C NMR δ: 168.0, 165.0, 161.0, 136.1, 131.0, 130.1, 128.5, 127.1, 107.4, 106.4, 75.2, 55.8, 51.5, 37.9, 28.8. LRMS (FAB$^+$) m/z: 386.3 (MH$^+$). Yield: 87%. HPLC purity: 72%.

4.4. General procedure for the synthesis of libraries of Ugi reaction products 7

A suspension of the amine (0.3–0.35 mmol) and aldehyde (0.3 mmol) in 3 mL water was stirred/shaken (by a wrist shaker) at rt for 30–45 min. Isonitrile (0.3 mmol) and acid (0.3–0.35 mmol) were added to the reaction mixture and

stirring/shaking was continued for 3–6 h. For solids, the product was isolated by filtration. The residue was washed with 3×1 mL of 10% $NaHCO_3$, 3×1 mL of 10% citric acid, and 2×1 mL water and dried under high vacuum. For an oily product, 2 mL of dichloromethane was added to the reaction mixture. The aqueous layer was separated, and the organic layer was washed with 3×1 mL of 10% $NaHCO_3$, 3×1 mL of 10% citric acid, and 2 mL of brine. This solution was passed through a plug of anhyd Na_2SO_4 and concentrated under reduced pressure to give the desired product. *Acid*: (1) 2-cyclopentylacetic acid (**9**); (2) 3-methylbut-2-enoic acid (**10**); (3) 4-methylbenzoic acid (**11**); (4) 3,5-dimethoxybenzoic acid (**12**). *Aldehyde*: (1) isobutyraldehyde (**15**); (2) 3-methylbutanal (**13**); (3) propionaldehyde (**16**). *Isonitrile*: (1) 1-(isocyanomethyl)-benzene (**17**); (2) 2-isocyano-2-methylpropane (**18**). *Amine*: (1) furan-2-ylmethanamine (**19**); (2) propan-2-amine (**20**).

4.4.1. *N*-Benzyl-2-(2-cyclopentyl-*N*-(furan-2-ylmethyl) acetamido)-3-methylbutanamide 7{1,1,1,1}. ^{1}H NMR δ: 7.37–7.17 (m, 6H), 7.05 (br s, 1H), 6.28 (t, J=3.0 Hz, 1H), 6.18 (d, J=3.0 Hz, 1H), 4.64 (d, J=17.1 Hz, 1H), 4.46–4.34 (m, 3H), 4.28 (dd, J=15.0, 6.0 Hz, 1H), 2.61–2.20 (m, 4H), 1.80 (m, 2H), 1.57 (m, 4H), 1.13 (m, 2H), 0.94 (d, J=6.6 Hz, 3H), 0.63 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 175.4, 170.7, 150.8, 142.3, 138.5, 128.8, 127.9, 127.5, 110.7, 108.7, 78.1, 43.4, 40.0, 32.8, 26.9, 25.2, 20.2, 18.9. LRMS (FAB^+) *m/z*: 397.2 (MH^+). Yield: 96%. HPLC purity: 88%.

4.4.2. *N*-(1-(Benzylamino)-3-methyl-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-3-methylbut-2-enamide 7{2,1,1,1}. ^{1}H NMR δ: 7.36–7.20 (m, 6H), 6.27 (t, J=3.0 Hz, 1H), 6.20 (d, J=3.3 Hz, 1H), 6.13 (s, 1H), 4.65 (d, J=16.8 Hz, 1H), 4.42–4.34 (m, 3H), 4.31 (dd, J=15.0, 5.7 Hz, 1H), 2.54 (m, 1H), 1.87 (s, 3H), 1.85 (s, 3H), 0.93 (d, J=6.3 Hz, 3H), 0.60 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 170.8, 170.5, 151.0, 150.0, 142.4, 138.6, 128.8, 127.7, 127.4, 118.5, 110.6, 108.9, 76.5, 43.4, 26.9, 20.5, 20.2, 19.0. LRMS (FAB^+) *m/z*: 369.9 (MH^+). Yield: 85%. HPLC purity: 96%.

4.4.3. *N*-(1-(Benzylamino)-3-methyl-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-4-methylbenzamide 7{3,1,1,1}. ^{1}H NMR δ: 7.78 (br s, 1H), 7.35–7.17 (m, 10H), 6.24 (br s, 1H), 6.09 (br s, 1H), 4.59 (d, J=17.4 Hz, 1H), 4.51–4.33 (m, 4H), 2.74 (m, 1H), 2.37 (s, 3H), 0.96 (d, J=6.0 Hz, 3H), 0.84 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 170.6, 169.7, 166.8, 149.9, 142.6, 140.5, 133.4, 129.4, 128.8, 127.8, 127.4, 110.7, 109.9, 78.7, 43.4, 27.0, 21.6, 20.3, 19.3. LRMS (FAB^+) *m/z*: 405.2 (MH^+). Yield: 93%. HPLC purity: 97%.

4.4.4. *N*-(1-(Benzylamino)-3-methyl-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-3,5-dimethoxybenzamide 7{4,1,1,1}. ^{1}H NMR δ: 7.70 (br s, 1H), 7.36–7.17 (m, 8H), 6.59 (br s, 1H), 6.26 (br s, 1H), 6.13 (br s, 1H), 4.62–4.30 (m, 5H), 3.77 (s, 6H), 2.48 (m, 1H), 0.97 (d, J=4.5 Hz, 3H), 0.81 (d, J=6.3 Hz, 3H). ^{13}C NMR δ: 170.4, 169.5, 161.1, 150.0, 142.6, 138.8, 138.0, 128.8, 127.7, 127.5, 110.8, 110.0, 107.7, 105.1, 79.0, 68.8, 55.7, 43.4, 27.0, 20.3, 19.3. LRMS (FAB^+) *m/z*: 451.2 (MH^+). Yield: 84%. HPLC purity: 98%.

4.4.5. *N*-Benzyl-2-(2-cyclopentyl-*N*-(furan-2-ylmethyl) acetamido)-4-methylpentanamide 7{1,2,1,1}. ^{1}H NMR δ: 7.40–7.17 (m, 6H), 6.69 (br s, 1H), 6.29 (m, 1H), 6.13 (br s, 1H), 4.64–4.31 (m, 5H), 2.52 (m, 1H), 2.31 (m, 1H), 2.05 (m, 1H), 1.80–1.54 (m, 4H), 1.54 (m, 5H), 1.15 (m, 2H), 0.95 (d, J=6.3 Hz, 3H), 0.86 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 175.2, 171.2, 150.9, 142.4, 141.6, 128.8, 127.9, 127.8, 110.7, 110.1, 78.0, 55.9, 43.6, 39.9, 36.9, 32.8, 29.4, 25.2, 23.0, 21.0. LRMS (FAB^+) *m/z*: 411.2 (MH^+). Yield: 95%. HPLC purity: 94%.

4.4.6. *N*-Benzyl-2-(*N*-(furan-2-ylmethyl)-3-methylbut-2-enamido)-4-methylpentanamide 7{2,2,1,1}. ^{1}H NMR δ: 7.39–7.17 (m, 6H), 6.93 (br s, 1H), 6.27 (m, 2H), 6.14 (s, 1H), 4.62–4.32 (m, 5H), 1.89 (s, 3H), 1.84 (s, 3H), 1.70 (m, 3H), 0.93 (d, J=6.3 Hz, 3H), 0.83 (d, J=6.3 Hz, 3H). ^{13}C NMR δ: 171,3, 170.4, 151.1, 150.3, 142.4, 138.5, 128.8, 127.8, 126.8, 118.1, 110.7, 108.4, 72.0, 56.0, 43.5, 41.2, 27.8, 24.9, 23.4, 22.9, 20.5. LRMS (FAB^+) *m/z*: 383.2 (MH^+). Yield: 91%. HPLC purity: 98%.

4.4.7. *N*-(1-(Benzylamino)-4-methyl-1-oxopentan-2-yl)-*N*-(furan-2-ylmethyl)-4-methylbenzamide 7{3,2,1,1}. ^{1}H NMR δ: 7.37–7.16 (m, 10H), 6.24 (m, 2H), 4.63–4.39 (m, 4H), 4.31 (dd, J=15.0, 5.7 Hz, 1H), 2.37 (s, 3H), 1.90 (t, J=4.8 Hz, 2H), 1.58 (m, 1H), 0.95 (d, J=6.0 Hz, 3H), 0.84 (d, J=5.7 Hz, 3H). ^{13}C NMR δ: 171.0, 170.6, 145.4, 142.5, 140.6, 138.6, 130.1, 129.4, 128.9, 127.9, 127.7, 127.4, 110.8, 109.5, 73.4, 56.0, 43.4, 41.1, 25.1, 24.0, 22.0, 21.7. LRMS (FAB^+) *m/z*: 419.2 (MH^+). Yield: 92%. HPLC purity: 83%.

4.4.8. *N*-(1-(Benzylamino)-4-methyl-1-oxopentan-2-yl)-*N*-(furan-2-ylmethyl)-3,5-dimethoxybenzamide 7{4,2,1,1}. ^{1}H NMR δ: 7.36–7.17 (m, 8H), 6.66 (br s, 1H), 6.26 (br s, 2H), 4.62–4.34 (m, 5H), 3.75 (s, 6H), 1.89 (t, J=6.9 Hz, 2H), 1.58 (m, 1H), 0.99–0.84 (m, 6H). ^{13}C NMR δ: 173.6, 170.9, 161.1, 142.4, 138.0, 137.8, 128.9, 127.7, 127.0, 110.9, 109.6, 105.1, 102.5, 76.7, 55.7, 43.7, 41.1, 31.2, 25.3, 23.2, 22.3. LRMS (FAB^+) *m/z*: 465.2 (MH^+). Yield: 86%. HPLC purity: 98%.

4.4.9. *N*-Benzyl-2-(2-cyclopentyl-*N*-(furan-2-ylmethyl) acetamido)butanamide 7{1,3,1,1}. ^{1}H NMR δ: 7.37–7.20 (m, 6H), 6.76 (br s, 1H), 6.28 (br s, 1H), 6.17 (d, J=3.3 Hz, 1H), 4.73 (t, J=7.8 Hz, 1H), 4.57 (d, J=17.1 Hz, 1H), 4.43 (d, J=17.4 Hz, 1H), 4.32 (m, 2H), 2.50 (d, J=6.9 Hz, 2H), 2.26 (m, 2H), 2.01 (m, 1H), 1.80 (m, 2H), 1.54 (m, 4H), 1.11 (m, 2H), 0.81 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 175.2, 171.0, 150.9, 142.4, 128.8, 127.8, 127.5, 110.7, 108.4, 59.9, 43.3, 42.5, 39.8, 36.9, 32.8, 25.2, 21.6, 10.9. LRMS (FAB^+) *m/z*: 383.2 (MH^+). Yield: 93%. HPLC purity: 93%.

4.4.10. *N*-(1-(Benzylamino)-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-3-methylbut-2-enamide 7{2,3,1,1}. ^{1}H NMR δ: 7.32–7.18 (m, 6H), 6.98 (br s, 1H), 6.28 (br s, 1H), 6.17 (d, J=3.0 Hz, 1H), 6.06 (s, 1H), 4.69 (t, J=7.8 Hz, 1H), 4.57 (d, J=17.1 Hz, 1H), 4.43 (d, J=17.1 Hz, 1H), 4.34 (t, J=5.1 Hz, 2H), 2.01 (m, 2H), 1.89 (s, 3H), 1.84 (s, 3H), 0.80 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 171.1, 170.3, 161.4, 151.2, 142.4, 134.9, 128.8, 127.8, 127.5, 118.1, 110.7, 108.4, 59.9, 43.5, 43.2, 26.9, 21.7, 20.6, 10.9. LRMS

(FAB$^+$) *m/z*: 355.2 (MH$^+$). Yield: 81%. HPLC purity: 97%.

4.4.11. *N*-(1-(Benzylamino)-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-4-methylbenzamide 7{3,3,1,1}. ^{1}H NMR δ: 7.36–7.16 (m, 10H), 6.24 (br s, 1H), 6.17 (br s, 1H), 4.63–4.35 (m, 5H), 2.36 (s, 3H), 2.10 (m, 1H), 1.95 (m, 1H), 0.90 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 174.2, 170.8, 150.2, 142.4, 140.5, 133.1, 130.0, 129.4, 128.9, 127.9, 127.3, 126.8, 110.8, 109.5, 61.5, 43.7, 34.9, 31.9, 21.6, 11.1. LRMS (FAB$^+$) *m/z*: 391.2 (MH$^+$). Yield: 82%. HPLC purity: 96%.

4.4.12. *N*-(1-(Benzylamino)-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-3,5-dimethoxybenzamide 7{4,3,1,1}. ^{1}H NMR δ: 7.35–7.10 (m, 8H), 6.57 (br s, 1H), 6.36–6.17 (m, 2H), 4.65–4.36 (m, 5H), 3.72 (s, 6H), 2.08 (m, 2H), 0.88 (m, 3H). ^{13}C NMR δ: 173.5, 170.6, 161.1, 142.5, 137.8, 129.2, 128.9, 127.9, 126.8, 110.9, 109.5, 107.6, 105.0, 102.5, 55.7, 43.6, 34.5, 32.0, 21.9, 11.1. LRMS (FAB$^+$) *m/z*: 437.2 (MH$^+$). Yield: 81%. HPLC purity: 93%.

4.4.13. *N*-*tert*-Butyl-2-(2-cyclopentyl-*N*-(furan-2-ylmethyl)acetamido)-3-methylbutanamide 7{1,1,2,1}. ^{1}H NMR δ: 7.32 (s, 1H), 6.38 (br s, 1H), 6.29 (t, J=3.3 Hz, 1H), 6.21 (d, J=3.3 Hz, 1H), 4.95 (d, J=4.5 Hz, 1H), 4.65 (d, J=16.8 Hz, 1H), 4.45 (J=17.1 Hz, 1H), 2.57–2.30 (m, 4H), 1.83 (m, 2H), 1.60 (m, 4H), 1.27 (s, 9H), 1.17 (m, 2H), 0.92 (d, J=6.6 Hz, 3H), 0.62 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 175.3, 170.4, 154.6, 142.2, 110.7, 108.6, 51.2, 40.0, 37.1, 32.7, 28.9, 27.0, 25.2, 20.0, 18.9. LRMS (FAB$^+$) *m/z*: 363.2 (MH$^+$). Yield: 90%. HPLC purity: 93%.

4.4.14. *N*-(1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-3-methylbut-2-enamide 7{2,1,2,1}. ^{1}H NMR δ: 7.30 (s, 1H), 6.71 (br s, 1H), 6.27 (t, J=1.8 Hz, 1H), 6.20 (d, J=3.0 Hz, 1H), 6.12 (s, 1H), 4.98 (d, J=3.9 Hz, 1H), 4.63 (d, J=16.8 Hz, 1H), 4.40 (d, J=16.5 Hz, 1H), 2.44 (m, 1H), 1.93 (s, 3H), 1.85 (s, 3H), 1.26 (s, 9H), 0.91 (d, J=1.2 Hz, 3H), 0.89 (d, J=2.1 Hz, 3H). ^{13}C NMR δ: 170.5, 170.1, 151.2, 148.9, 142.3, 118.9, 110.6, 108.8, 76.4, 51.1, 28.8, 27.0, 26.7, 20.5, 20.0, 19.4, 18.9. LRMS (FAB$^+$) *m/z*: 335.2 (MH$^+$). Yield: 88%. HPLC purity: 99%.

4.4.15. *N*-(1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-4-methylbenzamide 7{3,1,2,1}. ^{1}H NMR δ: 7.40–7.19 (m, 5H), 6.24 (br s, 1H), 6.10 (br s, 1H), 4.55–4.40 (m, 3H), 2.62 (br s, 2H), 2.37 (s, 3H), 1.28 (s, 9H), 0.94 (m, 3H), 0.80 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 168.9, 168.8, 149.9, 142.3, 140.3, 133.6, 129.6, 127.2, 110.6, 109.7, 78.7, 69.7, 51.1, 28.9, 21.6, 20.2, 19.3, 17.1. LRMS (EI$^+$) *m/z*: 370.0 (M$^+$). Yield: 88%. HPLC purity: 99%.

4.4.16. *N*-(1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-3,5-dimethoxybenzamide 7{4,1,2,1}. ^{1}H NMR δ: 7.29 (d, J=2.7 Hz, 1H), 7.19 (d, J=2.7 Hz, 2H), 6.67 (t, J=2.4 Hz, 1H), 6.25 (br s, 1H), 6.12 (br s, 1H), 4.57–4.37 (m, 3H), 3.77 (s, 6H), 2.64 (m, 1H), 1.30 (s, 9H), 0.94 (d, J=6.3 Hz, 3H), 0.80 (d, J=6.3 Hz, 3H). ^{13}C NMR δ: 169.5, 168.6, 161.1, 150.1, 148.0, 142.3, 110.7, 109.7, 107.6, 105.0, 79.1, 69.4, 55.7, 51.5, 30.9, 28.9, 20.1, 19.2, 17.1. LRMS (FAB$^+$) *m/z*: 417 (MH$^+$), 418 ([M+2H]$^+$). Yield: 84%. HPLC purity: 98%.

4.4.17. *N*-*tert*-Butyl-2-(2-cyclopentyl-*N*-(furan-2-ylmethyl)acetamido)-4-methylpentanamide 7{1,2,2,1}. ^{1}H NMR δ: 7.33 (br s, 1H), 6.30 (br s, 1H), 6.18 (br s, 1H), 4.60–4.40 (m, 3H), 2.51 (m, 2H), 2.39–2.14 (m, 4H), 1.81 (m, 2H), 1.58 (m, 4H), 1.28 (s, 9H), 1.16 (m, 2H), 0.91 (m, 3H), 0.83 (m, 3H). ^{13}C NMR δ: 175.0, 170.4, 151.1, 142.3, 110.7, 108.3, 73.1, 56.5, 51.1, 47.9, 41.9, 40.7, 39.8, 37.0, 32.7, 28.8, 25.0, 22.4. LRMS (FAB$^+$) *m/z*: 377.2 (MH$^+$). Yield: 80%. HPLC purity: 88%.

4.4.18. *N*-*tert*-Butyl-2-(*N*-(furan-2-ylmethyl)-3-methylbut-2-enamido)-4-methylpentanamide 7{2,2,2,1}. ^{1}H NMR δ: 7.32 (s, 1H), 6.29 (s, 1H), 6.19 (s, 1H), 6.08 (s, 1H), 4.52 (d, J=17.1 Hz, 1H), 4.41 (d, J=17.1 Hz, 1H), 2.18 (s, 3H), 1.92 (s, 3H), 1.77–1.48 (m, 3H), 1.31 (s, 9H), 0.93 (d, J=6.9 Hz, 3H), 0.81 (d, J=6.9 Hz, 3H). ^{13}C NMR δ: 172.8, 170.5, 151.4, 149.3, 142.3, 118.6, 110.7, 108.4, 72.3, 51.1, 42.7, 36.9, 28.8, 26.8, 24.8, 23.0, 22.4, 20.9. LRMS (FAB$^+$) *m/z*: 349.2 (MH$^+$). Yield: 88%. HPLC purity: 99%.

4.4.19. *N*-(1-(*tert*-Butylamino)-4-methyl-1-oxopentan-2-yl)-*N*-(furan-2-ylmethyl)-4-methylbenzamide 7{3,2,2,1}. ^{1}H NMR δ: 7.39–7.26 (m, 3H), 7.20 (m, 2H), 6.28–6.20 (m, 2H), 4.58 (m, 2H), 4.40 (d, J=16.2 Hz, 1H), 2.37 (s, 3H), 1.80 (m, 2H), 1.51 (m, 1H), 1.29 (s, 9H), 0.94 (m, 3H), 0.89 (m, 3H). ^{13}C NMR δ: 174.1, 170.1, 160.5, 150.1, 144.6, 135.7, 129.9, 129.4, 127.3, 110.9, 109.4, 58.7, 55.6, 39.4, 28.9, 24.9, 23.5, 21.6. LRMS (FAB$^+$) *m/z*: 385.2 (MH$^+$). Yield: 78%. HPLC purity: 97%.

4.4.20. *N*-(1-(*tert*-Butylamino)-4-methyl-1-oxopentan-2-yl)-*N*-(furan-2-ylmethyl)-3,5-dimethoxybenzamide 7{4,2,2,1}. ^{1}H NMR δ: 7.32 (s, 1H), 7.18 (d, J=1.8 Hz, 2H), 6.48 (t, J=1.8 Hz, 1H), 6.29–6.20 (m, 2H), 4.65–4.39 (m, 3H), 3.77 (s, 6H), 1.80 (m, 2H), 1.53 (m, 1H), 1.29 (s, 9H), 0.96–0.88 (m, 6H). ^{13}C NMR δ: 173.3, 169.9, 161.8, 151.0, 142.3, 141.6, 110.9, 109.4, 107.6, 1051, 74.0, 55.7, 51.2, 42.8, 41.0, 38.0, 28.9, 24.9, 23.2. LRMS (FAB$^+$) *m/z*: 431.2 (MH$^+$). Yield: 84%. HPLC purity: 98%.

4.4.21. *N*-*tert*-Butyl-2-(2-cyclopentyl-*N*-(furan-2-ylmethyl)acetamido)butanamide 7{1,3,2,1}. ^{1}H NMR δ: 7.32 (s, 1H), 6.30 (s, 1H), 6.18 (d, J=2.7 Hz, 1H), 4.63 (t, J=7.8 Hz, 1H), 4.55 (d, J=17.1 Hz, 1H), 4.44 (d, J=17.1 Hz, 1H), 2.52 (d, J=6.6 Hz, 2H), 2.32 (m, 2H), 1.94 (m, 1H), 1.83 (m, 2H), 1.59 (m, 4H), 1.24 (s, 9H), 1.19 (m, 2H), 0.79 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 175.0, 170.1, 152.0, 143.3, 110.7, 108.3, 60.3, 51.1, 42.1, 39.8, 37.0, 32.7, 28.9, 25.2, 21.5, 10.9. LRMS (FAB$^+$) *m/z*: 349.2 (MH$^+$). Yield: 86%. HPLC purity: 93%.

4.4.22. *N*-(1-(*tert*-Butylamino)-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-3-methylbut-2-enamide 7{2,3,2,1}. ^{1}H NMR δ: 7.33 (d, J=0.9 Hz, 1H), 6.45 (br s, 1H), 6.30 (br s, 1H), 6.18 (br s, 1H), 6.06 (br s, 1H), 4.60–4.52 (m, 2H), 4.40 (d, J=16.8 Hz, 1H), 1.96 (s, 3H), 1.85 (s, 3H), 1.65 (m, 2H), 1.25 (s, 9H), 0.78 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 170.4, 168.7, 151.4, 142.4, 141.1, 118.6, 110.7, 108.3, 72.7, 51.1, 42.9, 28.8, 26.7, 21.5, 10.9. LRMS

(FAB$^+$) *m/z*: 320.2 (MH$^+$). Yield: 80%. HPLC purity: 99%.

4.4.23. *N*-(1-(*tert*-Butylamino)-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-4-methylbenzamide 7{3,3,2,1}. ^{1}H NMR δ: 7.36–7.28 (m, 3H), 7.19 (d, J=7.8 Hz, 2H), 6.27–6.18 (m, 2H), 4.65–4.53 (m, 2H), 4.39 (d, J=16.2 Hz, 1H), 2.35 (s, 3H), 2.07 (m, 1H), 1.83 (m, 1H), 1.28 (s, 9H), 0.84 (m, 3H). ^{13}C NMR δ: 173.9, 169.8, 157.0, 140.4, 133.3, 129.9, 129.4, 127.1, 110.8, 109.3, 75.6, 51.4, 28.9, 25.3, 21.6, 11.1, 9.2. LRMS (FAB$^+$) *m/z*: 357.2 (MH$^+$). Yield: 81%. HPLC purity: 99%.

4.4.24. *N*-(1-(*tert*-Butylamino)-1-oxobutan-2-yl)-*N*-(furan-2-ylmethyl)-3,5-dimethoxybenzamide 7{4,3,2,1}. ^{1}H NMR δ: 7.32 (s, 1H), 7.19 (d, J=2.4 Hz, 2H), 6.48 (t, J=2.1 Hz, 1H), 6.29–6.20 (m, 2H), 4.65–4.39 (m, 3H), 3.77 (s, 6H), 2.01 (m, 1H), 1.82 (m, 1H), 1.30 (s, 9H), 0.85 (m, 3H). ^{13}C NMR δ: 173.3, 169.6, 161.1, 153.0, 143.2, 142.2, 110.9, 109.3, 105.0, 102.2, 55.7, 51.2, 42.8, 41.0, 28.9, 21.8, 11.1. LRMS (FAB$^+$) *m/z*: 403.2 (MH$^+$). Yield: 80%. HPLC purity: 97%.

4.4.25. *N*-Benzyl-2-(2-cyclopentyl-*N*-isopropylacetamido)-3-methylbutanamide 7{1,1,1,2}. ^{1}H NMR δ: 7.36–7.24 (m, 5H), 6.22 (br s, 1H), 5.14 (d, J=4.5 Hz, 1H), 4.47 (d, J=5.7 Hz, 2H), 4.15 (m, 1H), 2.38 (d, J=7.2 Hz, 2H), 2.21 (m, 1H), 1.77 (m, 2H), 1.54 (m, 4H), 1.22–1.10 (m, 5H), 0.96 (m, 9H). ^{13}C NMR δ: 172.3, 169.6, 138.1, 129.0, 128.0, 127.9, 78.1, 43.4, 40.6, 39.7, 32.7, 30.8, 28.0, 25.2, 19.1, 17.2. LRMS (FAB$^+$) *m/z*: 359.2 (MH$^+$). Yield: 88%. HPLC purity: 90%.

4.4.26. *N*-(1-(Benzylamino)-3-methyl-1-oxobutan-2-yl)-*N*-isopropyl-3-methylbut-2-enamide 7{2,1,1,2}. ^{1}H NMR δ: 7.36–7.25 (m, 5H), 6.32 (br s, 1H), 5.75 (s, 1H), 5.19 (d, J=4.2 Hz, 1H), 4.56–4.30 (m, 2H), 4.15 (m, 1H), 2.38 (m, 1H), 2.18 (s, 3H), 1.92 (s, 3H), 1.17 (d, J=6.0 Hz, 3H), 1.01–0.94 (m, 9H). ^{13}C NMR δ: 170.0, 165.4, 158.8, 138.3, 128.7, 127.9, 127.2, 115.1, 43.3, 30.9, 27.8, 26.8, 26.5, 20.7, 19.1, 17.2. LRMS (FAB$^+$) *m/z*: 331.2 (MH$^+$). Yield: 88%. HPLC purity: 91%.

4.4.27. *N*-(1-(Benzylamino)-3-methyl-1-oxobutan-2-yl)-*N*-isopropyl-4-methylbenzamide 7{3,1,1,2}. ^{1}H NMR δ: 7.35–7.21 (m, 9H), 6.39 (br s, 1H), 5.37 (d, J=6.0 Hz, 1H), 4.60–4.35 (m, 2H), 3.98 (m, 1H), 3.10 (m, 1H), 2.38 (s, 3H), 1.20 (d, J=6.6 Hz, 3H), 1.06 (d, J=6.0 Hz, 3H), 1.01 (d, J=8.7 Hz, 3H), 0.96 (d, J=8.1 Hz, 3H). ^{13}C NMR δ: 173.6, 170.5, 134.5, 130.0, 129.5, 128.7, 127.6, 126.4, 78.5, 43.3, 26.9, 21.6, 20.8, 20.2, 19.2, 17.3. LRMS (FAB$^+$) *m/z*: 367.2 (MH$^+$). Yield: 92%. HPLC purity: 98%.

4.4.28. *N*-(1-(Benzylamino)-3-methyl-1-oxobutan-2-yl)-*N*-isopropyl-3,5-dimethoxybenzamide 7{4,1,1,2}. ^{1}H NMR δ: 7.30 (m, 5H), 7.19 (d, J=2.4 Hz, 2H), 6.48 (t, J=2.1 Hz, 1H), 5.37 (d, J=6.0 Hz, 1H), 4.63–4.33 (m, 2H), 3.90 (m, 1H), 3.79 (s, 6H), 3.10 (m, 1H), 1.18 (d, J=6.6 Hz, 3H), 1.12 (d, J=6.9 Hz, 3H), 1.06 (d, J=6.6 Hz, 3H), 0.98 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 170.7, 168.4, 161.3, 135.8, 134.4, 128.7, 127.6, 127.3, 107.7, 104.1, 75.8, 55.7, 47.8, 43.3, 27.0, 20.8, 20.0. LRMS (FAB$^+$) *m/z*: 413.2 (MH$^+$). Yield: 83%. HPLC purity: 96%.

4.4.29. *N*-Benzyl-2-(2-cyclopentyl-*N*-isopropylacetamido)-4-methylpentanamide 7{1,2,1,2}. ^{1}H NMR δ: 7.34–7.24 (m, 1H), 4.41 (m, 2H), 4.1–3.9 (m, 2H), 2.37 (m, 2H), 2.21 (m, 1H), 1.74 (m, 3H), 1.56 (m, 4H), 1.21 (m, 6H), 1.09 (m, 2H), 0.94 (m, 6H). ^{13}C NMR δ: 174.7, 173.5, 138.9, 128.7, 127.7, 127.3, 50.0, 43.3, 41.4, 39.8, 37.1, 32.7, 25.1, 23.3, 21.2. LRMS (FAB$^+$) *m/z*: 373.2 (MH$^+$). Yield: 94%. HPLC purity: 93%.

4.4.30. *N*-Benzyl-2-(*N*-isopropyl-3-methylbut-2-enamido)-4-methylpentanamide 7{2,2,1,2}. ^{1}H NMR δ: 7.33–7.20 (m, 5H), 5.76 (s, 1H), 4.48 (dd, J=15.0, 6.3 Hz, 1H), 4.34 (dd, J=15.0, 5.4 Hz, 1H), 4.11 (m, 1H), 3.94 (m, 1H), 2.25 (m, 1H), 1.83 (s, 3H), 1.79 (s, 3H), 1.61 (m, 2H), 1.21 (m, 6H), 0.94 (m, 6H). ^{13}C NMR δ: 173.7, 170.3, 147.4, 138.5, 128.7, 127.7, 127.3, 119.6, 72.0, 59.4, 43.4, 39.4, 26.4, 39.4, 26.4, 25.6, 23.2, 22.8, 20.9, 20.4. LRMS (FAB$^+$) *m/z*: 345.2 (MH$^+$). Yield: 86%. HPLC purity: 95%.

4.4.31. *N*-(1-(Benzylamino)-4-methyl-1-oxopentan-2-yl)-*N*-isopropyl-4-methylbenzamide 7{3,2,1,2}. ^{1}H NMR δ: 7.35–7.21 (m, 9H), 4.53 (dd, J=15.0, 6.0 Hz, 1H), 4.41 (dd, J=15.0, 5.4 Hz, 1H), 3.94 (m, 2H), 2.38 (s, 3H), 1.93 (m, 1H), 1.71 (m, 2H), 1.23 (d, J=6.3 Hz, 3H), 1.13 (d, J=6.0 Hz, 3H), 0.98 (m, 6H). ^{13}C NMR δ: 173.9, 170.2, 140.3, 134.5, 129.5, 128.7, 127.6, 127.3, 126.5, 74.6, 60.3, 53.3, 43.5, 39.6, 25.7, 22.9, 21.6. LRMS (FAB$^+$) *m/z*: 381.2 (MH$^+$), 382.2 ([M+2H]$^+$). Yield: 88%. HPLC purity: 95%.

4.4.32. *N*-(1-(Benzylamino)-4-methyl-1-oxopentan-2-yl)-*N*-isopropyl-3,5-dimethoxybenzamide 7{4,2,1,2}. ^{1}H NMR δ: 7.35–7.18 (m, 7H), 6.48 (t, J=2.1 Hz, 1H), 4.58–4.36 (m, 2H), 3.95 (m, 2H), 3.78 (s, 6H), 1.89 (m, 1H), 1.71 (m, 2H), 1.20 (d, J=6.0 Hz, 3H), 1.15 (d, J=6.3 Hz, 3H), 0.98 (m, 6H). ^{13}C NMR δ: 173.6, 170.2, 161.2, 146.0, 139.2, 128.8, 127.6, 127.3, 104.1, 101.8, 60.2, 55.7, 53.0, 43.4, 39.6, 25.7, 23.1, 22.8, 20.8. LRMS (FAB$^+$) *m/z*: 427.2 (MH$^+$). Yield: 89%. HPLC purity: 98%.

4.4.33. *N*-Benzyl-2-(2-cyclopentyl-*N*-isopropylacetamido)butanamide 7{1,3,1,2}. ^{1}H NMR δ: 7.34–7.24 (m, 5H), 6.33 (br s, 1H), 4.64–4.31 (m, 2H), 4.09 (m, 1H), 3.69 (m, 1H), 2.38 (m, 2H), 2.19 (m, 2H), 1.77 (m, 2H), 1.56 (m, 4H), 1.20 (m, 6H), 1.11 (m, 2H), 0.89 (m, 3H). ^{13}C NMR δ: 174.5, 172.2, 136.8, 129.0, 127.9, 127.3, 75.0, 62.9, 43.4, 40.6, 36.7, 32.7, 25.2, 23.4, 21.1, 9.3. LRMS (FAB$^+$) *m/z*: 345.2 (MH$^+$). Yield: 84%. HPLC purity: 91%.

4.4.34. *N*-(1-(Benzylamino)-1-oxobutan-2-yl)-*N*-isopropyl-3-methylbut-2-enamide 7{2,3,1,2}. ^{1}H NMR δ: 7.32–7.21 (m, 5H), 5.77 (s, 1H), 4.59–4.30 (m, 2H), 4.12 (m, 1H), 3.68 (m, 1H), 2.17 (m, 2H), 1.83 (s, 3H), 1.80 (m, 2H), 1.17 (d, J=6.9 Hz, 6H), 0.91 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 173.9, 170.1, 154.3, 138.9, 128.7, 127.9, 127.3, 119.3, 74.2, 62.8, 43.4, 38.3, 26.5, 23.0, 21.4, 20.7, 11.7. LRMS (FAB$^+$) *m/z*: 317.2 (MH$^+$). Yield: 84%. HPLC purity: 87%.

4.4.35. *N*-(1-(Benzylamino)-1-oxobutan-2-yl)-*N*-isopropyl-4-methylbenzamide 7{3,3,1,2}. ^{1}H NMR δ: 7.32–7.20 (m, 9H), 6.44 (br s, 1H), 4.55 (dd, J=15.0, 6.0 Hz, 1H), 4.41 (dd, J=15.0, 5.7 Hz, 1H), 3.98 (m, 1H), 3.77 (m, 1H), 2.38 (s, 3H), 2.23 (m, 1H), 2.06 (m, 1H), 1.22 (d, J=

6.6 Hz, 3H), 1.12 (d, J=6.6 Hz, 3H), 1.03 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 167.9, 166.1, 140.3, 139.0, 134.4, 129.5, 128.8, 127.5, 127.3, 126.5, 75.3, 63.4, 43.4, 25.5, 23.1, 21.6, 20.8, 11.8. LRMS (FAB$^+$) m/z: 353.2 (MH$^+$). Yield: 83%. HPLC purity: 96%.

4.4.36. *N*-(1-(Benzylamino)-1-oxobutan-2-yl)-*N*-isopropyl-3,5-dimethoxybenzamide 7{4,3,1,2}. ^{1}H NMR δ: 7.30–7.16 (m, 7H), 6.42 (br s, 1H), 4.60–4.35 (m, 3H), 3.92 (m, 1H), 3.80 (s, 6H), 2.05 (m, 2H), 1.19–1.13 (m, 6H), 1.02 (m, 3H). ^{13}C NMR δ: 173.7, 169.9, 161.0, 143.3, 139.0, 129.0, 127.8, 127.6, 107.6, 106.1, 75.9, 55.8, 43.4, 25.5, 23.2, 21.3, 19.1, 11.8. LRMS (FAB$^+$) m/z: 399.2 (MH$^+$). Yield: 85%. HPLC purity: 93%.

4.4.37. *N*-*tert*-Butyl-2-(2-cyclopentyl-*N*-isopropylacetamido)-3-methylbutanamide 7{1,1,2,2}. ^{1}H NMR δ: 5.75 (br s, 1H), 4.94 (m, 1H), 4.08 (m, 1H), 2.42 (m, 2H), 2.27 (m, 2H), 1.85 (m, 2H), 1.59 (m, 4H), 1.29 (s, 9H), 1.24–0.98 (m, 8H), 0.97–0.92 (m, 6H). ^{13}C NMR δ: 168.7, 166.2, 78.2, 51.4, 40.7, 37.1, 32.8, 30.7, 28.8, 27.2, 25.2, 20.1, 19.0, 17.1. LRMS (FAB$^+$) m/z: 325.2 (MH$^+$). Yield: 90%. HPLC purity: 96%.

4.4.38. *N*-(1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl)-*N*-isopropyl-3-methylbut-2-enamide 7{2,1,2,2}. ^{1}H NMR δ: 5.78 (s, 1H), 4.99 (d, J=4.2 Hz, 1H), 4.14 (m, 1H), 2.30 (m, 1H), 2.18 and 1.93 (s, 3H), 1.91 and 1.85 (s, 3H), 1.33 and 1.29 (s, 9H), 1.08–0.99 (m, 6H), 0.97–0.88 (m, 6H). ^{13}C NMR δ: 170.1, 169.1, 146.9, 119.8, 115.2, 51.3, 50.5, 30.8, 28.8, 27.8, 26.8, 26.3, 20.7, 19.0, 17.0. LRMS (FAB$^+$) m/z: 297.2 (MH$^+$). Yield: 88%. HPLC purity: 96%.

4.4.39. *N*-(1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl)-*N*-isopropyl-4-methylbenzamide 7{3,1,2,2}. ^{1}H NMR δ: 7.97 (d, J=8.4 Hz, 2H), 7.29 (dd, J=8.1, 0.6 Hz, 2H), 5.83 (br s, 1H), 5.20 (d, J=4.2 Hz, 1H), 3.97 (m, 1H), 2.44 (s, 3H), 2.39 (m, 1H), 1.34 (s, 9H), 1.05–0.90 (m, 12H). ^{13}C NMR δ: 168.8, 165.6, 144.6, 128.9, 129.6, 127.0, 78.7, 51.5, 30.9, 28.9, 21.9, 19.2, 17.1. LRMS (EI$^+$) m/z: 332.0 (M$^+$). Yield: 88%. HPLC purity: 95%.

4.4.40. *N*-(1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl)-*N*-isopropyl-3,5-dimethoxybenzamide 7{4,1,2,2}. ^{1}H NMR δ: 7.20 (d, J=1.5 Hz, 2H), 6.69 (t, J=1.8 Hz, 1H), 5.82 (br s, 1H), 5.16 (d, J=4.2 Hz, 1H), 3.84 (s, 6H), 3.81 (m, 1H), 2.43 (m, 1H), 1.34 (s, 9H), 1.24–0.98 (m, 6H), 0.97–0.92 (m, 6H). ^{13}C NMR δ: 168.6, 165.4, 161.1, 131.5, 107.6, 105.9, 79.1, 55.8, 51.5, 30.9, 28.9, 19.1, 17.1. LRMS (FAB$^+$) m/z: 379.2 (MH$^+$). Yield: 82%. HPLC purity: 94%.

4.4.41. *N*-*tert*-Butyl-2-(2-cyclopentyl-*N*-isopropylacetamido)-4-methylpentanamide 7{1,2,2,2}. ^{1}H NMR δ: 5.77 (br s, 1H), 5.06 (m, 1H), 4.01 (m, 1H), 2.37 (m, 3H), 2.30–2.15 (m, 3H), 1.82 (m, 2H), 1.61 (m, 4H), 1.29 (s, 9H), 1.26–1.10 (m, 8H), 0.92 (m, 6H). ^{13}C NMR δ: 174.4, 169.7, 73.1, 50.7, 41.6, 40.7, 37.2, 32.6, 28.8, 25.7, 25.2, 23.2, 22.8, 22.0, 21.7. LRMS (FAB$^+$) m/z: 339.2 (MH$^+$), 340.2 ([M+2H]$^+$). Yield: 86%. HPLC purity: 99%.

4.4.42. *N*-*tert*-Butyl-2-(*N*-isopropyl-3-methylbut-2-enamido)-4-methylpentanamide 7{2,2,2,2}. ^{1}H NMR δ: 5.78 (s, 1H), 5.10 (t, J=5.7 Hz, 1H), 4.08 (m, 1H), 1.89 (s, 3H), 1.84 (s, 3H), 1.68 (m, 2H), 1.55 (m, 1H), 1.29 (s, 9H), 1.19 (m, 6H), 0.91 (m, 6H). ^{13}C NMR δ: 172.8, 170.1, 146.7, 120.0, 73.3, 50.7, 41.1, 39.1, 28.8, 26.3, 25.6, 24.8, 23.1, 22.9, 22.1, 20.4. LRMS (FAB$^+$) m/z: 311.2 (MH$^+$), 312.2 ([M+2H]$^+$). Yield: 91%. HPLC purity: 95%.

4.4.43. *N*-(1-(*tert*-Butylamino)-4-methyl-1-oxopentan-2-yl)-*N*-isopropyl-4-methylbenzamide 7{3,2,2,2}. ^{1}H NMR δ: 7.95 (d, J=8.4 Hz, 2H), 7.27 (dd, J=8.1, 0.6 Hz, 2H), 5.86 (br s, 1H), 5.32 (m, 1H), 3.95 (m, 1H), 2.43 (s, 3H), 1.90–1.72 (m, 3H), 1.33 (s, 9H), 1.10–0.90 (m, 12H). ^{13}C NMR δ: 170.0, 169.7, 144.6, 130.0, 129.6, 126.5, 73.6, 51.5, 47.0, 42.5, 37.8, 28.9, 24.9, 23.4, 22.9, 22.1. LRMS (FAB$^+$) m/z: 347.2 (MH$^+$). Yield: 85%. HPLC purity: 94%.

4.4.44. *N*-(1-(*tert*-Butylamino)-4-methyl-1-oxopentan-2-yl)-*N*-isopropyl-3,5-dimethoxybenzamide 7{4,2,2,2}. ^{1}H NMR δ: 7.19 (d, J=2.4 Hz, 2H), 6.68 (t, J=2.4 Hz, 1H), 5.83 (br s, 1H), 5.27 (m, 1H), 4.00 (m, 1H), 3.83 (s, 6H), 2.24–1.73 (m, 3H), 1.33 (s, 9H), 1.02–0.90 (m, 12H). ^{13}C NMR δ: 172.5, 169.5, 161.1, 132.0, 107.6, 106.1, 74.0, 55.8, 51.4, 41.0, 28.8, 24.9, 23.4, 23.1, 22.1. LRMS (FAB$^+$) m/z: 393.2 (MH$^+$). Yield: 83%. HPLC purity: 98%.

4.4.45. *N*-*tert*-Butyl-2-(2-cyclopentyl-*N*-isopropylacetamido)butanamide 7{1,3,2,2}. ^{1}H NMR δ: 5.03 (t, J=6.0 Hz, 1H), 4.05 (m, 1H), 3.50 (br s, 1H), 2.46–2.23 (m, 3H), 2.12 (m, 2H), 1.85 (m, 2H), 1.63 (m, 4H), 1.29 (s, 9H), 1.24–1.13 (m, 8H), 0.87 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 174.2, 169.5, 75.1, 50.6, 41.4, 37.1, 32.9, 32.7, 28.8, 25.2, 23.3, 21.5, 21.1, 11.7. LRMS (FAB$^+$) m/z: 311.2 (MH$^+$). Yield: 85%. HPLC purity: 92%.

4.4.46. *N*-(1-(*tert*-Butylamino)-1-oxobutan-2-yl)-*N*-isopropyl-3-methylbut-2-enamide 7{2,3,2,2}. ^{1}H NMR δ: 5.79 (s, 1H), 5.07 (t, J=6.0 Hz, 1H), 4.11 (m, 1H), 3.52 (br s, 1H), 2.12 (m, 2H), 1.92 (s, 3H), 1.86 (s, 3H), 1.31 (s, 9H), 1.20 (d, J=6.6 Hz, 3H), 1.16 (d, J=6.9 Hz, 3H), 0.89 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 169.2, 165.1, 147.0, 119.7, 76.0, 50.7, 32.5, 28.8, 26.4, 22.9, 21.4, 20.7, 20.4, 11.7. LRMS (FAB$^+$) m/z: 283.2 (MH$^+$). Yield: 86%. HPLC purity: 89%.

4.4.47. *N*-(1-(*tert*-Butylamino)-1-oxobutan-2-yl)-*N*-isopropyl-4-methylbenzamide 7{3,3,2,2}. ^{1}H NMR δ: 7.94 (d, J=8.4 Hz, 2H), 7.28 (d, J=8.0 Hz, 2H), 5.93 (br s, 1H), 5.27 (t, J=5.4 Hz, 1H), 3.73 (m, 1H), 2.42 (s, 3H), 1.98 (m, 2H), 1.35 (s, 9H), 1.24–1.06 (m, 6H), 0.98 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 169.1, 165.5, 144.6, 134.9, 129.6, 126.4, 75.6, 51.5, 42.6, 28.9, 25.3, 21.9, 17.1, 9.2. LRMS (FAB$^+$) m/z: 319.2 (MH$^+$). Yield: 86%. HPLC purity: 96%.

4.4.48. *N*-(1-(*tert*-Butylamino)-1-oxobutan-2-yl)-*N*-isopropyl-3,5-dimethoxybenzamide 7{4,3,2,2}. ^{1}H NMR δ: 7.19 (br s, 2H), 6.69 (br s, 1H), 5.90 (br s, 1H), 5.20 (m, 1H), 4.10 (m, 1H), 3.83 (s, 6H), 1.99 (m, 2H), 1.35 (s, 9H), 1.17 (m, 6H), 0.98 (br s, 3H). ^{13}C NMR δ: 168.9, 165.2, 161.1, 131.6, 107.5, 106.0, 76.0, 55.8, 51.5, 48.0, 28.9, 25.3, 12.0, 9.2. LRMS (FAB$^+$) m/z: 365.2 (MH$^+$). Yield: 80%. HPLC purity: 92%.

4.5. General procedure for the synthesis of libraries of β-lactams 8

Aldehyde (0.3–0.35 mmol) was added to a suspension of β-amino acid (0.1 mmol) in 3 mL water and stirred/shaken (by a wrist shaker) for 30–45 min. Isonitrile (0.1 mmol) was added and stirring/shaking was continued for 3–6 h. The solid products were separated by filtration and the residue was washed with 3×1 mL of 10% citric acid and 2 mL water. For oily products, dichloromethane was added to the reaction mixture. The organic layer was washed with 3× 1 mL of 10% citric acid, and 1 mL brine. This solution was passed through a plug of anhyd Na_2SO_4 and concentrated under reduced pressure to give the desired product. *Amino acid*: (1) 3-amino-butyric acid (**21**); (2) 3-amino-4-methyl-pentanoic acid (**22**); (3) 3-amino-2-methylpropionic acid (**24**); (4) 3-amino-3-phenyl-propionic acid (**23**). *Aldehyde*: (1) isobutyraldehyde (**15**); (2) 3-methylbutanal (**13**); (3) propionaldehyde (**16**); (4) 2-phenylacetaldehyde (**14**). *Isonitrile*: (1) 1-(isocyanomethyl)benzene (**17**); (2) 2-isocyano-2-methylpropane (**18**).

4.5.1. *N*-Benzyl-3-methyl-2-(2-methyl-4-oxoazetidin-1-yl)butanamide 8{1,1,1}. ^{1}H NMR δ: 7.33–7.23 (m, 5H), 4.42 (m, 2H), 3.75 (m, 1H), 3.48 and 3.37 (m, 1H), 3.01 (dd, J=15.0, 5.1 Hz, 1H), 2.53–2.31 (m, 2H), 1.36 and 1.29 (d, J=6.3 Hz, 3H), 0.97–0.90 (m, 6H). ^{13}C NMR δ: 170.5, 168.1, 138.4, 128.8, 127.9, 127.6, 66.2, 50.2, 48.7, 43.9, 43.6, 30.1, 28.7, 20.4, 20.0, 29.7, 19.2. LRMS (FAB^+) *m/z*: 275.2 (MH^+). Yield: 87%. HPLC purity: 83%.

4.5.2. *N*-Benzyl-2-(2-isopropyl-4-oxoazetidin-1-yl)-3-methylbutanamide 8{2,1,1}. ^{1}H NMR δ: 7.29–7.21 (m, 5H), 6.84 (br s, 1H), 4.47 (dd, J=15.0, 6.3 Hz, 1H), 4.38 (dd, J=15.0, 5.7 Hz, 1H), 3.52 and 3.45 (m, 1H), 2.89 (dd, J=15.0, 5.1 Hz, 1H), 2.65–2.44 (m, 2H), 2.07 and 1.95 (m, 1H), 1.04 (d, J=8.1 Hz, 3H), 1.01–0.91 (m, 6H), 0.81 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 170.2, 168.8, 138.3, 128.9, 127.8, 127.5, 66.7, 57.7, 43.7, 37.8, 30.4, 29.2, 20.4, 19.7, 16.5, 16.0. LRMS (FAB^+) *m/z*: 303.2 (MH^+). Yield: 87%. HPLC purity: 95%.

4.5.3. *N*-Benzyl-3-methyl-2-(3-methyl-2-oxoazetidin-1-yl)butanamide 8{3,1,1}. ^{1}H NMR δ: 7.32–7.24 (m, 5H), 7.02 (m, 1H), 4.50–4.31 (m, 2H), 3.74 and 3.71 (d, J= 3.0 Hz, 1H), 3.59 and 3.50 (m, 1H), 3.14–3.00 (m, 2H), 2.23 (m, 1H), 1.25 and 1.22 (d, J=7.5 Hz, 3H), 0.93 (m, 6H). ^{13}C NMR δ: 172.0, 169.5, 138.3, 128.9, 127.9, 127.6, 63.2, 47.5, 43.9, 43.6, 28.7, 19.5, 14.0, 13.6. LRMS (CI^+) *m/z*: 275.0 (MH^+). Yield: 82%. HPLC purity: 96%.

4.5.4. *N*-Benzyl-3-methyl-2-(2-oxo-4-phenylazetidin-1-yl)butanamide 8{4,1,1}. ^{1}H NMR δ: 7.39–7.25 (m, 10H), 6.82 (br s, 1H), 4.64–4.37 (m, 2H), 4.35 (m, 1H), 3.39 (m, 1H), 1.35–3.14 (m, 2H), 2.54 (m, 1H), 0.97–0.87 (m, 6H). ^{13}C NMR δ: 169.9, 168.6, 138.4, 137.2, 129.1, 127.7, 127.4, 126.9, 67.8, 55.1, 43.7, 43.6, 29.2, 20.7, 19.6. LRMS (FAB^+) *m/z*: 337.2 (MH^+). Yield: 82%. HPLC purity: 89%.

4.5.5. *N*-Benzyl-4-methyl-2-(2-methyl-4-oxoazetidin-1-yl)pentanamide 8{1,2,1}. ^{1}H NMR δ: 7.35–7.24 (m, 5H), 4.46–4.36 (m, 2H), 4.04 (m, 1H), 3.76 (m, 1H), 3.99 (m, 1H), 2.44 (m, 1H), 1.82 (m, 2H), 1.63 (m, 1H), 1.35 and 1.26 (d, J=6.0 Hz, 3H), 0.93 (m, 6H). ^{13}C NMR δ: 170.8, 168.0, 138.2, 128.9, 127.9, 127.6, 55.7, 49.5, 43.8, 39.6, 37.9, 25.2, 22.8, 22.0, 20.1, 19.5. LRMS (FAB^+) *m/z*: 289.2 (MH^+). Yield: 82%. HPLC purity: 98%.

4.5.6. *N*-Benzyl-2-(2-isopropyl-4-oxoazetidin-1-yl)-4-methylpentanamide 8{2,2,1}. ^{1}H NMR δ: 7.32–7.23 (m, 5H), 6.88 (m, 1H), 4.45–4.39 (m, 2H), 4.11 (t, J=8.4 Hz, 1H), 3.81 (m, 1H), 3.52 and 3.47 (m, 1H), 2.86–2.75 (m, 1H), 2.61–2.50 (m, 1H), 1.97 (m, 2H), 1.72 (m, 1H), 0.93–0.84 (m, 12H). ^{13}C NMR δ: 170.6, 168.9, 138.2, 128.8, 128.0, 127.5, 59.3, 57.7, 43.8, 39.4, 37.7, 29.7, 25.3, 22.8, 19.5, 16.2. LRMS (FAB^+) *m/z*: 317.2 (MH^+). Yield: 85%. HPLC purity: 95%.

4.5.7. *N*-Benzyl-4-methyl-2-(3-methyl-2-oxoazetidin-1-yl)pentanamide 8{3,2,1}. ^{1}H NMR δ: 7.35–7.22 (m, 5H), 4.48–4.36 (m, 2H), 4.25 (m, 1H), 3.52 and 3.44 (m, 1H), 3.09 (m, 1H), 2.99 and 2.93 (m, 1H), 1.67 (m, 2H), 1.54 (m, 1H), 1.22 and 1.19 (d, J=7.2 Hz, 3H), 0.95–0.89 (m, 6H). ^{13}C NMR δ: 171.9, 170.3, 138.3, 128.9, 127.8, 127.7, 66.5, 54.2, 46.4, 43.7, 37.9, 25.1, 23.0, 22.1, 13.6. LRMS (FAB^+) *m/z*: 289.2 (MH^+). Yield: 82%. HPLC purity: 97%.

4.5.8. *N*-Benzyl-4-methyl-2-(2-oxo-4-phenylazetidin-1-yl)pentanamide 8{4,2,1}. ^{1}H NMR δ: 7.38–7.21 (m, 10H), 6.84 (br s, 1H), 4.69 and 4.59 (m, 1H), 4.49–4.30 (m, 2H), 3.97 and 3.83 (t, J=7.2 Hz, 1H), 3.33 (dd, J=15.0, 5.4 Hz, 1H), 2.99–2.83 (m, 1H), 1.82 (m, 1H), 1.62 (m, 1H), 1.50 (m, 1H), 0.89 (m, 3H), 0.77 (m, 3H). ^{13}C NMR δ: 170.6, 168.8, 138.4, 137.5, 129.2, 129.1, 127.9, 127.1, 126.9, 57.7, 55.0, 45.7, 43.7, 38.7, 25.3, 22.8, 21.9. LRMS (FAB^+) *m/z*: 350.2 (MH^+). Yield: 86%. HPLC purity: 89%.

4.5.9. *N*-Benzyl-2-(2-methyl-4-oxoazetidin-1-yl)butanamide 8{1,3,1}. ^{1}H NMR δ: 7.33–7.23 (m, 5H), 7.10 (br s, 1H), 4.48–4.34 (m, 2H), 3.89–3.70 (m, 2H), 3.05–2.95 (m, 1H), 2.49–2.34 (m, 1H), 2.09–1.78 (m, 2H), 1.35 and 1.27 (d, J=6.0 Hz, 3H),0.95 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 170.4, 168.1, 138.3, 128.9, 127.9, 127.6, 60.2, 48.1, 43.6, 24.5, 22.8, 20.1, 19.5, 11.4. LRMS (FAB^+) *m/z*: 261.2 (MH^+). Yield: 71%. HPLC purity: 70%.

4.5.10. *N*-Benzyl-2-(2-isopropyl-4-oxoazetidin-1-yl)butanamide 8{2,3,1}. ^{1}H NMR δ: 7.33–7.23 (m, 5H), 6.90 (br s, 1H), 4.43 (m, 2H), 3.90 and 3.64 (t, J=7.2 Hz, 1H), 3.52 (m, 1H), 2.89–2.78 (m, 1H), 2.63–2.53 (m, 1H), 2.14–1.83 (m, 3H), 0.97–0.88 (m, 6H), 0.85–0.79 (m, 3H). ^{13}C NMR δ: 170.4, 169.0, 138.4, 128.9, 128.0, 127.6, 60.0, 57.6, 43.8, 37.9, 29.8, 24.7, 19.5, 16.2, 11.4. LRMS (FAB^+) *m/z*: 289.2 (MH^+). Yield: 85%. HPLC purity: 99%.

4.5.11. *N*-Benzyl-2-(3-methyl-2-oxoazetidin-1-yl)butanamide 8{3,3,1}. ^{1}H NMR δ: 7.32–7.23 (m, 5H), 6.93 (br s, 1H), 4.47–4.35 (m, 2H), 4.05 (m, 1H), 3.54 and 3.47 (t, J= 5.4 Hz, 1H), 3.11 (m, 1H), 2.97 (dd, J=18.6, 5.4 Hz, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.25 and 1.21 (d, J=7.5 Hz, 3H), 0.92 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 172.1, 170.0, 138.3, 128.9, 127.8, 127.7, 72.0, 57.8, 46.6, 43.8, 22.8, 13.6, 11.0. LRMS (FAB^+) *m/z*: 261.2 (MH^+). Yield: 84%. HPLC purity: 93%.

4.5.12. *N*-Benzyl-2-(2-oxo-4-phenylazetidin-1-yl)butanamide 8{4,3,1}. ^{1}H NMR δ: 7.40–7.20 (m, 10H), 6.84 (br s, 1H), 4.71–4.59 (m, 1H), 4.55–4.34 (m, 1H), 4.32 (m, 1H), 3.79 and 3.65 (t, J=7.5 Hz, 1H), 3.34 (dd, J=15.0, 5.1 Hz, 1H), 2.96–2.81 (m, 1H), 1.97 (m, 1H), 1.71 (m, 1H), 0.94 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 170.2, 168.8, 138.3, 137.7, 129.2, 128.9, 127.9, 127.0, 126.8, 61.3, 54.9, 45.9, 43.7, 23.5, 11.5. LRMS (FAB$^+$) *m/z*: 323.2 (MH$^+$). Yield: 82%. HPLC purity: 94%.

4.5.13. *N*-Benzyl-2-(2-methyl-4-oxoazetidin-1-yl)-3-phenylpropanamide 8{1,4,1}. ^{1}H NMR δ: 7.35–7.24 (m, 10H), 4.40 (m, 2H), 4.03 (m, 1H), 3.65 (m 1H), 3.31–3.17 (m, 2H), 2.95–2.84 (m, 1H), 2.43–2.33 (m, 1H), 1.25 and 0.78 (d, J=6.0 Hz, 3H). ^{13}C NMR δ: 170.6, 168.3, 138.1, 137.4, 129.0, 128.7, 127.7, 127.2, 61.7, 48.6, 43.7, 37.3, 36.0, 19.7. LRMS (ESI$^+$) *m/z*: 323.4 (MH$^+$), 345.4 ([M+Na]$^+$). Yield: 85%. HPLC purity: 81%.

4.5.14. *N*-Benzyl-2-(2-isopropyl-4-oxoazetidin-1-yl)-3-phenylpropanamide 8{2,4,1}. ^{1}H NMR δ: 7.34–7.19 (m, 10H), 6.91 (br s, 1H), 4.64–4.26 (m, 3H), 3.46 (m, 1H), 3.37–3.20 (m, 1H), 2.73–2.40 (m, 3H), 1.71 (m, 1H), 0.81–0.72 (m, 6H). ^{13}C NMR δ: 170.2, 169.2, 138.0, 137.2, 129.0, 128.9, 127.9, 127.3, 126.8, 64.5, 59.7, 43.8, 38.1, 43.8, 38.1, 35.5, 29.8, 19.4, 16.0. LRMS (FAB$^+$) *m/z*: 351.2 (MH$^+$), 352.2 ([M+2H]$^+$). Yield: 85%. HPLC purity: 83%.

4.5.15. *N*-Benzyl-2-(3-methyl-2-oxoazetidin-1-yl)-3-phenylpropanamide 8{3,4,1}. ^{1}H NMR δ: 7.43–7.18 (m, 10H), 6.64 (m, 1H), 4.45–4.31 (m, 2H), 3.45–3.22 (m, 2H), 3.12–2.99 (m, 2H), 2.89 and 2.75 (m, 1H), 1.13 and 1.06 (d, J=7.2 Hz, 3H). ^{13}C NMR δ: 172.1, 169.6, 138.9, 136.9, 129.3, 128.9, 127.8, 127.7, 127.2, 64.5, 59.7, 47.2, 43.7, 36.0, 13.4. LRMS (FAB$^+$) *m/z*: 323.1 (MH$^+$). Yield: 85%. HPLC purity: 80%.

4.5.16. *N*-Benzyl-2-(2-oxo-4-phenylazetidin-1-yl)-3-phenylpropanamide 8{4,4,1}. ^{1}H NMR δ: 7.41–6.99 (m, 15H), 6.74 (br s, 1H), 4.65 (m, 1H), 4.51 (m, 1H), 3.37 (m, 1H), 4.00–3.89 (m, 1H), 3.36 (m, 1H), 3.30–3.13 (m, 2H), 2.83–2.70 (m, 1H). ^{13}C NMR δ: 171.5, 170.1, 138.0, 137.2, 136.1, 130.5, 129.3, 128.9, 128.7, 127.9, 126.7, 126.6, 61.3, 55.0, 47.2, 43.8, 40.0. LRMS (FAB$^+$) *m/z*: 385.2 (MH$^+$). Yield: 83%. HPLC purity: 74%.

4.5.17. *N-tert*-Butyl-3-methyl-2-(2-methyl-4-oxoazetidin-1-yl)butanamide 8{1,1,2}. ^{1}H NMR δ: 3.83 (d, J=3.3 Hz, 1H), 3.05 (dd, J=15.0, 5.1 Hz, 1H), 2.53 (dd, J=15.0, 2.4 Hz, 1H), 2.37 (m, 1H), 2.09 (m, 1H), 1.38 (d, J=6.0 Hz, 3H), 1.33 (s, 9H), 0.99 (d, J=6.9 Hz, 3H), 0.84 (d, J=6.9 Hz, 3H). ^{13}C NMR δ: 172.6, 169.6, 66.8, 55.2, 48.5, 43.9, 32.2, 28.9, 20.3, 19.5, 15.6. LRMS (ESI$^+$) *m/z*: 241.3 (MH$^+$), 263.3 ([M+Na]$^+$). Yield: 89%. HPLC purity: 92%.

4.5.18. *N-tert*-Butyl-2-(2-isopropyl-4-oxoazetidin-1-yl)-3-methylbutanamide 8{2,1,2}. ^{1}H NMR δ: 3.57 and 3.46 (m, 1H), 2,78 (dd, J=14.4, 5.4 Hz, 1H), 2.65–2.53 (m, 1H), 2.40 (m, 1H), 2.20 (m, 1H), 2.00 (m, 1H), 1.32 (s, 9H), 1.05–0.82 (m, 12H). ^{13}C NMR δ: 169.8, 169.2, 67.1, 60.0, 57.3, 51.6, 37.1, 30.4, 28.8, 20.5, 19.0, 15.7. LRMS (FAB$^+$) *m/z*: 269.2 (MH$^+$). Yield: 77%. HPLC purity: 93%.

4.5.19. *N-tert*-Butyl-3-methyl-2-(3-methyl-2-oxoazetidin-1-yl)butanamide 8{3,1,2}. ^{1}H NMR δ: 3.49 (m, 2H), 3.14 (m, 1H), 3.07 (m, 1H), 2.18 (m, 1H), 1.32 (s, 9H), 1.27 (d, J=7.2 Hz, 3H), 0.92 (d, J=6.6 Hz, 6H). ^{13}C NMR δ: 172.0, 168.7, 64.1, 57.7, 47.4, 43.8, 28.8, 28.6, 19.6, 13.7. LRMS (FAB$^+$) *m/z*: 241.2 (MH$^+$). Yield: 82%. HPLC purity: 99%.

4.5.20. *N-tert*-Butyl-3-methyl-2-(2-oxo-4-phenylazetidin-1-yl)butanamide 8{4,1,2}. ^{1}H NMR δ: 7.34 (m, 5H), 6.19 (br s, 1H), 4.54 (m, 1H), 3.34 (dd, J=15.0, 5.1 Hz, 1H), 3.14–2.89 (m, 2H), 2.49 (m, 1H), 1.28 (s, 9H), 0.94 (d, J=6.6 Hz, 3H), 0.88 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 169.1, 168.6, 137.7, 129.0, 127.3, 126.8, 68.5, 54.9, 51.6, 45.9, 29.4, 28.9, 20.6, 19.4. LRMS (FAB$^+$) *m/z*: 303.2 (MH$^+$). Yield: 81%. HPLC purity: 98%.

4.5.21. *N-tert*-Butyl-4-methyl-2-(2-methyl-4-oxoazetidin-1-yl)pentanamide 8{1,2,2}. ^{1}H NMR δ: 6.24 (br s, 1H), 3.90 (m, 1H), 3.76 (m, 1H), 3.04 (m, 1H), 2.49 (m, 1H), 2.22 (m, 1H), 1.65 (m, 2H), 1.31 (br s, 12H), 0.91 (m, 6H). ^{13}C NMR δ: 169.9, 167.9, 73.1, 56.0, 51.5, 47.9, 43.9, 37.6, 28.8, 25.2, 22.5, 20.2. LRMS (ESI$^+$) *m/z*: 255.3 (MH$^+$), 277.4 ([M+Na]$^+$). Yield: 89%. HPLC purity: 70%.

4.5.22. *N-tert*-Butyl-2-(2-isopropyl-4-oxoazetidin-1-yl)-4-methylpentanamide 8{2,2,2}. ^{1}H NMR δ: 3.98 (t, J=6.9 Hz, 1H), 3.54–3.44 (m, 1H), 2.80 (dd, J=15.0, 5.1 Hz, 1H), 2.61 (dd, J=15.0, 2.7 Hz, 1H), 1.95 (m, 1H), 1.81 (m, 1H), 1.69–1.53 (m, 2H), 1.31 (s, 9H), 0.96–0.82 (m, 12H). ^{13}C NMR δ: 170.5, 168.8, 73.1, 56.4, 51.4, 43.6, 37.4, 29.8, 28.8, 25.3, 22.8, 19.5, 16.2. LRMS (FAB$^+$) *m/z*: 283.2 (MH$^+$). Yield: 78%. HPLC purity: 85%.

4.5.23. *N-tert*-Butyl-4-methyl-2-(3-methyl-2-oxoazetidin-1-yl)pentanamide 8{3,2,2}. ^{1}H NMR δ: 4.07 (t, J=7.5 Hz, 1H), 3.55 and 3,42 (t, J=5.2 Hz, 1H), 3.17 - 3.09 (m, 1H), 2.98–2.89 (m, 1H), 1.63–1.49 (m, 3H), 1.31 (s, 9H), 1.27 (d, J=7.5 Hz, 3H), 0.93–0.88 (m, 6H). ^{13}C NMR δ: 171.8, 169.4, 60.0, 54.8, 51.6, 46.4, 43.7, 37.7, 28.9, 25.1, 23.0, 14.0. LRMS (FAB$^+$) *m/z*: 255.2 (MH$^+$). Yield: 81%. HPLC purity: 88%.

4.5.24. *N-tert*-Butyl-4-methyl-2-(2-oxo-4-phenylazetidin-1-yl)pentanamide 8{4,2,2}. ^{1}H NMR δ: 7.34 (m, 5H), 6.24 (br S, 1H), 4.68 and 4.58 (m, 1H), 3.73 (t, J=7.5 Hz, 1H), 3.39–3.31 (m, 1H), 2.99–2.85 (m, 1H), 1.76 (t, J=7.2 Hz, 1H), 1.51 (m, 2H), 1.31 (s, 9H), 0.89 (d, J=6.3 Hz, 3H), 0.77 (d, J=6.6 Hz, 3H). ^{13}C NMR δ: 169.5, 168.8, 137.8, 129.2, 127.1, 126.9, 58.9, 54.7, 51.5, 45.6, 38.5, 28.8, 25.3, 22.8, 21.9. LRMS (FAB$^+$) *m/z*: 317.2 (MH$^+$). Yield: 85%. HPLC purity: 93%.

4.5.25. *N-tert*-Butyl-2-(2-methyl-4-oxoazetidin-1-yl) butanamide 8{1,3,2}. ^{1}H NMR δ: 6.31 (br s, 1H), 3.78 (m, 1H), 3.69 (m, 1H), 3.11–3.03 (m, 1H), 2.55–2.40 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.37 (d, J=6.0 Hz, 3H), 1.34 (s, 9H), 0.95 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 169.8, 168.0, 60.1, 51.5, 47.9, 43.9, 28.8, 22.6, 19.7, 11.2. LRMS (ESI$^+$) *m/z*: 227.3 (MH$^+$), 249.3 ([M+Na]$^+$). Yield: 81%. HPLC purity: 99%.

4.5.26. *N-tert*-Butyl-2-(2-isopropyl-4-oxoazetidin-1-yl) butanamide 8{2,3,2}. ^{1}H NMR δ: 3.58–3.41 (m, 2H),

2.89–2.79 (m, 1H), 2.66–2.56 (m, 1H), 2.01 (m, 2H), 1.78 (m, 1H), 1.33 (br s, 12H), 0.97–0.85 (m, 9H). ^{13}C NMR δ: 169.4, 168.6, 60.4, 57.4, 51.6, 37.3, 29.7, 28.8, 19.4, 16.2, 11.3. LRMS (FAB$^+$) *m/z*: 255.2 (MH$^+$). Yield: 88%. HPLC purity: 99%.

4.5.27. *N-tert*-Butyl-2-(3-methyl-2-oxoazetidin-1-yl) butanamide 8{3,3,2}. ^{1}H NMR δ: 6.06 (br s, 1H), 3.88 (t, J=6.3 Hz, 1H), 3.46 (t, J=5.7 Hz, 1H), 3.20–3.13 (m, 1H), 3.00–2.93 (m, 1H), 1.86 (m, 1H), 1.69 (m, 1H), 1.32 (s, 9H), 1.28 (d, J=7.5 Hz, 3H), 0.91 (t, J=7.5 Hz, 3H). ^{13}C NMR δ: 172.0, 169.2, 58.5, 51.6, 46.4, 43.7, 28.9, 22.6, 13.8, 10.9. LRMS (FAB$^+$) *m/z*: 227.1 (MH$^+$). Yield: 86%. HPLC purity: 99%.

4.5.28. *N-tert*-Butyl-2-(2-oxo-4-phenylazetidin-1-yl)butanamide 8{4,3,2}. ^{1}H NMR δ: 7.33 (m, 5H), 6.24 (br s, 1H), 4.80 and 4.60 (m, 1H), 3.61 and 3.53 (t, J=8.1 Hz, 1H), 3.36 (dd, J=15.0, 5.4 Hz, 1H), 2.96–2.81 (m, 1H), 1.99 (m, 1H), 1.63 (m, 1H), 1.35 (s, 9H), 0.90 (t, J=7.2 Hz, 3H). ^{13}C NMR δ: 169.4, 168.8, 138.0, 129.1, 127.0, 126.8, 61.8, 54.7, 51.5, 45.9, 28.8, 23.3, 11.3. LRMS (FAB$^+$) *m/z*: 289.2 (MH$^+$). Yield: 85%. HPLC purity: 96%.

4.5.29. *N-tert*-Butyl-2-(2-methyl-4-oxoazetidin-1-yl)-3-phenylpropanamide 8{1,4,2}. ^{1}H NMR δ: 7.28 (m, 5H), 6.50 (br s, 1H), 3.90 (m, 1H), 3.65 (m, 1H), 3.20 (m, 2H), 2.93 (dd, J=15.0, 4.8 Hz, 1H), 2.42 (dd, J=12.3, 2.4 Hz, 1H), 1.33 (br s, 12H). ^{13}C NMR δ: 169.6, 168.1, 137.6, 129.3, 128.8, 127.1, 61.2, 51.7, 48.4, 43.7, 35.9, 28.8, 18.6. LRMS (FAB$^+$) *m/z*: 289.2 (MH$^+$). Yield: 81%. HPLC purity: 75%.

4.5.30. *N-tert*-Butyl-2-(2-isopropyl-4-oxoazetidin-1-yl)-3-phenylpropanamide 8{2,4,2}. ^{1}H NMR δ: 7.23 (m, 5H), 6.22 (br s, 1H), 4.18 (t, J=6.6 Hz, 1H), 3.47 (m, 1H), 3.28 (m, 1H), 3.15 (m, 1H), 2.71–2.42 (m, 2H), 1.82 (m, 1H), 1.34 (s, 9H), 0.82 (d, J=6.9 Hz, 3H), 0.78 (d, J=6.7 Hz, 3H). ^{13}C NMR δ: 169.7, 1169.0, 137.4, 129.2, 128.8, 127.0, 60.1, 57.7, 51.7, 37.8, 35.3, 29.7, 28.8, 19.4, 16.0. LRMS (FAB$^+$) *m/z*: 317.2 (MH$^+$), 318.2 ([M+Na]$^+$). Yield: 89%. HPLC purity: 82%.

4.5.31. *N-tert*-Butyl-2-(3-methyl-2-oxoazetidin-1-yl)-3-phenylpropanamide 8{3,4,2}. ^{1}H NMR δ: 7.32–7.08 (m, 5H), 6.16 (br s, 1H), 4.15 (t, J=6.6 Hz, 1H), 3.43 (t, J=5.4 Hz, 1H), 3.20 (dd, J=15.0, 6.6 Hz, 1H), 3.05 (m, 2H), 2.77 (dd, J=6.0, 2.4 Hz, 1H), 1.29 (s, 9H), 1.19 (d, J=7.2 Hz, 3H). ^{13}C NMR δ: 172.0, 168.8, 137.2, 128.3, 128.9, 127.1, 59.6, 51.7, 47.4, 43.6, 36.0, 28.8, 13.5. LRMS (FAB$^+$) *m/z*: 289.3 (MH$^+$). Yield: 88%. HPLC purity: 89%.

4.5.32. *N-tert*-Butyl-2-(2-oxo-4-phenylazetidin-1-yl)-3-phenylpropanamide 8{4,4,2}. ^{1}H NMR δ: 7.32–7.17 (m, 10H), 6.10 (br s, 1H), 4.52 (m, 1H), 3.97 (m, 1H), 3.27 (m, 2H), 3.02 (m, 1H), 2.82–2.72 (m, 1H), 1.24 (s, 9H). ^{13}C NMR δ: 169.0, 168.9, 138.5, 137.7, 129.3, 129.1, 128.3, 127.1, 126.6, 61.6, 54.9, 51.7, 46.3, 36.0, 28.8. LRMS (FAB$^+$) *m/z*: 351.2 (MH$^+$). Yield: 85%. HPLC purity: 84%.

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Sulfur dioxide mediated one-pot, four-component synthesis of polyfunctional sulfones and sulfonamides, including medium-ring cyclic derivatives

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Abstract—In previous papers (*Synthesis* **2002**, 232 and *J. Org. Chem.* **2004**, *69*, 6413), we have shown that the hetero-Diels–Alder addition of sulfur dioxide to 1-oxy or 1,3-dioxy-1,3-dienes generates zwitterions that add to enoxysilanes or allylsilanes giving silyl sulfinates that can be converted in the same pot into polyfunctional sulfones, sulfonamides or sulfonic esters. We are presenting further applications of this method, including the synthesis of new medium-size heterocyclic systems of the type tetrahydro-2*H*-thiocines and hexahydro-1,2-thiazonine.

1. Introduction

Organosulfones are important compounds[1] because of their chemical properties[2] and biological properties.[3] They are important synthetic targets and are widely used synthons.[4] The sulfone functional group is found in various drugs, including the recently selective COX-2 inhibitor Vioxx.[5] Sulfones have been shown also to inhibit HIV-1 reverse transcriptase.[6] Their preparation involves oxidation of the corresponding sulfides and sulfoxides[7a–d] or displacement reaction of sodium arenesulfinate with an appropriate alkyl halides.[7e,f] Diaryl sulfones are prepared also through the classical Friedel–Crafts sulfonylation using of arenesulfonyl chlorides and arenes, and Lewis acids catalysts.[7g,h] Recently, biaryl sulfones were derived from sulfinic acid salts and aryl iodides using copper[8] and palladium catalyst.[9] In 2004, we[10a] and Bandgar[1n] have reported that diaryl sulfones can be prepared through palladium-catalyzed cross-coupling reactions between areneboronic acids and arenesulfonyl chlorides.

The sulfonamides constitute an important class of drugs (the sulfa drugs), with several types of pharmacological agents possessing antibacterial, anticarbonic anhydrase, diuretic hypoglycemic anti-thyroid, anti-hypertensive, anti-inflammatory, and antiviral properties.[11,12] Recently, structurally novel sulfonamide derivatives have shown substantial antitumor activities,[13,14] or are caspase-1[15] inhibitors.[16] The majority of sulfonamides are prepared from the reaction of sulfonyl chlorides with ammonia, primary or secondary amines.[17] Arenesulfonyl chlorides are prepared from arenes by electrophilic substitution with $ClSO_3H$ or from arenesulfonic acids by reaction with PCl_5,[18] $POCl_3$[19] or $COCl_2$.[20] Other methods imply the reactions of arenediazonium salts with $SO_2/CuCl_2$,[21] the oxidation of thioesters[22] or sulfenyl chlorides,[23] or the reaction of organolithium[24] or organomagnesium[25] reagents with SO_2Cl_2 or SO_2+Cl_2. Alkanesulfonyl chlorides can be obtained by reaction of the corresponding alkane with SO_2 and Cl_2 under radical conditions.[26] All these methods[27] are relatively harsh (acidic, basic) and cannot be applied to polyfunctional substrates. Recently, the direct synthesis of sulfonamides and sulfonic esters from sulfonic acids[28] and a one-pot synthesis of sulfonamides from Grignard reagents and SO_2[28,29] has been reported. Both procedures are amenable to aromatic and heteroaromatic sulfonamides.

Enoxysilanes **1**,[30] allylsilanes **2**,[30] and allylstannanes **3**[31] undergo ene-reactions with sulfur dioxide giving the corresponding silyl or stannyl sulfinate intermediates **4** that react with Bu_4NF and carbon electrophiles R^3Y to produce the corresponding sulfones **5** in one-pot operations (Scheme 1).[30] Chlorination (Cl_2 or NCS) or bromination

Keywords: Ene reaction; Oxyallylation; Silyl sulfinates; Polyfunctional sulfones; Polyfunctional sulfonamides; Thiocines; 1,2-Thiazonines.
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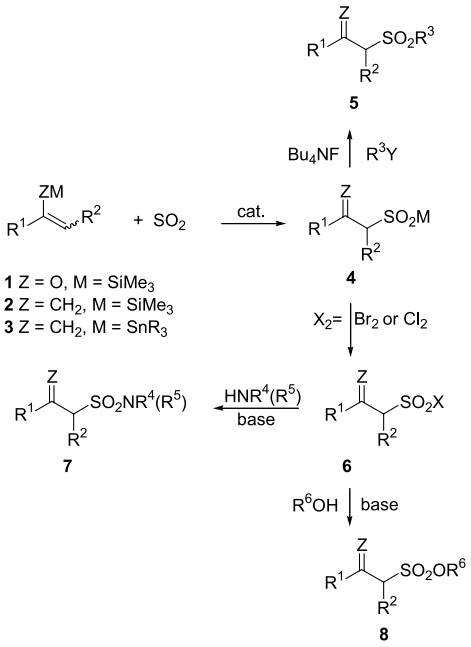
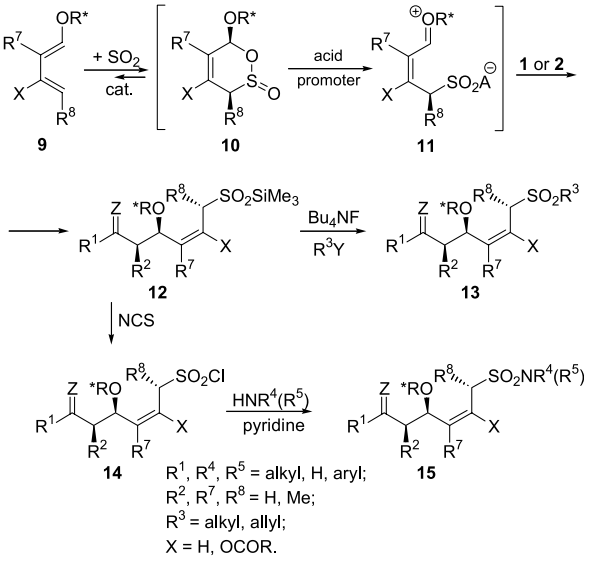


Scheme 1. One-pot, three-component synthesis of polyfunctional sulfones **5**, sulfonamides **7** and sulfonic esters **8**.

(Br_2 or NBS) of silyl sulfinates **4** generate the corresponding sulfonyl halides **6** that react in situ with primary or secondary amines to produce the corresponding sulfonamides **7**, or with alcohols to generate the corresponding sulfonic esters **8** (Scheme 1).[32]

We have found a new C–C bond forming reaction (Scheme 2),[33–38] involving a cascade of reactions starting with the hetero-Diels–Alder addition of sulfur dioxide to 1,3-dienyl ethers **9**. This generates unstable sultines **10** that are ionized in the presence of an acid promoter giving zwitterionic species **11**. In the presence of enoxysilanes **1** or allylsilanes **2**, the latter are quenched forming the corresponding silyl sulfinates **12** with high diastereoselectivity. Desilylation of **12** with Bu_4NF followed by



Scheme 2. One-pot, four-component synthesis of polyfunctional sulfones **13** and sulfonamides **15**.

addition of electrophile R^3Y generates the corresponding sulfones **13**, thus, realizing a one-pot, four-component method for the synthesis of polyfunctional sulfones.[34,39] Chlorination or bromination of silyl sulfinates **12** provides the corresponding sulfonyl chlorides or bromides that react with primary or secondary amines in pyridine to produce the corresponding polyfunctional sulfonamides **15**.[32,40] Using enantiomerically enriched dienes **9** (R*=1-arylethyl), enantiomerically enriched sulfones **13** and sulfonamides **15** are obtained.

We present here new applications of our one-pot, four-component synthesis of sulfones and sulfonamides.[41] New β,γ-unsaturated sulfones have been obtained, including cyclic derivatives resulting from intramolecular sulfinates allylation. Furthermore, we have found that not only (*Z*)-β,γ-unsatured sulfones can be formed. Depending on the nature of the enoxysilanes and 1-oxydienes and upon the nature of the acid catalyst, the (*E*)-isomeric sulfones can also be obtained. For the first time, intramolecular allylation of sulfonamides have allowed to prepare hexahydro-1,2-thiazonine derivatives, a new kind of medium-size heterocyclic compounds.[42]

2. Results and discussion

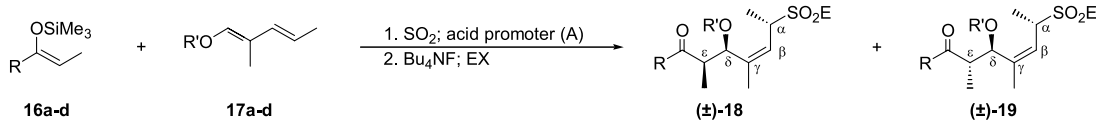
2.1. Diastereoselectivity of the oxyallylations of enoxysilanes

In our previous work[34,38] we found that the δ,ε-*syn* versus *anti* diastereoselectivity of the oxyallylations of (*Z*)-enoxysilane **16a** using (*E*,*E*)-1-oxy-2-methylpenta-1,3-dienes never surpass 3:1 (product ratio **18**/**19**, Scheme 3). As we shall see, the diasteroselectivity varies with the nature of the enoxysilane **16** and of the diene **17** and that it can be increased to 9:1.

For instance, when a 2:1 mixture of enoxysilane **16b** (R=*p*-$MeOC_6H_4$) and diene **17b** (R=Bn) was reacted with an excess of SO_2 premixed with 0.2 equiv of Tf_2NH (Tf=trifluoromethanesulfonyl) or $TfOSiR_3$ (R=Me, *t*-Bu) at −78 °C for 12 h, a mixture of silyl sulfinates was obtained that was quenched with 1 equiv of Bu_4NF and 2.5 equiv of methallyl bromide to give a 5:1 mixture of sulfonylketones (±)-**18b** and (±)-**19b** from which the major isomer (±)-**18b** was isolated pure in 76% yield (Table 1). Its structure was not established unambigiously but it is proposed to be similar (δ,ε-*syn*, α,δ-unlike) to those of similar compounds obtained under similar conditions.[34,38]

Under the same conditions, enoxysilane **16c**+ diene **17b** gave a 6:1 mixture of sulfonylketones (±)-**18c** and (±)-**19c** from which (±)-**18c** could be isolated pure in 70% yield. With enoxysilane **16d** [(*Z*)-1,2-bis(trimethyl-silyloxy)but-1-ene][43] and racemic diene (±)-**17c** a 3:1 mixture of (±)-**18d** and (±)-**19d** (electrophile, EX=MeI) was obtained. Pure (±)-**19d** could be isolated by flash column chromatography on silica gel. The combination of more sterically bulky diene **17d** (R′=$SiMe_2t$-Bu) with enoxysilane **16c** (R=2,4,6-$(MeO)_3$–C_6H_2) resulted in enhanced 9:1 δ,ε-*syn* versus *anti* diastereoselectivity (Table 1, entry 6).

Table 1. Synthesis of (*Z*)-β,γ-unsaturated sulfones



Entry	Reactants				Products	
	16	**17**	EX	A	Ratio	Total yield (%)
1	**16a**: R = Me	**17a**: R′ = $SiMe_3$	MeI	Tf_2NTMS, 45%	**18a**:**19a** = 1:1[a]	72 [Ref. 38]
2	**16b**: R = *p*-$MeOC_6H_4$	**17b**: R′ = Bn		Tf_2NH, 20%	**18b**:**19b** = 5:1	91
3	**16c**: R = 2,4,6-$(MeO)_3C_6H_2$	**17b**: R′ = Bn		Tf_2NH, 20%	**18c**:**19c** = 6:1	90
4	**16d**: R = CH_2OSiMe_3	**17c**: R′ = (*RS*)-2,4,6-(*i*-$Pr)_3C_6H_2$(Me)CH	MeI	Tf_2NH, 20%	**18d**:**19d** = 3:1	29
5	**16c**: R = 2,4,6-$(MeO)_3C_6H_2$	**17a**: R′ = $SiMe_3$		Tf_2NH, 20%	**18e**:**19e** = 6:1[a]	82
6	**16c**: R = 2,4,6-$(MeO)_3C_6H_2$	**17d**: R′ = $SiMe_2t$-Bu		Tf_2NH, 20%	**18f**:**19f** = 9:1[b]	60

[a] Products **18a/19a** and **18e/19e** are obtained in their desilylated form where R′ = H.
[b] This represents the yield and ratio of **18f/19f** after additional silylation of the crude reaction mixture. For more details see Section 4.

On increasing the amount of the protic acid promoter the oxyallylation reaction produced mixtures of (*Z*)- and (*E*)-β,γ-unsatured sulfinates.[38] For instance, when using 0.5 equiv (instead of 0.1–0.2 equiv) of Tf_2NH, the reaction of enoxysilane **16a** with diene **17a** led to a mixture of (*E*)-β,γ-unsatured silyl sulfinates that reacted with Bu_4NF and Me_2CHCH_2I giving a 1:1 mixture of (*E*)-β,γ-unsatured sulfones (±)-**20a** and (±)-**21a**. When treated with TfOH in THF, this mixture generated a single (*E*,*E*)-dienone (±)-**22** demonstrating that the relating configuration for (±)-**20a** and (±)-**21a** are δ,ε-*syn*, α,δ-unlike and δ,ε-*anti*, α,δ-unlike, respectively, (Table 2).

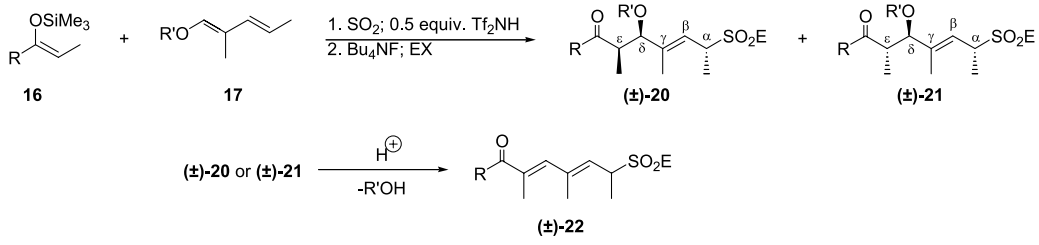
Similarly, when enoxysilane **16c** and diene **17d** were treated as above with 0.5 equiv of Tf_2NH in an excess of SO_2 at −78 °C, a mixture of (*E*)-β,γ-unsaturated sulfones (±)-**20b** and (±)-**21b** was obtained. Flash chromatography of this mixture allowed the obtainment of a 9:1 mixture of (±)-**20b** and (±)-**21b** in 60% yield. The relative configuration of these compounds was not established unambiguously, it is proposed to be the same as that of related compounds prepared under similar conditions.[38] However, the (*E*)- or (*Z*)-configurations of the alkene units were confirmed by NOESY ^1H NMR experiments.

2.2. Oxyallylation of allylsilanes

We had shown[35] that the oxyallylation of allylsilanes **23** fails when reacting them with 1-oxy-1,3-dienes such as **17** and SO_2 activated by a Lewis or protic acid. Nevertheless, successful oxyallylation of allylsilanes could be realized using 1,3-dioxy-1,3-dienes of type **24**. As a new illustration of the reaction, we report here that 2:1 mixture of allylsilane **23a** with the enantiomerically enriched diene (−)-**24a** (97% ee, derived from the inexpensive (1*S*)-1-phenylethanol)[35] produces a single silyl sulfinate **25a**, when treated in anhyd CH_2Cl_2/SO_2 premixed with 0.3 equiv of Tf_2NSiMe_3 (Scheme 3). After evaporation of SO_2 and CH_2Cl_2 at −50–20 °C, the residue was treated with *N*-chlorosuccinimide (NCS) in acetonitrile at −30 °C. This produced the corresponding sulfonyl chloride that was not isolated but mixed with benzylamine (10 equiv) in pyridine at −40 °C.

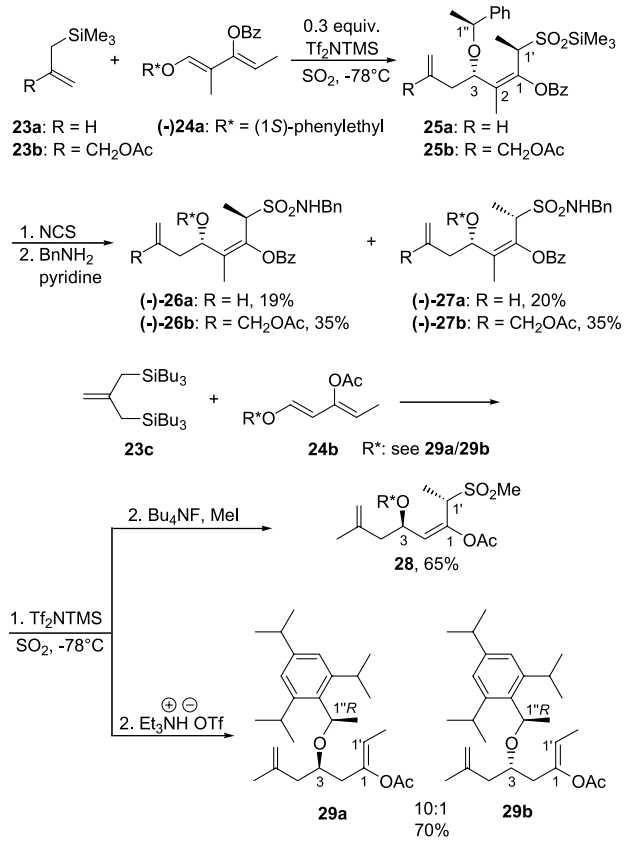
After 4 h at −20 °C, the formation of sulfonamides was

Table 2. Synthesis of (*E*)-β,γ-unsaturated sulfones



Entry	Reactants			Products	
	16	**17**	EX	Ratio	Total yield (%)
1	**16a**: R = Me	**17a**: R′ = $SiMe_3$		**20a**:**21a** = 1:1[a]	82
2	**16c**: R = 2,4,6-$(MeO)_3C_6H_2$	**17d**: R′ = $SiMe_2t$-Bu		**20b**:**21b** = 9:1[b]	60

[a] Products **20a/21a** are obtained in their desilylated form where R′ = H.
[b] This represents the yield and ratio of **20b/21b** after additional silylation of the crude reaction mixture. For more details see Section 4.



Scheme 3. Oxyallylation of allysilanes and synthesis of sulfonamides and sulfones.

over and, after flash column chromatography on silica gel, isomeric *N*-benzylsulfonamides (−)-**26a** and (−)-**27a** were isolated in 19 and 20% yield, respectively. Although the sulfonamide formation reaction was carried out low temperature, these results demonstrated that basicity of the medium is sufficient to promote a complete epimerization (−)-**26a**↔(−)-**27a**. The structure of sulfonamide (−)-**27a** was established by X-ray diffraction studies (Fig. 1). That of (−)-**26a** was deduced from its spectral data and by comparison with those collected for (−)-**27a**.

With the hope to carry out two successive oxyallylations on disilyl system **23c**[45] we reacted it with the enantiomerically pure diene **24b** (derived from (1*R*)-1(2,4,6-tri(isopropyl))-phenylethanol: the Greene's chiral auxiliary)[46] in the presence of SO_2 and an acid promoter. For 2:1–1:3 mixtures of **23c** and **24b** as major product only sulfone **28** (10:1 epimers at C(3)) was isolated in 65% yield, when the reaction mixture was methylated with MeI/Bu_4NF. Under the conditions used, only one oxyallylation occurred and the second allylsilane moiety in intermediate underwent desilylation with Bu_4NF. The relative configuration in **28** was not established unambiguously, but it is proposed to be similar to that observed in related product proposed under similar conditions.[35] When the reaction mixture **23c**+**24b** was submitted to desilylation and desulfitation by retro-ene reaction (triethylamonium trifluoromethanesulfonate buffer, see Scheme 3), a 10:1 mixture of diastereomeric dienes **29a** and **29b** was obtained. As the analogous retro-ene eliminations have all shown high stereoselectivity in the chirality transfer between centers C(1′) and C(2) in the corresponding diene, the 10:1 mixture of diastereomers **29a**+**29b** is proposed to correspond to the like (1″*R*, 3*R*) for the major isomer **29a**, and unlike (1″*R*, 3*S*) for the minor product **29b**.

The reaction of a 2:1 mixture of allylsilane **23b** and enantiomerically enriched (ee 97%) diene (−)-**24a** in SO_2/toluene premixed with 0.3 equiv of Tf_2NSiMe_3 (−78 °C, 36 h) gave a single silyl sulfinate **25b** (by ^1H NMR of the crude) that was oxidized with NCS to the corresponding sulfonyl chloride that was not isolated but treated with an excess of benzylamine in pyridine. Flash column chromatography provided pure sulfonamides (−)-**26b** and (−)-**27b** each in 35% yield (Scheme 3). Both compounds were treated with 1 equiv of Cs_2CO_3 in anhyd DMF in the presence of 0.1 equiv of $(Ph_3P)_4Pd$. After heating to 100 °C for 40 min., the 1,2-thiazonin-8-yl benzoates (−)-**30** (81%) and (−)-**31** (79%) were obtained. They resulted from intramolecular *N*-allylation[47] of the *N*-benzylsulfonamides (Scheme 4). Except for the relative configuration between the (1*S*)-phenylethyl group and the stereogenic centers C(6), which was assumed to be the same as that observed for other related systems obtained under similar conditions,[35] the

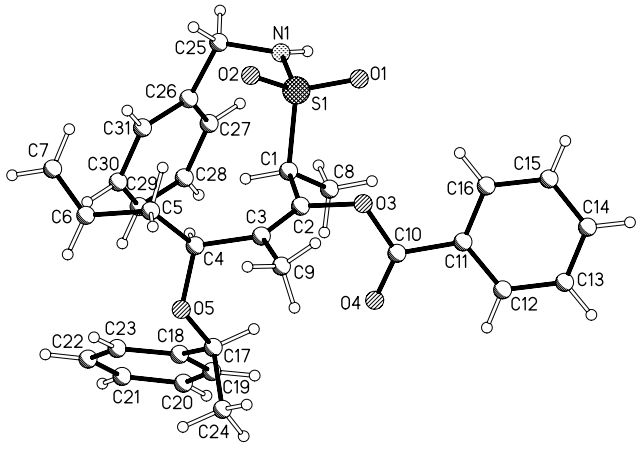
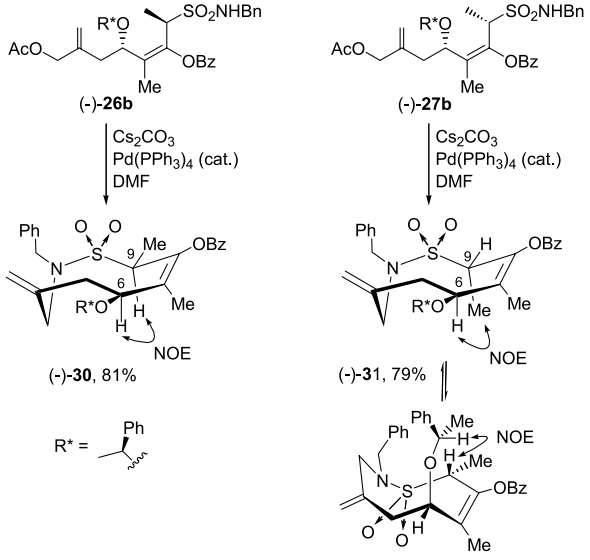
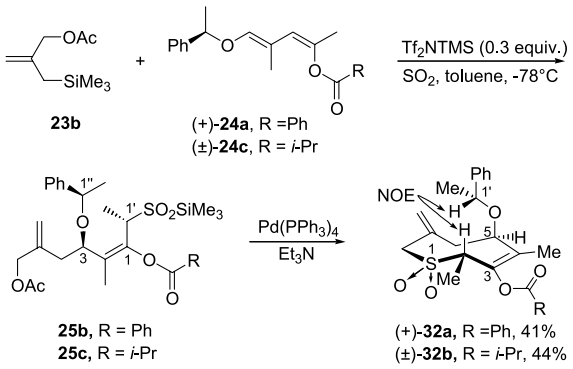


Figure 1. Representation of the X-ray molecular structure of (−)-**27a**.[44]



Scheme 4. Synthesis of 1,2-thiazonin-8-yl derivatives.



Scheme 5. Synthesis of a 5,6,7,8-tetrahydro-2*H*-thiocines.

relative configuration 6,9-*cis* in (−)-**30** and 6,9-*trans* in (−)-**31** was established by the 2D-^{1}H NMR spectra and especially by the NOESY spectra. Compounds (−)-**30** and (−)-**31** are the first members of the 2,3,4,5,6,9-hexahydro-1,2-thiazonine class of heterocycles.[42]

We have also explored the possibility to generate 5,6,7,8-tetrahydro-2*H*-thiocine derivatives by intramolecular electrophilic quenching of our intermediate silyl sulfinates. An example is given (Scheme 5) by the reaction of the racemic silyl sulfinate **25c** obtained by oxyallylation of allylsilane **23b** with diene (±)-**24c**. Its treatment with 2 equiv of Et_3N and 0.1 equiv of $(Ph_3P)_4Pd$ in THF provided the cyclic sulfone (±)-**32b**, which was purified by column chromatography on silica gel and isolated in 44% yield. Its structure has been established by single crystal X-ray diffraction studies (Fig. 2). The same reaction sequence has been applied to the enantiomerically enriched (97% ee) diene (+)-**24a**[35,37] (Scheme 5), which produced (+)-**32a** through **25b** in 41% overall yield. As for other related systems obtained under similar conditions[35] the relative configuration between C(1″) of the 1-phenylethyl group (chiral auxiliary) and the adjacent stereogenic center C(3) in the open chain system **25b** is assumed to be like. Moreover, NMR data proved the unlike relative configuration between C(5) and C(2) in the thiocine structure (+)-**32a**.

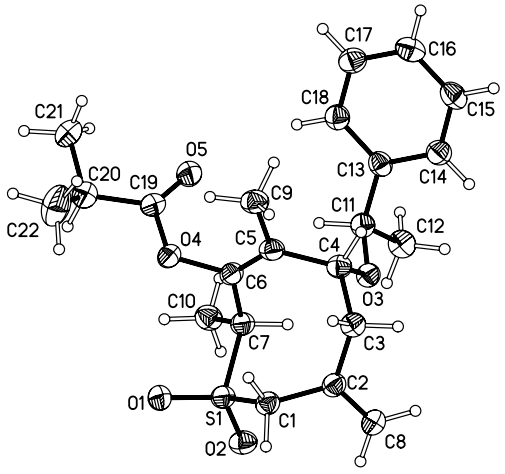


Figure 2. Molecular structure of (±)-**32b** by single crystal X-ray diffraction.[48]

3. Conclusion

Our one-pot, four-component syntheses of polyfunctional sulfones and sulfonamides have been extended to a large variety of 1,3-dienes, enoxysilanes and allylsilanes. In the case of sulfonamide formation, epimerization of the stereogenic α-center of the β,γ-unsaturated sulfonamides cannot be avoided in several instances. For the first time new heterocyclic synthesis such as 2,3,4,5,6,9-hexahydro-1,2-thiazonine derivatives have been obtained. This was possible by intramolecular Pd-catalyzed *N*-allylation reactions. In a similar way, intramolecular S-allylation of intermediate silyl sulfinate has allowed the preparation of a new tetrahydro-2*H*-thiocine derivatives. Using enantiomerically enriched 1-oxy- or 1,3-dioxy-1,3-dienes enantiomerically enriched polyfunctional sulfones and sulfonamides are prepared readily.

4. Experimental

4.1. General remarks

Reagents were purchased from Acros, Fluka, Senn, Aldrich or Merk and used without further purification. All solvents for extraction and chromatography were distilled prior to use. Anhyd THF, Et_2O and toluene were distilled from sodium benzophenone, CH_2Cl_2 from CaH_2, and methanol from magnesium. Reactions were monitored by TLC (Merk Kiesegel $60F_{254}$) silica gel plates; detection with UV (254 nm) light or molybdic reagent (21 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 1 g of $Ce(SO_4)_2$, 31 mL H_2SO_4 and 470 mL of H_2O). Flash chromatography (FC) used 230–400 mesh silica gel (Merk no.9385). Melting points were measured with a Mettler FP52 and were uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. UV spectra were recorded on a Kontron Uvikon 810 CW spectrophotometer. IR spectra were recorded on Perkin Elmer Paragon 1000 FT-IR spectrometer. Mass spectra were recorded on a Nermag R 10-10C in chemical ionisation mode. Electron spray mass analyses were recorded on a Finnigan MAT SSQ 710C spectrometer in positive ionisation mode. ^{1}H NMR spectra were recorded on Bruker DPX-400 FT, Bruker ARX-400 FT spectrometers. ^{13}C NMR spectra were recorded on Bruker DPX-400 FT (100.61 MHz), Bruker ARX-400 FT (100.61 MHz) machines; all ^{13}C signal assignments were confirmed by HMQC spectra. Chemical shifts in ppm, relative to internal standard such as residual signals of solvents, coupling constants in hertz. All structures and signal assignments were confirmed by 2D-NOESY ^{1}H NMR and 2D-COSY ^{1}H NMR spectra. Microanalyses were performed by the Ilse Beetz Laboratory, Kronach (Germany).

Starting materials **16a**[49] (risk of explosion in the preparation of this compound!), **16b**,[50] **16c**,[51] **16d**,[43] **17a**,[33b,51] **17b**,[32,52] **17c**,[34,39b] **17d**,[53] **24a**,[35–37] and **24c**,[35–37] were prepared according to the literature procedures.

4.2. General procedure for the preparation of oxo-(*Z*)-β, γ-unsaturated sulfones 18, 19 using enoxysilanes

Tf_2NH (0.5 M in CH_2Cl_2, 1.35 mL, 0.68 mmol, 0.2 equiv) in anhyd CH_2Cl_2 (2 mL) was degassed by freeze-thaw cycles on the vacuum line. SO_2 (5 mL, 114.0 mmol, 34 equiv), dried through a column packed with basic alumina and phosphorus pentoxide, was transferred on the vacuum line to the CH_2Cl_2 solution frozen at −196 °C. The mixture was allowed to melt and to warm to −78 °C. After 1 h at this temperature a solution of 1,3-diene **17** (1 equiv) and the enoxysilane **16** (2–5 equiv) in CH_2Cl_2 (3 mL) was added slowly. The mixture was stirred at −78 °C for 12 h. Excess of SO_2 and solvent were evaporated under reduced pressure (10^{-1} Torr) to dryness, while temperature was rising to 25 °C in ca. 1 h. A 1 M solution of Bu_4NF in THF (1 equiv) and electrophile **EX** (2.5–7 equiv) were added under Ar atmosphere. The mixture was stirred at −40 °C for 1 h, then allowed to reach 20 °C in about 10 h. After the addition of H_2O (40 mL) and neutralization with satd aq soln of $NaHCO_3$ (10 mL), the mixture was extracted with CH_2Cl_2 (30 mL, three times). The combined organic extracts were washed with brine (30 mL, two times), dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (FC).

4.2.1. (±)-(2*RS*,3*RS*,4*Z*,6*SR*)-3-benzyloxy-1-(4-methoxyphenyl)-2,4-dimethyl-6-((2-methylprop-2-enyl)sulfonyl-(-1-phenylhept-4-en-1-one ((±)-18b). This preparation followed the above procedure and used (*Z*)-1-(4-methoxyphenyl)-1-trimethylsilyloxypropylene (**16b**)[50] (2.09 g, 8.8 mmol) and (*E*,*E*)-1-benzyloxy-2-methyl-penta-1,3-diene **17b**[32] (870 mg, 4.41 mmol) and 3-bromo-2-methylpropene (1.11 mL, 11.01 mmol). A 5:1 mixture of (±)-**18b** and (±)-**19b** was obtained. FC (light petroleum ether/EtOAc 8:2, R_f=0.30), gave 1.04 g (76%) of pure (±)-**18b** as a colorless oil. IR (film): *ν* 2975, 2935, 1670, 1405, 1375, 1305, 1210, 1120, 1070, 970, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.92 (d, 2H, ^3J=8.9 Hz, H–C(ar)), 7.51 (t, 2H, ^3J=8.8 Hz, H–C(ar)), 7.41 (d, 2H, ^3J=8.0 Hz, H–C(ar)), 7.38 (t, 2H, ^3J=7.1 Hz, H–C(ar)), 7.30 (d, 1H, ^3J=7.5 Hz, H–C(ar)), 5.32 (br s, 1H, H–C(3′)), 5.29 (d, 1H, $^3J(H_5,H_6)$=10.7 Hz, H–C(5)), 5.18 (br s, 1H, H–C(3′)), 4.63 (d, 1H, ^2J=11.8 Hz, H–CH_2Bn), 4.54 (d, 1H, $^3J(H_3,H_2)$=9.8 Hz, H–C(3)), 4.49 (d, 1H, ^2J=11.8 Hz, CH_2Bn), 4.34 (dq, 2H, $^3J(H_6,H_5)$=10.7 Hz, $^3J(H_6,H_7)$=6.6 Hz, H–C(2)) 3.89 (m, 1H, H–C(6)), 3.89 (s, 3H, O*Me*), 3.79 (d, 1H, ^2J=13.2 Hz, Hb–C(1′)), 3.59 (d, 1H, ^2J=13.2 Hz, Ha–C(1′)), 2.03 (s, 3H, *Me*-C(2′)), 1.79 (s, 3H, *Me*-C(4)), 1.39 (d, 6H, ^3J=6.6 Hz, *Me*-C(2) and *Me*-C(6)). ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* 164.0 (s, CO), 133.2 (s, C(2′)), 129.8 (m, C(ar)), 126.3 (s, C(4)), 122.3 (t, ^1J(C,H)=152 Hz, C(3′)), 114.1 (d, ^1J(C,H)=160 Hz, C(5)), 78.7 (d, ^1J(C,H)=167 Hz, C(6)), 70.9 (t, ^1J(C,H)=158 Hz, *C*H_2–Bn), 58.1 (t, ^1J(C,H)=157 Hz, C(1′)), 56.6 (q, ^1J(C,H)=125 Hz, O*Me*), 55.5 (d, ^1J(C,H)=168 Hz, C(3)), 43.5 (d, ^1J(C,H)=138 Hz, C(2)), 23.1 (q, ^1J(C,H)=126 Hz, *Me*-C(4)), 18.6 (q, ^1J(C,H)=132 Hz, *Me*-C(6)), 16.3 (q, ^1J(C,H)=126 Hz, *Me*-C(2′)), 15.5 (q, ^1J(C,H)=132 Hz, *Me*-C(2)). CI-MS (NH_3): *m/z* 392 (100, $[M+18]^+$), 375 (57, $[M+1]^+$). MALDI-HRMS: calcd for $C_{27}H_{34}SO_4+Na^+$: 493.2025; found: 493.2019.

4.2.2. (±)-(2*RS*,3*RS*,4*Z*,6*SR*)-3-benzyloxy-6-[(2-methylprop-2-en-yl)sulfonyl]-2,4-dimethyl-1-(2,4,6-trimethoxyphenyl)hept-4-en-1-one ((±)-18c). This preparation followed the above general procedure using trimethyl{[(1*E*)-1-(2,4,6,-trimethoxyphenyl)prop-1-enyl]-oxy}silane[51] (**16c**, 3.5 g, 11.8 mmol, 2.8 equiv), (*E*,*E*)-1-benzyloxy-penta-1,3-diene[32] (**17b**, 800 mg, 4.2 mmol, 1 equiv) and 3-bromo-2-methylpropene (1.72 g, 1.3 mL, 12.8 mmol, 3 equiv). A 6:1 mixture of (±)-**18c** and (±)-**19c** was obtained. FC (light petroleum ether/EtOAc 4:1, R_f=0.27), gave 1.63 g (77%) of pure (±)-**18c** and 0.27 g (13%) of (±)-**19c**, both yellowish oils. Data of **18c**: UV (CH_3CN): λ_{max}=214 nm (*ε*=19600). IR (film): *ν* 2973, 2842, 1693, 1645, 1587, 1455, 1414, 1305, 1229, 1207, 1158, 1130, 1068, 1029, 968, 914, 856 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.39 (d, 2H, ^3J=7.7 Hz, H–C(ar)), 7.34 (t, 2H, ^3J=7.7 Hz, H–C(ar)), 7.28 (t, 1H, ^3J=7.7 Hz, H–C(ar)), 6.10 (s, 2H, H–C(ar)), 5.42 (d, 1H, $^3J(H_5–H_6)$=9.6 Hz, H–C(5)), 5.27 (br s, 1H, H–C(3′)), 5.15 (br s, 1H, H–C(3′)), 4.58 (d, 1H, ^2J=11.8 Hz, H–*C*H_2–Bn), 4.55 (d, 1H, $^3J(H_3,H_2)$=8.6 Hz, H–C(3)), 4.47 (dq, 1H, $^3J(H_6,H_5)$=9.6 Hz, $^3J(H_6,H_7)$=6.7 Hz, H–C(6)), 4.42 (d, 1H, ^2J=11.8 Hz, *C*H_2–Bn), 3.84 (s, 3H, H–O*Me*), 3.76 (s, 6H, H–O*Me*), 3.73 (d, 1H, ^2J=13.4 Hz, Ha–C(1′)), 3.64 (d, 1H, ^2J=13.4 Hz, Hb–C(1′)), 3.43 (dq, 1H, $^3J(H_2–H_3)$=8.6 Hz, $^3J(H_2–Me_2)$=7.1 Hz, H–C(2)), 2.02 (s, 3H, *Me*-C(4)), 1.85 (s, 3H, *Me*-C(2′)), 1.49 (d, 3H, $^3J(H_7,H_6)$=6.7 Hz, H–C(7)), 1.29 (d, 3H, ^3J(Me, 2H)=7.1 Hz, *Me*-C(2)). ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* 206.2 (s, CO), 163.1–158.9 and 139.3 (s, 5C(ar)), 143.1 (s, C(2′)), 133.6 (s, C(4)), 128.1–128.06 (d, 7C, ^1J(C,H)=149 Hz, C(ar)), 122.1 (t, ^1J(C,H)=159 Hz, C(3′)), 120.7 (d, ^1J(C,H)=152 Hz, C(5)), 79.9 (t, ^1J(C,H)=156 Hz, *C*H_2–Bn), 71.1 (t,^1J(C,H)=148 Hz, C(1′)), 58.5 (d, ^1J(C,H)=132 Hz, C(3)), 57.4 (d, ^1J(C,H)=140 Hz, C(6)), 55.5 (q, ^1J(C,H)=138 Hz, C(O*Me*)), 51.4 (d, ^1J(C,H)=128 Hz, C(2)), 23.5 (q, ^1J(C,H)=125 Hz, *Me*-C(2′)), 19.4 (q, ^1J(C,H)=129 Hz, *Me*-C(4)), 15.8 (q, ^1J(C,H)=134 Hz, C(7)), 14.6 (q, ^1J(C,H)=130 Hz, *Me*-C(2)). CI-MS (NH_3): $C_{29}H_{38}SO_7$, *m/z* 548 (12, $[M+18]^+$), 531 (100, $[M+1]^+$), 225 (69). MALDI-HRMS: calcd for $C_{29}H_{38}SO_7+Na^+$: 553.2236; found: 553.2229.

4.2.3. (±)-(3*RS*,4*RS*,5*Z*,8*SR*)-1-hydroxy-3,5-dimethyl-7-(methylsulfonyl)-4-{1-(*RS*)-[2,4,6-tris(isopropyl)phenyl]-ethoxy}octa-5-en-2-one ((±)-18d). This compound was prepared applying the above general procedure using (*Z*)-1,2-bis(trimethylsilyloxy)but-1-ene (**16d**)[43] (0.3 g, 1.28 mmol, 1.2 equiv), (±)-1,3,5-triisopropyl-2-{(*R*,*S*)-1-[(*E*,*E*)-2-methylpenta-1,3-dien-1-yloxy]ethyl}benzene (**17c**)[34,39c] (0.2 g, 0.64 mmol) and MeI (0.3 mL, 4.8 mmol). A 3:1 mixture of (±)-**18d** and (±)-**19d** was obtained. FC (light petroleum ether/AcOEt 2:1) gave 66 mg (23%) of pure (±)-**18d**, colorless oil. Data for (±)-**18d**: ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.0–6.9 (m, 2H arom); 5.45 (d, 1H, $^3J(H_6,H_7)$=11 Hz, H–C(6)); 4.98 (q, 1H, $^3J(H_{1'}–H_{2'})$=6.7 Hz, H–C(1′)); 4.43 (d, 1H, $^3J(H_4,H_3)$=9.9 Hz, H–C(4)); 4.35 (s, 1H, H_1); 4.21 (dq, 1H, $^3J(H_7,H_6)$=11 Hz, $^3J(H_7,H_8)$=6.7 Hz, H–C(7)); 3.7, 3.09 (2 sept. 2H, $^3J((CH_3)_2CH$-Ar, $(CH_3)_2CH$-Ar)=6.7 Hz, 2 $(CH_3)_2CH$-Ar); 2.9 (s, 3H, $–SO_2CH_3$); 2.87 (m, 1H, $(CH_3)_2CH$-Ar); 2.87 (m, 1H, H–C(3)); 1.91 (d, 3H, $^4J(Me_5–H_6)$=1.3 Hz, Me-C(5)); 1.52 (d, 3H, $^3J(Me_{2'}–H_{1'})$=6.7 Hz, Me(2′)); 1.43

(d, 3H, $^3J(Me_8,H_7)=6.7$ Hz, Me-C(8)); 1.27–1.19 (m, 3H, 3 $(CH_3)_2CH$-Ar); 1.15 (d, 3H, $^3J(Me_3,H_3)=6.7$ Hz, Me-C(3)). ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 211.9 148.0, 147.5, 145.8, 141.6, 135.0, 123.1, 120.4, 121.8, 84.6, 73.7, 68.0, 58.2, 46.7, 36.8, 34.0, 29.6, 29.2, 24.99, 24.56, 24.05, 23.9, 21.4, 14.5, 14.2, 10.46. CI-MS (NH_3): 512 (36, $[M+18]^+$), 479 (6), 231 (100), 189 (3), 167 (8.29), 141 (17), 84 (26).

4.2.4. 6:1 Mixture of (±)-(2*RS*,3*RS*,4*Z*,6*SR*)-3-hydroxy-6-[(3-hydroxy-2-methylpropen-2-yl)sulfonyl]-2,4-dimethyl-1-(2,4,6-trimethoxyphenyl)hept-4-en-1-one (±)-18e and (±)-(2*RS*,3*SR*,4*Z*,6*RS*)-3-hydroxy-6-[(3-hydroxy-2-methylpropen-2-yl)sulfonyl]-2,4-dimethyl-1-(2,4,6-trimethoxyphenyl)hept-4-en-1-one (±)-19e. This preparation followed the above general procedure using (*E*,*E*)-2-methyl-1-trimethylsilyloxy-1,3-pentadiene (580 mg, 3.41 mmol, 1 equiv) and trimethyl{[(1*E*)-1-(2,4,6,-trimethoxyphenyl)prop-1-enyl]oxy}silane (1.7 g, 5.8 mmol, 1.7 equiv). The reaction mixture was quenched with a 1 M solution of Bu_4NF in THF (3.41 mL, 3.41 mmol, 1 equiv) and 3-bromo-2-methylpropene (1.15 g, 0.86 mL, 8.52 mmol, 2.5 equiv) in CH_2Cl_2 (5 mL). Crude reaction mixture contains (±)-**18e** and (±)-**19e** with the ratio 6:1. FC (light petroleum ether/EtOAc 1:1, $R_f=0.33$) gives 0.95 g (82%) of 6:1 mixture of (±)-**18e** and (±)-**19e** as a yellowish oil. Only (±)-**18e** can be analyzed from the spectra of the mixture. UV (CH_3CN): $\lambda_{max}=224$ nm ($\varepsilon=13737$), 200.6 (9177). IR (film): ν 3410, 2980, 2940, 2840, 1670, 1605, 1455, 1415, 1300, 1205, 1160, 1000, 900, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) of (±)-**18e**: δ 6.12 (s, 2H, H–C(ar)), 5.26 (br s, 1H, H–C(3′)), 5.18 (d, 1H, $^3J(H_5–H_6)=9.6$ Hz, H–C(5)), 5.11 (br s, 1H, H–C(3′)), 4.80 (d, 1H, $^3J(H_3–H_2)=7.0$ Hz, H–C(3)), 4.43 (dq, 1H, $^3J(H_6–H_5)=9.6$ Hz, $^3J(H_6–H_7)=7.0$ Hz, H–C(6)), 3.83 (s, 3H, H–OMe), 3.79 (s, 6H, H–OMe), 3.71 (d, 1H, $^2J=13.4$ Hz, Ha–C(1′)), 3.64 (d, 1H, $^2J=13.4$ Hz, Hb–C(1′)), 3.28 (qd, 1H, $^3J(H_2–Me_2)=(H_2–H_3)=7.0$ Hz, H–C(2)), 2.73 (br s, 1H, H–OH)), 1.98 (s, 3H, Me-C(4)), 1.84 (s, 3H, Me-C(2′)), 1.49 (d, 3H, $^3J(H_7–H_6)=7.0$ Hz, H–C(7)), 1.23 (d, 3H, $^3J(Me_2–H_2)=7.1$ Hz, Me-C(2)). ^{13}C NMR (100.6 MHz, $CDCl_3$) of (±)-**18e**: δ 206.0 (s, CO), 162.6–158.4 (s, 4Car), 145.4 (s, C(2′)), 133.2 (s, C(4)), 122.8 (t, $^1J(C,H)=162$ Hz, C(3′)), 119.4 (d, $^1J(C,H)=159$ Hz, C(5)), 90.8 and 90.6 (d, 2C, $^1J(C,H)=159$ Hz, C(ar)), 70.8 (t, $^1J(C,H)=144$ Hz, C(1′)), 58.1 (d, $^1J(C,H)=134$ Hz, C(3)), 55.9 (d, $^1J(C,H)=140$, Hz C(6)), 55.6 (q, $^1J(C,H)=145$ Hz, C(OMe)), 51.1 (d, $^1J(C,H)=131$ Hz, C(2)), 23.1 (q, $^1J(C,H)=129$ Hz, Me-C(2′)), 19.2 (q, $^1J(C,H)=130$ Hz, Me-C(4)), 14.7 (q, $^1J(C,H)=131$ Hz, C(7)), 12.4 (q, $^1J(C,H)=130$ Hz, Me-C(2)). CI-MS (NH_3): $C_{22}H_{32}O_7S$: *m*/*z* 441 (62, $[M+1]^+$), 225 (100). Anal. Calcd for $C_{28}H_{50}O_3Si_2$ (440.19): C, 59.98; H, 7.32. Found: C, 59.83; H, 7.29.

4.2.5. 9:1 Mixture of (±)-(2*RS*,3*RS*,4*E*,6*RS*)-3-{[(*tert*-butyl)dimethylsilyl]oxy}-6-[(2-methylprop-2-enyl) sulfonyl]-2,4-dimethyl-1-(2,4,6-trimethoxyphenyl)hept-4-en-1-one ((±)-18f) and (±)-(2*RS*,3*RS*,4*E*,6*SR*)-3-{[(*tert*-butyl)dimethylsilyl]oxy}-6-[(2-methylprop-2-enyl) sulfonyl]-2,4-dimethyl-1-(2,4,6-trimethoxyphenyl)hept-4-en-1-one ((±)-19f). This preparation followed the above general procedure using from (*E*,*E*)-2-methyl-1-trimethylsilyloxy-1,3-pentadiene (580 mg, 3.41 mmol, 1 equiv) and trimethyl{[(1*E*)-1-(2,4,6,-trimethoxyphenyl)prop-1-enyl]oxy}silane (1.7 g, 5.8 mmol, 1.7 equiv) in CH_2Cl_2 (3 mL). The reaction mixture was quenched with a 1 M solution of Bu_4NF in THF (3.41 mL, 3.41 mmol, 1 equiv) and 3-bromo-2-methylpropene (1.15 g, 0.86 mL, 8.52 mmol, 2.5 equiv) in CH_2Cl_2 (5 mL). Then 2,6-lutidine (1.82 g, 1.97 mL, 17.05 mmol, 5 equiv) followed by TBSOTf (2.69 g, 2.35 mL, 10.23 mmol, 3 equiv) were added to the resulting residue stirred at −78 °C (1.49 g, 3.41 mmol, 1 equiv) in anhyd CH_2Cl_2 (10 mL). After 2 h at −78 °C, the crude reaction mixture was allowed to warm to room temperature within 1 h. The mixture was then treated with 2 M aqueous solution of NaOH (2 mL) and extracted with CH_2Cl_2 (40 mL, three times). The combined organic extracts were washed with 1 M HCl (20 mL) and with brine (40 mL, twice), dried (Na_2SO_4) and the solvent eliminated under reduced pressure. Crude reaction mixture contains (±)-**18f** and (±)-**19f** with the ratio 9:1. FC (light petroleum ether/EtOAc 4:2, $R_f=0.30$) gives 1.14 g (60%) of a 9:1 mixture of (±)-**18f** and (±)-**19f** as a yellow oil. Both diastereoisomers can be analyzed from the specta of the mixture. UV (CH_3CN): $\lambda_{max}=209$ nm ($\varepsilon=7924$). IR (film): ν 2987, 1694, 1606, 1456, 1421, 1305, 1266, 1157, 1132, 898, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) of (±)-**18f**: δ 6.09 (s, 2H, Har), 5.54 (d, 1H, $^3J(H_5–H_6)=10.5$ Hz, H–C(5)), 5.26 (br s, 1H, H–C(3′)), 5.05 (br s, 1H, H–C(3′)), 4.58 (d, 1H, $^3J(H_3–H_2)=6.2$ Hz, H–C(3)), 3.92 (dq, 1H, $^3J(H_6–H_5)=10.5$ Hz, $^3J(H_6–H_7)=7.1$ Hz, H–C(6)), 3.82 (s, 3H, H–O*Me*), 3.77 (s, 6H, H–O*Me*), 3.59 (d, 1H, $^2J=12.1$ Hz, Ha–C(1′)), 3.57 (d, 1H, $^2J=12.1$ Hz, Hb–C(1′)), 3.2 (qd, 1H, $^3J(H_2–Me_2)=7.4$ Hz, $^3J(H_2–H_3)=6.2$ Hz, H–C(2)), 1.97 (s, 3H, *Me*-C(4)), 1.73 (s, 3H, *Me*-C(2′)), 1.42 (d, 3H, $^3J(H_7–H_6)=7.1$ Hz, H–C(7)), 1.11 (d, 3H, $^3J(Me_2–H_2)=7.4$ Hz, *Me*-C(2)). ^{13}C NMR (100.6 MHz, $CDCl_3$) of (±)-**18f**: δ 209.2 (s, CO), 162.3–158.4 (s, 4C, C(ar)), 144.4 (s, C(2′)), 133.1 (s, C(4)), 120.4 (t, $^1J(C,H)=149$ Hz, C(3′)), 117.9 (d, $^1J(C,H)=161$ Hz, C(5)), 90.6 and 90.5 (d, 2C, $^1J(C,H)=161$ Hz, C(ar)), 70.4 (t, $^1J(C,H)=154$ Hz, C(1′)), 58.1 (d, $^1J(C,H)=148$ Hz, C(3)), 56.9 (d, $^1J(C,H)=133$ Hz, C(6)), 55.6 (q, $^1J(C,H)=151$ Hz, C(O*Me*)), 51.6 (d, $^1J(C,H)=146$ Hz, C(2)), 25.8 (q, $^1J(C,H)=142$ Hz, *t*-Bu), 23.1 (q, $^1J(C,H)=133$ Hz, *Me*-C(2′)), 18.3 (q, $^1J(C,H)=132$ Hz, *Me*-C(4)), 15.1 (s, Cquat-*t*Bu)), 14.6 (q, $^1J(C,H)=131$ Hz, *Me*-C(6)), 12.6 (q, $^1J(C,H)=139$ Hz, *Me*-C(2)), −4.2 (q, $^1J(C,H)=127$ Hz, Me_2Si–C(3)), −5.0 (q, $^1J(C,H)=129$ Hz, Me_2Si–C(3)). ^1H NMR (400 MHz, $CDCl_3$) of (±)-**19f**: δ 6.09 (s, 2H, H–C(ar)), 5.54 (d, 1H, $^3J(H_5–H_6)=10.5$ Hz, H–C(5)), 5.21 (br s, 1H, H–C(3′)), 5.14 (br s, 1H, H–C(3′)), 4.80 (d, 1H, $^3J(H_3–H_2)=7.6$ Hz, H–C(3)), 4.4 (qd, 1H, $^3J(H_6–H_5)=10.5$ Hz, $^3J(H_6–H_7)=6.5$ Hz, H–C(6)), 3.82 (s, 3H, H–O*Me*), 3.77 (s, 6H, H–O*Me*), 3.56 (d, 1H, $^2J=12.7$ Hz, H–C(1′)), 3.54 (d, 1H, $^2J=12.7$ Hz, H–C(1′)), 3.2 (dq, 1H, $^3J(H_2–Me_2)=7.4$ Hz, $^3J(H_2–H_3)=6.5$ Hz, H–C(2)), 2.01 (s, 3H, *Me*-C(4)), 1.82 (s, 3H, *Me*-C(2′)), 1.37 (d, 3H, $^3J(H_7–H_6)=6.5$ Hz, H–C(7)), 1.11 (d, 3H, $^3J(Me_2–H_2)=7.4$ Hz, *Me*-C(2)). ^{13}C NMR (100.6 MHz, $CDCl_3$) of (±)-**19f**: δ 209.1 (s, CO), 162.3–158.4 (s, 4C, C(ar)), 145.6 (s, C(2′)), 133.3 (s, C(4)) 120.6 (t, $^1J(C,H)=146$ Hz, C(3′)), 117.9 (d, $^1J(C,H)=161$ Hz, C(5)), 90.6 and 90.5 (d, 2C, $^1J(C,H)=161$ Hz, C(ar)), 70.4 (t, $^1J(C,H)=154$ Hz, C(2′)), 57.6 (d, $^1J(C,H)=143$ Hz, C(3)), 56.7 (d, $^1J(C,H)=131$ Hz, C(6)), 55.6 (q, $^1J(C,H)=151$ Hz, C(O*Me*)), 53.4 (d,

^1J(C,H)=139 Hz, C(2)), 25.8 (q, ^1J(C,H)=142 Hz, *t*-Bu), 23.2 (q, ^1J(C,H)=130 Hz, *Me*-C(2′)), 18.2 (q, ^1J(C,H)=129 Hz, *Me*-C(4)), 15.4 (q, ^1J(C,H)=128 Hz, *Me*-C(6)), 15.0 (s, Cquat-*t*Bu), 13.8 (q, ^1J(C,H)=132 Hz, *Me*-C(2)), −4.7 (q, ^1J(C,H)=126 Hz, *Me*Si–C(3)), −5.3 (q, ^1J(C,H)=129 Hz, *Me*Si–C(3)). CI-MS (NH_3): $C_{28}H_{46}SSiO_7$, *m/z* 555 (25, $[M+1]^+$), 108 (100). Anal. Calcd for $C_{28}H_{46}O_7SSi$ (554.27): C, 60.62; H, 8.36. Found: C, 60.80; H, 8.49.

4.3. General procedure for the preparation of oxo-(*E*)-β,γ-unsaturated sulfones (20,21) using enoxysilanes

Same procedure for the preparation of **18**, **19**, but using 0.5 equiv of Tf_2NH introduced to the $SO_2+CH_2Cl_2$ solution as a 0.5 M solution in anhyd CH_2Cl_2.

4.3.1. 1:1 Mixture of (±)-(3*RS*,4*RS*,5*E*,7*RS*)-4-hydroxy-7-(2-methyl-propyl-1-sulfonyl)-3,5-dimethyloct-5-en-2-one and ((±)-20a) (±)-(3*RS*,4*SR*,5*E*,7*SR*)-4-hydroxy-7-(2-methyl-propyl-1-sulfonyl)-3,5-dimethyloct-5-en-2-one ((±)-21a). This preparation applies the above procedure using a 1:1 mixture of (*E*) and (*Z*)- 2-triethylsilyloxybut-2-ene (7.92 g, 43 mmol, 2 equiv), (*E*,*E*)-2-methyl-1-trimethylsilyloxypenta-1,3-diene (4 g, 21.25 mmol, 1 equiv) and 1-iodo-2-methylpropane (4.84 g, 26.3 mmol, 5 equiv) in CH_3CN (15 mL) DMF (55 mL). FC (light petroleum ether/EtOAc 7:3, R_f=0.31) gave 6.7 g (82%), colorless oil. UV (CH_3CN): λ=219 nm (ε=5800). IR (film, cm^{-1}): ν 3470, 2970, 2930, 2855, 1710, 1650, 1460, 1340, 1285, 1195, 1135, 1040, 740. ^{1}H NMR (400 MHz, $CDCl_3$, 283 K) of (±)-**20a**: δ 5.58 (d, 1H, $^3J(H_6,H_7)$=10.3 Hz, H–C(6)), 4.46 (m, 2H, H–C(4)), 3.87 (dq, 1H, $^3J(H_7,H_6)$=10.3 Hz, $^3J(H_7,H_8)$=7.1 Hz, H–C(7)), 3.15 (d, 1H, $^3J(H_4,OH)$=2.6 Hz, H–OH), 2.77 (m, 3H, H–C(1′), H–C(3)), 2.41 (tqq, 1H, $^3J(H_{2'},H_{1'})$=6.4 Hz, $^3J(H_{2'},H_{3'a})$=6.4 Hz, $^3J(H_{2'},H_{3'b})$=6.4 Hz, H–C(2′)), 2.26 (s, 3H, H–C(1)), 1.87 (s, 3H, *Me*-C(5)), 1.50 (d, 3H, $^3J(H_8,H_7)$=7.1 Hz, H–C(8)), 1.16 (d, 3H, $^3J(Me_3,H_3)$=6.4 Hz, *Me*-C(3)), 1.15 (d, 3H, $^3J(H_{3'},H_{2'})$=6.4 Hz, H–C(3′)), 1.13 (d, 3H, $^3J(H_{3'},H_{2'})$=6.4 Hz, H–C(3′)). ^{13}C NMR (100 MHz, $CDCl_3$, 283K) of (±)-**20a**: δ 211.2 (s, C(2)), 142.7 (s, C(5)), 121.1 (d, ^1J(C,H)=155 Hz, C(6)), 75.2 (d, ^1J(C,H)=140 Hz, C(7)), 64.1 (d, ^1J(C,H)=130 Hz, C(3)), 58.9 (d, ^1J(C,H)=142 Hz, C(4)), 56.9 (t, ^1J(C,H)=136 Hz, C(1′)), 49.5 (d, ^1J(C,H)=135 Hz, C(2′)), 29.4 (q, ^1J(C,H)=129 Hz, C(1)), 23.5 (q, ^1J(C,H)=140 Hz, *Me*-C(5)), 23.3 (q, ^1J(C,H)=134 Hz, C(8)), 15.3 (q, ^1J(C,H)=131 Hz, *Me*-C(3)), 14.2 (q, ^1J(C,H)=132 Hz, C(3′)), 14.1 (q, ^1J(C,H)=133 Hz, C(3′)). ^{1}H NMR (400 MHz, $CDCl_3$, 283 K) of (±)-**21a**: δ 5.57 (d, 1H, $^3J(H_6,H_7)$=10.3 Hz, H–C(6)), 4.46 (m, 2H, H–C(4)), 3.86 (dq, 1H, $^3J(H_7,H_6)$=10.3 Hz, $^3J(H_7,H_8)$=7.1 Hz, H–C(7)), 3.08 (d, 1H, $^3J(H_4,OH)$=2.6 Hz, H–OH), 2.77 (m, 3H, H–C(1′), H–C(3)), 2.41 (tqq, 1H, $^3J(H_{2'},H_{1'})$=6.4 Hz, $^3J(H_{2'},H_{3'a})$=6.4 Hz, $^3J(H_{2'},H_{3'b})$=6.4 Hz, H–C(2′)), 2.24 (s, 3H, H–C(1)), 1.86 (s, 3H, *Me*-C(5)), 1.48 (d, 3H, $^3J(H_8,H_7)$=7.1 Hz, H–C(8)), 1.16 (d, 3H, $^3J(Me,H_3)$=6.4 Hz, *Me*-C(3)), 1.15 (d, 3H, $^3J(H_{3'},H_{2'})$=6.4 Hz, H–C(3′)), 1.13 (d, 3H, $^3J(H_{3'},H_{2'})$=6.4 Hz, H–C(3′)). ^{13}C NMR (100 MHz, $CDCl_3$, 283K) of (±)-**21a**: δ 211.1 (s, C(2)), 142.2 (s, C(5)), 119.5 (d, ^1J(C,H)=150 Hz, C(6)), 74.3 (d, ^1J(C,H)=148 Hz, C(7)), 63.9 (d, ^1J(C,H)=130 Hz, C(3)), 58.5 (d, ^1J(C,H)=141 Hz, C(4)), 56.7 (t, ^1J(C,H)=132 Hz, C(1′)), 49.1 (d, ^1J(C,H)=140 Hz, C(2′)), 29.3 (q, ^1J(C,H)=133 Hz, C(1)), 23.4 (q, ^1J(C,H)=133 Hz, *Me*-C(5)), 23.2 (q, ^1J(C,H)=136 Hz, C(8)), 14.9 (q, ^1J(C,H)=132 Hz, *Me*-C(3)), 10.7 (q, ^1J(C,H)=129 Hz, C(3′)), 9.8 (q, ^1J(C,H)=130 Hz, C(3′)). MALDI-HRMS: calcd for $C_{14}H_{26}O_4S+K^+$: 329.1189 and $C_{14}H_{26}O_4S+Na^+$: 313.1449, found: 313.2285. Anal. Calcd for $C_{14}H_{26}O_4S$ (290.16): C, 57.90; H, 9.02. Found: C, 57.86; H, 9.02.

4.3.2. 9:1 Mixture of (±)-(2*RS*,3*RS*,4*E*,6*RS*)-3-{[(*tert*-butyl)dimethylsilyl]oxy}-6-[(2-methylprop-2-enyl) sulfonyl]-2,4-dimethyl-1-(2,4,6-trimethoxyphenyl)hept-4-en-1-one ((±)-20b) and (±)-(2*RS*,3*RS*,4*E*,6*SR*)-3-{[(*tert*-butyl)dimethylsilyl]oxy}-6-[(2-methylprop-2-enyl) sulfonyl]-2,4-dimethyl-1-(2,4,6-trimethoxyphenyl)hept-4-en-1-one ((±)-21b). This preparation followed the above general procedure and used **16c**[49] (1.7 g, 5.8 mmol, 1.7 equiv), (*E*,*E*)-2-methyl-1-[(*tert*-butyl)dimethylsilyl]-oxy-penta-1,3-diene **17d**[33b,51] (580 mg, 3.41 mmol, 1 equiv) and 3-bromo-2-methylpropene (1.15 g, 0.86 mL, 8.52 mmol, 2.5 equiv) in CH_2Cl_2 (5 mL). This provided a mixture of alcohols that was treated with 2,6-lutidine (1.82 g, 1.97 mL, 17.05 mmol, 5 equiv) and by TBSOTf (2.7 g, 2.35 mL, 10.23 mmol, 3 equiv) at −78 °C (1.49 g, 3.41 mmol, 1 equiv) in anhyd CH_2Cl_2 (10 mL). for 1 h. The mixture was then treated with 2 M aq soln of NaOH (2 mL) and extracted with CH_2Cl_2 (40 mL, three times). The combined organic extracts were washed with 1 M HCl (20 mL) and with brine (40 mL, twice), dried (Na_2SO_4) and the solvent was eliminated under reduced pressure. The residue contained α,β-*syn* and α,β-*anti* diastereoisomers (±)-**20c** and (±)-**21c** with the ratio 9:1. FC (light petroleum ether/EtOAc 4:2, R_f=0.30) gave 1.14 g (60%) of a 9:1 mixture of (±)-**20c** and (±)-**21c**, yellow oil. UV (CH_3CN): λ_{max}=209 nm (ε=7924). IR (film): ν 2987, 1694, 1606, 1456, 1421, 1305, 1265, 1155, 1130, 900, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) of (±)-**20c**: δ 6.09 (s, 2H, Har), 5.54 (d, 1H, $^3J(H_5,H_6)$=10.5 Hz, H–C(5)), 5.26 (br s, 1H, H–C(3′)), 5.05 (br s, 1H, H–C(3′)), 4.58 (d, 1H, $^3J(H_3,H_2)$=6.2 Hz, H–C(3)), 3.92 (dq, 1H, $^3J(H_6,H_5)$=10.5 Hz, $^3J(H_6,H_7)$=7.1 Hz, H–C(6)), 3.82 (s, 3H, H–O*Me*), 3.77 (s, 6H, H–O*Me*), 3.59 (d, 1H, ^2J=12.1 Hz, Ha–C(1′)), 3.57 (d, 1H, ^2J=12.1 Hz, Hb–C(1′)), 3.2 (qd, 1H, $^3J(H_2,Me_2)$=7.4 Hz, $^3J(H_2,H_3)$=6.2 Hz, H–C(2)), 1.97 (s, 3H, *Me*-C(4)), 1.73 (s, 3H, *Me*-C(2′)), 1.42 (d, 3H, $^3J(H_7,H_6)$=7.1 Hz, H–C(7)), 1.11 (d, 3H, $^3J(Me_2,H_2)$=7.4 Hz, *Me*-C(2)). ^{13}C NMR (100.6 MHz, $CDCl_3$) of (±)-**20c**: δ 209.2 (s, CO), 162.3–158.4 (s, 4C, C(ar)), 144.4 (s, C(2′)), 133.1 (s, C(4)), 120.4 (t, ^1J(C,H)=149 Hz, C(3′)), 117.9 (d, ^1J(C,H)=161 Hz, C(5)), 90.6 and 90.5 (d, 2C, ^1J(C,H)=161 Hz, C(ar)), 70.4 (t, ^1J(C,H)=154 Hz, C(1′)), 58.1 (d, ^1J(C,H)=148 Hz, C(3)), 56.9 (d, ^1J(C,H)=133 Hz, C(6)), 55.6 (q, ^1J(C,H)=151 Hz, C(O*Me*)), 51.6 (d, ^1J(C,H)=146 Hz, C(2)), 25.8 (q, ^1J(C,H)=142 Hz, *t*-Bu), 23.1 (q, ^1J(C,H)=133 Hz, *Me*-C(2′)), 18.3 (q, ^1J(C,H)=132 Hz, *Me*-C(4)), 15.1 (s, Cquat-*t*Bu)), 14.6 (q, ^1J(C,H)=131 Hz, *Me*-C(6)), 12.6 (q, ^1J(C,H)=139 Hz, *Me*-C(2)), −4.2 (q, ^1J(C,H)=127 Hz, *Me*$_2$Si–C(3)), −5.0 (q, ^1J(C,H)=129 Hz, *Me*$_2$Si–C(3)). ^{1}H NMR (400 MHz, $CDCl_3$) of (±)-**21c**: δ 6.09 (s, 2H, H–C(ar)), 5.54 (d, 1H, $^3J(H_5,H_6)$=10.5 Hz, H–C(5)), 5.21 (br s, 1H, H–C(3′)), 5.14 (br s, 1H, H–C(3′)), 4.80 (d, 1H, $^3J(H_3,H_2)$=7.6 Hz,

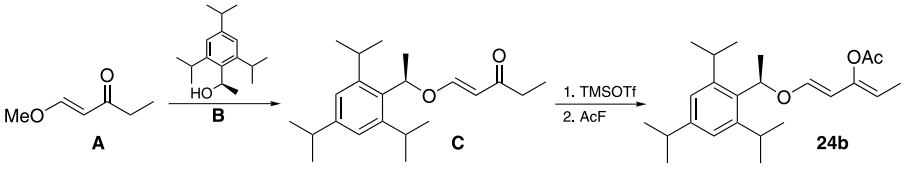
H–C(3)), 4.4 (qd, 1H, $^3J(H_6,H_5)=10.5$ Hz, $^3J(H_6,H_7)=6.5$ Hz, H–C(6)), 3.82 (s, 3H, H–O*Me*), 3.77 (s, 6H, H–O*Me*), 3.56 (d, 1H, $^2J=12.7$ Hz, H–C(1′)), 3.54 (d, 1H, $^2J=12.7$ Hz, H–C(1′)), 3.2 (dq, 1H, $^3J(H_2,Me_2)=7.4$ Hz, $^3J(H_2,H_3)=6.5$ Hz, H–C(2)), 2.01 (s, 3H, *Me*-C(4)), 1.82 (s, 3H, *Me*-C(2′)), 1.37 (d, 3H, $^3J(H_7,H_6)=6.5$ Hz, H–C(7)), 1.11 (d, 3H, $^3J(Me_2,H_2)=7.4$ Hz, *Me*-C(2)). ^{13}C NMR (100.6 MHz, $CDCl_3$) of (±)-**21c**: δ 209.1 (s, CO), 162.3–158.4 (4s, C(ar)), 145.6 (s, C(2′)), 133.3 (s, C(4)) 120.6 (t, $^1J(C,H)=146$ Hz, C(3′)), 117.9 (d, $^1J(C,H)=161$ Hz, C(5)), 90.6 and 90.5 (d, 2C, $^1J(C,H)=161$ Hz, C(ar)), 70.4 (t, $^1J(C,H)=154$ Hz, C(2′)), 57.6 (d, $^1J(C,H)=143$ Hz, C(3)), 56.7 (d, $^1J(C,H)=131$ Hz, C(6)), 55.6 (q, $^1J(C,H)=151$ Hz, C(O*Me*)), 53.4 (d, $^1J(C,H)=139$ Hz, C(2)), 25.8 (q, $^1J(C,H)=142$ Hz, *t*-Bu), 23.2 (q, $^1J(C,H)=130$ Hz, *Me*-C(2′)), 18.2 (q, $^1J(C,H)=129$ Hz, *Me*-C(4)), 15.4 (q, $^1J(C,H)=128$ Hz, *Me*-C(6)), 15.0 (s, Cquat-*t*Bu), 13.8 (q, $^1J(C,H)=132$ Hz, *Me*-C(2)), −4.7 (q, $^1J(C,H)=126$ Hz, *Me*Si–C(3)), −5.3 (q, $^1J(C,H)=129$ Hz, *Me*Si–C(3)). CI-MS (NH_3): $C_{28}H_{46}SSiO_7$, *m/z* 555 (25, $[M+1]^+$), 108 (100). Anal. Calcd for $C_{28}H_{46}O_7SSi$ (554.27): C, 60.62; H, 8.36. Found: C, 60.80; H, 8.49.

4.3.3. Tributyl{2-[(tributylsilyl)methyl]prop-2-enyl}-silane (23c). A mixture of 3-chloro-2-(chloromethyl)prop-1-ene (0.84 mL, 7.93 mmol) and tributylsilyl chloride (4.30 mL, 16.00 mmol, 2 equiv) in anhyd THF (16 mL) was added dropwise (cannulated) to a stirred mixture of anhyd THF (16 mL), naphthalene (104 mg, 0.81 mmol, 0.1 equiv) and lithium shots (0.420 g, 60.51 mmol, 7.6 equiv) at −78 °C. The mixture was stirred overnight after removal of the cooling bath. The mixture was then treated with water (10 mL), extracted with ether (15 mL, three times), the organic phase dried ($MgSO_4$). The crude yellow liquid was distilled over CaH_2 under reduced pressure (0.2 mbar, $T=170$ °C) to yield 2.0 g (4.43 mmol, 56%) of a colorless oil. UV (CH_3CN): $\lambda_{max}=274$ ($\varepsilon=225$), 217 (5160), 200 (3990), 186 (330). IR (neat): 2955, 2920, 2870, 2860, 1620, 1465, 1410, 1375, 1340, 1295, 1275, 1195, 1160, 1080, 1030, 1000, 965, 885, 850, 790, 760, 730. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.37 (s, 2H, H–C(1)), 1.48 (s, 4H, H–C(3)), 1.35–1.24 (m, 24H, H–C(2′), H–C(3′)), 0.89 (t, 18H, $^3J=7.0$ Hz, H–C(4′)), 0.57–0.53 (m, 12H, H–C(1′)). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 145.4 (C(2)), 105.3 (C(1)), 26.8 (C(2′) or C(3′)), 26.1 (C(2′) or C(3′)), 17.8 (C(4′)), 12.2 (C(1′)). MS-CI (NH_3): 453 (1, [M+1]), 425 (1), 397 (2), 374 (4), 340 (4), 199 (49), 143 (100), 87 (29). Anal. Calcd for $C_{28}H_{60}Si_2$ (452.42): C, 74.25; H, 13.65; Si, 12.40. Found: C, 74.36; H, 13.26.

Diene **24b** was prepared according to the synthetic sequence shown below (Scheme 6).

4.3.4. (+)-(1*E*)-1-[1(*R*)-(2,4,6-triisopropylphenyl) ethoxy]pent-1-en-3-one (C). In a 25 mL round bottom flask were added successively (*E*)-1-methoxypent-1-en-3-one (**A**) (1.02 g, 8.93 mmol, 1.03 equiv), (*R*)-(+)-Greene's alcohol (**B**) (2.15 g, 8.65 mmol), pyridinium *p*-toluenesulfonic acid (0.024 g, 0.095 mmol, 1.1%) and toluene (0.5 mL). The flask was placed under vacuum (20 mbar, 30 °C) for 15 h. The mixture was purified by column chromatography (light petroleum ether/ether 4:1) to give 2.664 g (90%) of **C**, colorless solid. $[\alpha]_{589}^{25}+32$; $[\alpha]_{577}^{25}+37$; $[\alpha]_{546}^{25}+40$; $[\alpha]_{435}^{25}+98$; $[\alpha]_{405}^{25}+130$ (*c* 1.0, $CHCl_3$). $R_f=0.24$ (light petroleum ether/ether 4:1). UV (CH_3CN): $\lambda_{max}=261$ ($\varepsilon=7605$), 249 (8300), 225 (7060), 218 (6770), 203 (5400), 188 (1170). IR (KBr): ν 2960, 2930, 2870, 1680, 1660, 1635, 1610, 1590, 1460, 1380, 1360, 1225, 1190, 1110, 1060, 1030, 1000, 945, 880, 650. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 1H, $^3J=12.1$ Hz, H–C(1)), 7.02 (s, 2 arom CH), 5.67 (d, 1H, $^3J=12.1$ Hz, H–C(2)), 5.64 (q, 1H, $^3J=7.0$ Hz, H–C(1′)), 2.88 (sept, 1H, $^3J=6.8$ Hz, Me_2CH), 2.39 (q, 2H, $^3J=7.7$ Hz, H–C(4)), 1.71 (d, 3H, $^3J=7.0$ Hz, H–C(2′)), 1.31–1.22 (m, 20H, Me_2CH, Me_2CH), 1.06 (t, 3H, $^3J=7.7$ Hz, H–C(5)). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 200.3 (C(3)), 161.0 (C(1)), 148.5 (arom C), 131.3 (arom C), 122.2 (arom C), 106.7 (C(2)), 77.6 (C(1′)), 34.0 (Me_2CH), 29.3 (Me_2CH), 24.6, 24.4, 23.9, 23.8, 22.4, 8.5 (C(5)). MS-CI (NH_3): 331 (4, [M+1]), 231 (100), 215 (20), 189 (12), 147 (28), 131 (15), 91 (9). Anal. Calcd for $C_{22}H_{34}O_2$ (330.51): C, 79.95; H, 10.37; O, 9.68. Found: C, 79.80; H, 10.34.

4.3.5. 3:1 Mixture of (+)-(1*E*,3*E* and 1*E*,3*Z*,1*R*′)-1-[1′-(2,4,6-triisopropylphenylethoxy)]penta-1,3-dien-3-yl acetate (24b). To a solution of (+)-(1*E*)-1-[1-(1*R*)-(2,4,6-triisopropylphenyl)ethoxy]pent-1-en-3-one (**C**) (1.995 g, 6.04 mmol), in 22 mL of anhyd ether were added at −20 °C triethylamine (1.90 mL, 13.63 mmol, 2.25 equiv) and trimethylsilyl triflate (1.22 mL, 6.75 mmol, 1.11 equiv). The mixture was stirred at −20 °C for 2 h and 50 mL of precooled (−78 °C) pentane were added. The organic phase was extracted with a satd soln of aq $NaHCO_3$ (50 mL, three times), $CuSO_4$ (50 mL), brine (50 mL) and dried over Na_2SO_4 and concentrated under vacuum. To the crude mixture were added 4.6 mL of anhyd THF and acetyl fluoride (0.8 mL, 12.89 mmol) was transferred on the vacuum line to the THF frozen solution at −196 °C. The solution was warmed up to −20 °C and TBAF (1 M solution in THF, 0.1 mL) was added dropwise. The temperature was then rised to −15 °C and the reaction mixture was stirred overnight. THF was evaporated under vacuum. FC (light petroleum ether/ether 4:1): 1.35 g (3.62 mmol, 60%), unseparable 3:1 mixture of 1*E*,3*E* and 1*E*,3*ZE* geometric isomers of **24b**. $R_f=0.44$ (light petroleum ether/ether 9:1). UV (CH_3CN): $\lambda_{max}=250$ ($\varepsilon=8345$), 198 (4510), 189 (1100). IR (KBr): ν 2960, 2930, 2870, 1760, 1675, 1635, 1610, 1575, 1460, 1375, 1210,



Scheme 6.

1165, 1125, 1100, 1065, 1020, 910, 880, 840, 780, 650. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (s, 2 arom CH), 6.35 (d, 1H, ^3J=12.3 Hz, H–C(1) *E*,*Z*), 6.30 (d, 1H, ^3J=12.3 Hz, H–C(2) *E*,*E*), 5.67 (d, 1H, ^3J=12.3 Hz, H–C(1) *E*,*E*), 5.47 (d, 1H, ^3J=12.3 Hz, H–C(2) *E*,*Z*), 5.42 (q, 3H, ^3J=6.8 Hz, H–C(1′) *E*,*E*+*E*,*Z*), 5.04 (q, 1H, ^3J=7.4 Hz, H–C(4) *E*,*Z*), 4.94 (q, 1H, ^3J=7.4 Hz, H–C(4) *E*,*E*), 2.85 (sept, 2H, ^3J=6.8 Hz, Me_2CH *E*,*Z*+*E*,*E*), 2.08 (s, 3H, MeCO *E*,*Z*), 2.08 (s, 3H, MeCO *E*,*E*), 1.64 (d, 3H, ^3J=6.8 Hz, H–C(5) *E*,*E*), 1.62 (d, 3H, ^3J=6.8 Hz, H–C(5) *E*,*Z*), 1.53 (d, 3H, ^3J=6.8 Hz, H–C(2′) *E*,*E*), 1.49 (d, 3H, ^3J=6.8 Hz, H–C(2′) *E*,*Z*), 1.26–1.20 (m, 20H, Me_2CH, Me_2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 169.1 (CO), 148.1–147.8 (C(3), *E*,*Z*+*E*,*E*), 146.3 (C(1)), 144.8 (arom C), 144.0 (arom C), 132.2 (arom C), 122.2 (arom C), 110.4 (C(4)), 103.0 (C(2)), 75.6 (C(1′)), 34.0 (Me_2CH), 29.0 (Me_2CH), 24.5 (Me_2CH), 23.9, 23.8, 22.4 (C(2′)), 20.2 (MeCO)), 11.0 (C(5)). MS (EI): 372 (11, M), 305 (15), 245 (3), 231 (100), 215 (7), 147 (10), 91 (3). MS (EI): calcd for $C_{24}H_{36}O_3$: 372.2664; found: 372.2679.

4.4. General procedure for the preparation of methylidene (*Z*)-β,γ-unsaturated sulfonamides 26, 27 using allysilanes

A mixture of allyltrimethylsilane (0.12 mL, 0.61 mmol, 0.3 equiv) and 0.5 M bistrifluoromethanesulfonimide Tf_2NH in CH_2Cl_2 (1.21 mL, 0.61 mmol, 0.3 equiv) were mixed and stirred at 20 °C for 30 min. The mixture frozen at −196 °C (vacuum line, freeze/thaw cycles for degassing) and SO_2 (through a column of P_2O_5 and alumina) was transferred (9 mL). The mixture was allowed to melt at −78 °C. After 30 min at this temperature a mixture of allylsilane (**23a** or **23b**) (4 mmol, 2 equiv) and diene **24a** (2 mmol, 1.0 equiv) in anhyd CH_2Cl_2 (5 mL) was added. After stirring at −78 °C 16 h, the solvents were evaporated under vacuum to dryness (−78–20 °C, 1.5 h). The residue was taken in CH_3CN (10 mL) and a solution of *N*-chlorosuccinimide (1.35 g, 10.1 mmol, 5 equiv) in CH_3CN (10 mL) was added slowly under stirring at −40 °C. The mixture was stirred at −40 °C for 15 min, then for more 15 min at −30 °C. It was cannulated into a solution of $BnNH_2$ (2.16 g, 20.2 mmol) in pyridine (10 mL) under stirring at −30 °C. The mixture was stirred for 4 h at −20 °C, then 1 h at 0 °C, and 1.5 h at 20 °C. EtOAc (600 mL) was added and the solution washed with a satd aq soln of $CuSO_4$. The aq phase was separated and extracted with EtOAc (100 mL). The combined organic extracts were washed with satd aq soln of $NaHCO_3$ (100 mL), then with brine (100 mL), dried (Na_2SO_4). After solvent evaporation under vacuum, the residue was purifed by FC.

4.4.1. (−)-(1*E*,3*S*)-1-((1*S*)-1-((benzylamino)sulfonyl)ethyl)-2-methyl-3-((1*S*)-1-phenylethoxy)hexa-1,5-dien-1-yl benzoate ((−)-26a) and (−)-(1*E*,3*S*)-1-((1*R*)-1-((benzylamino)sulfonyl)ethyl)-2methyl-3-((1*S*)-1-phenylethoxy)hexa-1,5-dien-1-yl benzoate ((−)-27a).

A 1:1 mixture of (−)-**26a** and (−)-**27a** was prepared following the above procedure. FC (toluene/EtOAc 97:3) gave 0.202 g (19% of (−)-**26a**, R_f=0.37, toluene/EtOAc 9:1) and 0.208 g (20%) of (−)-**27a** (R_f=0.45, toluene/EtOAc 9:1). Compound (−)-**27a** was recrystallized from light petroleum ether and submitted to X-ray diffraction studies (Fig. 1). Data of (−)-**26a**: yellowish oil; $[\alpha]_{589}^{25}$−111; $[\alpha]_{577}^{25}$−94; $[\alpha]_{435}^{25}$−192; $[\alpha]_{405}^{25}$−247 (*c* 0.25, $CHCl_3$). IR (film): ν 3295, 3060, 2970, 2930, 2355, 1735, 1640, 1600, 1490, 1450, 1375, 1315, 1275, 1230, 1155, 1080, 1070. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, 2H, ^3J=7.7 Hz), 7.64 (t, 1H, ^3J=7.7 Hz), 7.50 ((t, 2H, ^3J=7.7 Hz), 7.39–7.35, 7.33–7.31, 7.28–7.24, 7.23–7.19, 7.05–7.03 (5m, 10H, H–C(Ar)), 5.68 (ddt, 1H, ^3J=17.3 Hz, 9.6, 7.4, H–C(5)), 5.05 (d, 1H, ^3J=17.3 Hz, Ha–C(6)), 5.03 (d, 1H, ^3J=9.6 Hz, Hb–C(6)), 4.71 (q, 1H, ^3J=6.4 Hz, H–C(1″)), 4.55 (m, 1H, H–N), 4.20 (dd, 1H, AB syst, ^2J=14.71, 5.8 Hz, Ha-PhCH_2), 4.10 (dd, 1H, AB syst, ^2J=14.7, 6.4 Hz, Hb-PhCH_2), 3.98 (q, 1H, ^3J=7.0 Hz, H–C(1′)), 3.98 (t, 1H, ^3J=7.0 Hz, H–C(3)), 2.47 (dt, 1H, ^2J=14.1 Hz, ^3J=7.0 Hz, Ha–C(4)), 2.35 (dt, 1H, ^2J=14.08 Hz, ^3J=7.0 Hz, Hb–C(4)), 1.69 (s, 3H, CH_3–C(2)), 1.41 (d, 3H, ^3J=6.4 Hz, H–C(2′)), 1.35 (d, 3H, ^3J=7.0 Hz, H–C(2″)). ^{13}C NMR (C_6D_6, 100.6 MHz): δ 164.9, 144.7, 138.8, 137.9, 137.3, 134.1, 132.3, 130.7, 129.3, 128.9, 128.7, 127.9, 118.3, 75.8, 75.2, 59.2, 47.7, 39.5, 30.11, 25.6, 13.7. MALDI-HRMS: calcd for $C_{31}H_{35}NO_5SK^+$ 572.1873; found: 572.1870. Anal. Calcd for $C_{31}H_{35}NO_5S$ (533.22): C, 69.77; H, 6.61; N, 2.62; O, 14.99; S, 6.01. Found: C, 69.69; H, 6.69; N, 2.75; O, 14.90; S, 5.97. Data of (−)-**27a**: white crystals, mp 97–99 °C. $[\alpha]_{589}^{25}$−56; $[\alpha]_{577}^{25}$−57; $[\alpha]_{435}^{25}$−106; $[\alpha]_{405}^{25}$−125 (*c* 0.5, $CHCl_3$). IR (KBr): ν 3295, 3060, 2970, 2930, 2355, 1735, 1640, 1600, 1490, 1450, 1375, 1315, 1275, 1230, 1155, 1080, 1070. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, 2H, ^3J=7.7 Hz), 7.66 (t, 1H, ^3J=7.7 Hz), 7.52 ((t, 2H, ^3J=7.7 Hz), 7.42–7.34, 7.35–7.33, 7.31–7.28, 7.23–7.24, 7.22–7.21 (5m, 10H, H–C(Ar)), 5.91 (ddt, 1H, ^3J=17.3, 10.2, 7.0 Hz, H–C(5)), 5.13 (dd, 1H, ^3J=17.3 Hz, ^2J=3.5 Hz, Ha–C(6)), 5.10 (dd, 1H, ^3J=10.3 Hz, ^2J=3.5 Hz, Hb–C(6)), 4.51 (m, 1H, H–C(1″)), 4.51 (d, 1H, ^3J=5.8 Hz, H–N), 4.16 (dd, 1H, AB syst, ^2J=14.1, 5.8 Hz, Ha-PhCH_2), 4.05 (dd, 1H, AB syst, ^2J=14.1, 5.8 Hz, Hb-PhCH_2), 4.06 (dd, 1H, ^3J=7.0, 2.9 Hz, H–C(3)), 3.69 (q, 1H, ^3J=6.4 Hz, H–C(1′)), 2.54 (ddd, 1H, ^2J=14.4 Hz, ^3J=9.9, 7.0 Hz, Ha–C(4)), 2.41 (ddd, 1H, ^2J=14.4 Hz, ^3J=7.0, 2.9 Hz, Hb–C(4)), 1.69 (s, 3H, CH_3–C(2)), 1.45 (d, 3H, ^3J=6.4 Hz, H–C(2′)), 1.44 (d, 3H, ^3J=5.1 Hz, H–C(2″)). ^{13}C NMR (C_6D_6, 100.6 MHz): δ 164.9, 144.6, 139.2, 137.9, 136.3, 133.9, 132.7, 130.8, 129.1, 129.0, 128.9, 127.1, 117.3, 74.6, 74.5, 58.7, 47.8, 38.6, 25.5, 13.0, 11.5. MALDI-HRMS: calcd for $C_{31}H_{35}NO_5SK^+$ 572.1873; found: 572.1879. Anal. Calcd for $C_{31}H_{35}NO_5S$ (533.22): C, 69.77; H, 6.61; N, 2.62; O, 14.99; S, 6.01. Found: C, 69.75; H, 6.61; N, 2.59; O, 14.99; S, 6.06.

4.4.2. (−)-(1*E*,3*S*)-5-((acetyloxy)methyl)-1-((1*S*)-1-((benzylamino)sulfonyl)ethyl)-2-methyl-3-((1*S*)-1-phenylethoxy)hexa-1,5-dien-1-yl benzoate ((−)-26b) and (−)-(1*E*,3*S*)-5-((acetyloxy)methyl)-1-((1*R*)-1-((benzylamino)sulfonyl)ethyl)-2-methyl-3-((1*S*)-1-phenylethoxy)hexa-1,5-dien-1-yl benzoate ((−)-27b).

A 1:1 mixture of a (−)-**26b** and (−)-**27b** was obtained applying the above procedure and using (2-acetoxy)allyltrimethylsilane[54] (**23b**, 5 g, 26.8 mmol, 2 equiv) and diene (−)-**24a** (4.3 g, 13.4 mmol). FC (toluene/EtOAc 95:5) gave (−)-**26b**, R_f=0.29 (2.85 g, 35%) and (−)-**27b**, R_f=0.38 (toluene/EtOAc 9:1) (2.85 g, 35%). Their structures were established by their transformation into the cyclic derivatives (−)-**30** and (−)-**31** (see below). Data of (−)-**26b**: colorless oil. $[\alpha]_{589}^{25}$−32; $[\alpha]_{577}^{25}$−34; $[\alpha]_{435}^{25}$−64;

$[\alpha]_{405}^{25}$ −77 (*c* 1.0, $CHCl_3$). IR (film): *ν* 3060, 3030, 2970, 2925, 1735, 1730, 1600, 1490, 1450, 1375, 1325, 1275, 1235, 1150, 1085, 1065. ^{1}H NMR ($DMSO_{d\text{-}6}$, 400 MHz, +80 °C): *δ* 8.12 (dm, 2H, ^3J=8.0 Hz, H–C(Bz)), 7.72 (t, 1H, ^3J=7.5 Hz, H–C(Bz)), 7.58 (t, 2H, ^3J=7.5 Hz, H–C(Bz)), 7.39–7.22 (5m, 10H, H–C(Ar)), 5.08, 5.03 (2 br s, 2H, H–C(6)), 4.60, 4.53 (2d, 2H, AB syst, ^2J=13.7 Hz, AcOCH_2–C(5)), 4.50 (q, 1H, ^3J=6.5 Hz, H–C(1″)), 4.15 (t, 1H, ^3J=6.1 Hz, H–C(3)), 4.04, 3.95 (2dd, 2H, AB syst, ^2J=15.1 Hz, ^3J=6.2 Hz, PhCH_2–N), 3.66 (q, 1H, ^3J=6.9 Hz, H–C(1′)), 3.61–3.39 (br s, 1H, NH), 2.41 (d, 2H, ^3J=6.5 Hz, H–C(4)), 2.02 (s, 3H, CH_3COOCH_2–C(5)), 1.64 (s, 3H, CH_3–C(2)), 1.38 (d, 3H, ^3J=6.5 Hz, H–C(2″)), 1.31 (d, 3H, ^3J=6.9 Hz, CH_3–C(2′)). ^{13}C NMR ($DMSO_{d\text{-}6}$, 100.6 MHz, +80 °C): *δ* 169.1, 163.1, 142.6, 141.0, 138.2, 137.8, 133.2, 130.3, 129.2, 128.2, 127.7, 127.6, 127.0, 126.8, 126.5, 125.8, 113.0, 110.7, 73.3, 73.1, 65.8, 57.3, 46.0, 36.2, 23.6, 19.8, 11.6, 10.3. MALDI-HRMS: calcd for $C_{34}H_{39}NO_7SNa^+$ 628.2345; found: 628.2349. Anal. Calcd for $C_{34}H_{39}NO_7S$ (605.74): C, 67.42; H, 6.49; N, 2.31; S, 5.29. Found: C, 67.35; H, 6.63; N, 2.33; S, 5.33. Data of (−)-**27b**: colorless oil. $[\alpha]_{589}^{25}$ −114; $[\alpha]_{577}^{25}$ −123; $[\alpha]_{435}^{25}$ −246; $[\alpha]_{405}^{25}$ −301 (*c* 0.5, $CHCl_3$). IR (film): *ν* 3060, 3030, 2970, 2925, 1735, 1600, 1490, 1450, 1375, 1325, 1275, 1235, 1150, 1085, 1065. ^{1}H NMR (C_6D_6, 400 MHz, +70 °C): *δ* 8.23 (dm, 2H, ^3J=7.7 Hz, H–C(Bz)), 7.52 (d, 2H, ^3J=6.8 Hz, H–C(Ar)), 7.21–7.02 (m, 11H, H–C(Ar)), 5.06, 5.03 (2 br s, 2H, H–C(6)), 4.86 (q, 1H, ^3J=6.5 Hz, H–C(1′)), 4.54, 4.45 (2d, 2H, AB syst, ^2J=13.6 Hz, AcOCH_2–C(5)), 4.45 (q, 1H, ^3J=6.5 Hz, H–C(1″)), 4.36 (t, 1H, ^3J=6.5 Hz, H–C(3)), 4.14 (br t, 1H, ^3J=5.9 Hz, NH), 4.05 (m, 2H, PhCH_2–N), 2.56 (dd, 1H, AB syst, ^2J=13.6 Hz, ^2J=7.4 Hz, Ha–C(4)), 2.40 (dd, 1H, AB syst, ^2J=13.6 Hz, ^2J=6.2 Hz, Ha–C(4)), 1.74 (s, 3H, CH_3COOCH_2–C(5)), 1.68 (s, 3H, CH_3–C(2)), 1.45 (d, 3H, ^3J=6.8 Hz, H–C(2″)), 1.40 (d, 3H, ^3J=6.5 Hz, CH_3–C(2′)). ^{13}C NMR (C_6D_6, 100.6 MHz, +70 °C): *δ* 169.7, 164.4, 144.7, 140.8, 139.9, 138.8, 133.4, 132.3, 130.7, 130.2, 128.9, 128.8, 128.6, 127.9, 127.2, 116.5, 115.3, 75.8, 75.6, 67.1, 59.7, 47.7, 39.5, 24.8, 20.3, 13.7, 12.5. MALDI-HRMS: calcd for $C_{34}H_{39}NO_7SNa^+$ 628.2345; found: 628.2346. Anal. Calcd for $C_{34}H_{39}NO_7S$ (605.74): C, 67.42; H, 6.49; N, 2.31; S, 5.29. Found: C, 67.37; H, 6.40; N, 2.24; S, 5.30.

4.4.3. (2*S*,3*E*,5*R*)-5-[(1*R*)-(2,4,6-triisopropylphenyl)-ethyloxy]-7-methylsulfonylocta-3,7-dien-3-yl acetate (28). Allyltrimethylsilane (0.03 mL, 0.188 mmol, 0.28 equiv) and Tf_2NH (0.5 M in CH_2Cl_2) (0.27 mL, 0.35 mmol, 0.20 equiv) were stirred at 20 °C for 20 min. Anhyd CH_2Cl_2 (1.4 mL) was added. SO_2 (0.5 mL, 11.18 mmol) dried by passing through a column of P_2O_5 and alumina was transfered on the vaccum line to the CH_2Cl_2 solution frozen at −196 °C. The mixture was allowed to melt and to warm to −78 °C. After 30 min at this temperature a mixture of **24b** (247.0 mg, 0.663 mmol) and **23c** (607 mg, 13.4 mmol) in anhyd CH_2Cl_2 (0.8 mL) was added dropwise at −80 °C After stirring at −78 °C overnight, SO_2 was evaporated at −78 °C for 1 h. Then MeI (0.41 mL, 6.58 mmol, 10 equiv) followed by TBAF (1 M in THF, 3.40 mmol, 5.13 equiv) were added. The reaction mixture was allowed to reach slowly 0 °C. After 2 h at this temperature an aqueous solution of $NaHCO_3$ (5%) was added (10 mL). The reaction mixture was warmed to room temperature and CH_2Cl_2 (10 mL) was added. The organic phase was washed with a satd aq solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated under vacuum. FC (light petroleum ether/EtOAc 3:2) 220 mg (65%) of a 10:1 mixture of diastereoisomers **28** and 3-epi-**28**. Only the isomer **28** can be analyzed from the spectra of the mixture UV (CH_3CN): λ_{max}=265 (*ε*=488), 225 (5565), 189 (660). IR (neat): *ν* 3075, 2960, 2930, 2870, 1760, 1700, 1645, 1460, 1370, 1220, 1180, 1075, 1020, 890, 880, 780. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.03–6.94 (2s, 2 arom CH), 5.55 (d, 1H, ^3J=6.9 Hz, H–C(2)), 5.18 (q, 1H, ^3J=6.6 Hz, H–C(1″)), 4.78–4.68 (2s, 2H, H–C(6)), 4.38 (q, 1H, ^3J=7.0 Hz, H–C(1′)), 4.19 (m, 1H, H–C(3)), 3.85–3.25 (2 br s, 2H, Me_2–CH)), 3.06 (s, 3H, SO_2Me), 2.85 (sept, ^3J=6.5 Hz, Me_2–CH), 2.40 (br d, 1H, H–C(4)), 2.23 (s+m, 4H, MeCO+H–C(4)), 1.63 (s, 3H, Me-C(5)), 1.57 (2d, 6H, ^3J=7.0 Hz, H–C(2′), ^3J=6.6 Hz, H–C(2″)), 1.26–1.22 (m, 18H, Me_2–CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* 168.8 (CO), 147.5–147.1–140.9–140.7–133.9–129.0 (4 arom C+C(5)+C(1)), 128.2 (C(2)), 123.2–120.5 (2 arom C.), 114.2 (C(6)), 74.4 (C(3)), 73.0 (C(1″)), 59.9 (C(1′)), 44.3 (C(4)), 38.6 (SO_2Me), 34.0 (Me_2C), 29.1–28.6 (Me_2–C), 24.8–24.3–23.9–23.3 (2Me_2–C+Me-C(7)+C(2″)), 20.9 (MeCO), 14.2 (Me_2–C)), 11.2 (C(1)). HRMS (MALDI): calcd for $C_{29}H_{46}O_5SNa^+$ 529.2963 [M+Na^+]; found: 529.2912.

4.4.4. (1*Z*)-1-ethylidene-5-methyl-3-[1-(2,4,6-triisopropyl-phenyl)ethoxy]hex-5-enyl acetate (29a). Allyltrimethylsilane (0.03 mL, 0.19 mmol, 0.20 equiv) and Tf_2NH (0.5 M in CH_2Cl_2) (0.33 mL, 0.17 mmol, 0.20 equiv) were mixed and stirred for 20 min at room temperature. Anhyd CH_2Cl_2 (1.8 mL) was added. SO_2 (0.5 mL, 11.18 mmol, 13.8 equiv) dried over a column of P_2O_5 and alumina was transferred on the vacuum line to the CH_2Cl_2 solution frozen at −196 °C. The mixture was allowed to melt and to warm at −78 °C. After 30 min at this temperature a mixture of diene **24b** (304.0 mg, 0.81 mmol) and **23c** (477 mg, 1.67 mmol, 2.06 equiv) in anhyd CH_2Cl_2 (1.8 mL) was added dropwise at −80 °C. The resulting reaction mixture was stirred at −78 °C for 16 h. SO_2 was then evaporated at −78 °C for 1 h. A solution of triethylamine (0.14 mL, 1.00 mmol, 1.22 equiv), trimethylsilyl trifluoromethanesulfonate (0.18 mL, 0.99 mmol, 1.22 equiv) in anhyd MeOH (0.20 mL) was added. The temperature was kept at −78 °C for 3 h and a satd aq solution of $NaHCO_3$ (10 mL) was added. The reaction mixture was warmed to room temperature and diluted with CH_2Cl_2 (10 mL). The organic phase was washed with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated. The crude was purified on chromatographic column (petroleum ether 95/Ethyl acetate 5) to yield 237 mg (70%) as a 10:1 mixture of diastereoisomers **29a/29b**. R_f=0.51 (petrol ether/ether 85:15). Only **29a** can be analyzed from the spectra of the mixture. UV (CH_3CN): 265 (490), 225 (5560), 189 (660). IR (neat): 30745 2960, 2930, 2870, 1760, 1700, 1645, 1460, 1370, 1220, 1180, 1080, 1020, 890, 880, 780 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.03–6.94 (2s, 2 arom CH), 5.20 (q, 1H, ^3J=6.9 Hz, H–C(1′)), 5.10 (q, 1H, ^3J=6.6 Hz, H–C(1″)), 4.71–4.60 (2s, 2H, H–C(6)), 3.91 (br s, 1H, Me_2–C*H*)), 3.67 (m, 1H, H–C(3)), 3.91 (br s, 1H, Me_2–C*H*)), 2.85 (sept, ^3J=6.5 Hz, Me_2–C*H*), 2.49 (br d, 1H, H–C(4)), 2.45 (s, 3H, H–C(2′)), 2.44–2.42 (m, 2H,

H–C(2)), 2.11–2.05 (m, 2H, H–C(4)), 1.58 (s, 3H, Me-C(5)), 1.55 (d, 3H, ^3J=6.9 Hz, H–C(2″)), 1.50 (d, 3H, ^3J=6.6 Hz, H–C(2′)), 1.26–1.22 (m, 17H, *Me*$_2$–CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): 168.7 (C(1′)), 147.2 (C(1)), 147.1–146.6–142.3–134.6, 123.1–120.3 (arom C+C(5)), 113.4 (C(1″)), 112.9 (C(6)), 73.7 (C(3)), 71.6 (C(1‴)), 43.3 (C(2)), 38.6 (C(4)), 34.0 (Me$_2$–*C*H), 25.2–24.8–24.2–23.9–23.8 (Me$_2$–*C*H+*Me*$_2$–CH), 22.7 (Me-C(5)), 22.3 (C(Ac)), 20.7 (C(2″)), 10.8 (C(2′)). MS-CI (NH_3): 446 (1, [M+18]), 429 (1, [M+1]$^+$), 344 (1), 231 (100). El. Anal. Calcd $C_{28}H_{44}O_3$ (428.66): C, 78.46; H, 10.35; O, 11.20. Found: C, 78.40; H, 10.33.

4.4.5. (−)-(6*S*,7*E*,9*R*)-2-benzyl-7,9-dimethyl-4-methylene-1,1-dioxido-6-((1*S*)-1 phenylethoxy)-2,3,4,5,6,9-hexahydro-1,2-thiazonin-8-yl benzoate ((−)-30). A mixture of (−)-**26b** (0.40 g, 0.66 mmol), Cs_2CO_3 (0.215 g, 0.66 mmol) and Pd(PPh$_3$)$_4$ (76 mg, 0.07 mmol) in anhyd DMF (20 mL) was heated to 100 °C for 40 min (control by TLC). The resulting black solution was evaporated under vacuum to dryness. The residue was purified by FC (toluene/EtOAc 9:1, R_f=0.62), 0.291 g (81%), $[\alpha]^{25}_{589}$ −93; $[\alpha]^{25}_{577}$ −99; $[\alpha]^{25}_{435}$ −176; $[\alpha]^{25}_{405}$ −211 (*c* 0.3, $CHCl_3$). IR (film): *ν* 3065, 2975, 2925, 1735, 1730, 1715, 1605, 1595, 1500, 1470, 1455, 1330, 1265, 1240, 1170, 1145, 1085, 1065, 1025. ^{1}H NMR (DMSO$_{d\text{-}6}$, 400 MHz, +80 °C): *δ* 8.08 (dm, 2H, ^3J=7.4 Hz, H–C(Bz)), 7.73 (t, 1H, ^3J=7.4 Hz, H–C(Bz)), 7.60 (t, 2H, ^3J=7.4 Hz, H–C(Bz)), 7.48–7.42, 7.39–7.33, 7.30–7.26, 7.17–7.13, 6.79–6.74 (5m, 10H, H–C(Ar)), 4.96, 4.82 (2s, 2H, CH_2=C(4)), 4.50 (q, 1H, ^3J=6.6 Hz, H–C(1′)), 4.30 (dd, 1H, ^3J=9.6, 5.5 Hz, H–C(6)), 4.07, 3.99 (2d, 2H, AB syst, ^2J=15.8 Hz, PhC*H*$_2$–N(2)), 3.81 (d, 1H, AB syst, ^2J=15.8 Hz, Ha–C(3)), 3.62 (q, 1H, ^3J=7.0 Hz, H–C(9)), 3.50 (d, 1H, AB syst, ^2J=15.8 Hz, Hb–C(3)), 2.69–2.58 (m, 2H, H–C(5)), 1.64 (s, 3H, CH_3–C(7)), 1.43 (d, 3H, ^3J=6.6 Hz, H–C(2′)), 1.31 (d, 3H, ^3J=7.0 Hz, CH_3–C(9)). ^{13}C NMR (DMSO$_{d\text{-}6}$, 100.6 MHz, +80 °C): *δ* 163.1, 142.9, 140.1, 138.0, 135.6, 133.3, 130.8, 129.1, 128.6, 128.4, 128.0, 127.8, 127.2, 126.9, 125.9, 118.2, 118.0, 114.9, 74.0, 71.9, 57.6, 50.8, 50.6, 38.4, 23.3, 10.5, 9.8. MALDI-HRMS: calcd for $C_{32}H_{35}NO_5SNa^+$ 584.1873; found: 584.1879. Anal. Calcd for $C_{32}H_{35}NO_5S$ (545.69): C, 70.43; H, 6.46; N, 2.57; S, 5.88. Found: C, 70.52; H, 6.46; N, 2.58; S, 5.86.

4.4.6. (−)-(6*S*,7*E*,9*R*)-2-benzyl-7,9-dimethyl-4-methylene-1,1-dioxido-6-((1*S*)-1-phenylethoxy)-2,3,4,5,6,9-hexahydro-1,2-thiazonin-8-yl benzoate ((−)-31). Same procedure as that applied for the preparation of (−)-**30**, using (−)-**27b** (0.40 g, 0.66 mmol). Yield 0.285 g (79%). R_f=0.72, toluene/EtOAc 9:1), colorless oil. $[\alpha]^{25}_{589}$ −108; $[\alpha]^{25}_{577}$ −113; $[\alpha]^{25}_{435}$ −257; $[\alpha]^{25}_{405}$ −320 (*c* 0.2, $CHCl_3$). IR (film): *ν* 3060, 3030, 2970, 2925, 1735, 1730, 1680, 1600, 1495, 1455, 1330, 1270, 1225, 1210, 1140, 1085, 1065, 1025. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 8.21 (d, 2H, ^3J=7.4 Hz, H–C(Bz)), 7.63 (t, 1H, ^3J=7.7 Hz, H–C(Bz)), 7.70 (t, 2H, ^3J=7.4 Hz, H–C(Bz)), 7.43–7.28 (m, 10H, H–C(Ar)), 5.23 (s, 2H, CH_2=C(4)), 5.21 (q, 1H, ^3J=7.1 Hz, H–C(9)), 4.89 (d, 1H, AB syst, ^2J=15.1 Hz, Ha-(PhC*H*$_2$–N(2))), 4.86 (q, 1H, ^3J=6.5 Hz, H–C(1′)), 4.07 (d, 1H, AB syst, ^2J=15.1 Hz, Ha–C(3)), 4.02 (d, 1H, AB syst, ^2J=15.1 Hz, Hb-(PhC*H*$_2$–N(2))), 3.89 (dd, 1H, ^3J=8.6, 4.9 Hz, H–C(6)), 3.41 (d, 1H, AB syst, ^2J=15.1 Hz, Hb–C(3)), 2.68 (dd, 1H, AB syst, ^2J=15.2 Hz, ^3J=8.6 Hz, Ha–C(5)), 2.54 (dd, 1H, AB syst, ^2J=15.2 Hz, ^3J=5.0 Hz, Hb–C(5)), 1.58 (s, 3H, CH_3–C(7)), 1.57 (d, 3H, ^3J=6.5 Hz, CH_3–C(9)), 1.43 (d, 3H, ^3J=6.5 Hz, H–C(2′)). ^{13}C NMR ($CDCl_3$, 100.6 MHz): *δ* 164.1, 143.4, 140.6, 137.2, 136.9, 133.9, 132.4, 130.4, 128.9, 128.8, 128.7, 128.6, 128.3, 127.8, 126.6, 122.8, 75.0, 74.8, 61.8, 54.2, 52.9, 38.7, 24.9, 20.2, 11.4. MALDI-HRMS: calcd for $C_{32}H_{35}NO_5SK^+$ 568.2134; found: 568.2104. Anal. Calcd for $C_{32}H_{35}NO_5S$ (545.69): C, 70.43; H, 6.46; N, 2.57; S, 5.88. Found: C, 70.47; H, 6.50; N, 2.42; S, 5.77.

4.4.7. (±)-(2*RS*,5*SR*)-2,4-dimethyl-7-methylene-1,1-dioxido-5-((1*SR*)-1-phenylethoxy)-5,6,7,8-tetrahydro-2*H*-thiocin-3-yl isobutyrate ((±)-32b). Allyltrimethylsilane (0.194 mL, 1.22 mmol) was added to Tf_2NH (0.5 M in CH_2Cl_2) (2.44 mL, 1.22 mmol) diluted with toluene (6 mL). The mixture was stirred at 20 °C for 20 min. SO_2 (7 mL, 157 mmol, 51 equiv) dried over a column of P_2O_5 and alumina was transferred on the vacuum line to the toluene solution frozen at −196 °C. The mixture was allowed to melt and to warm at −78 °C. After 30 min at −78 °C a mixture of (±)-**24c**[37] (0.88 g, 3.05 mmol, 1 equiv) and 2-acetoxymethyl allyltrimethylsilane **23b** (0.68 g, 3.66 mmol, 1.2 equiv) in anhyd toluene (2 mL) was added dropwise under stirring at −78 °C. The mixture was stirred overnight. SO_2 was then evaporated at −78 °C for 2 h, followed by evaporation to dryness at 20 °C. The residue (crude **25c**) was taken in THF (15 mL) and added at 20 °C to a mixture of (Ph$_3$P)$_4$Pd (0.35 g, 0.30 mmol, 0.1 equiv) and NEt_3 (0.85 mL, 6.10 mmol, 2 equiv) in THF (15 mL) and stirred at 20 °C for 3 h. The mixture was then poured in brine, extracted by EtOAc. The collected organic layers were washed with brine, dried (Na_2SO_4) and evaporated under vacuum. FC (light petroleum ether/EtOAc 7:3): 0.55 g (44%) of (±)-**32b**, that was recrystallized from pentane/CH_2Cl_2 to yield a sample suitable for X-ray crystallography (Fig. 2). White solid, mp 90 °C, R_f=0.63 (light petroleum ether/EtOAc 7:3). IR (KBr): *ν* 2950, 2880, 1745, 1680, 1455, 1380, 1295, 1315, 1240, 1190, 1140, 1125, 1115, 1080, 1045. ^{1}H NMR ($CDCl_3$, 400 MHz, +60 °C): *δ* 7.38–7.27 (m, 5H, H–C(Ph)), 5.64, 5.45 (2s, 2H, CH_2=C(7)), 5.37 (br s, 1H, H–C(2)), 4.55 (q, 1H, ^3J=6.2 Hz, H–C(1′)), 4.03 (d, 1H, ^2J=14.2 Hz, Ha–C(8)), 3.77 (br s, 1H, H–C(5)), 3.67 (d, 1H, ^2J=14.2 Hz, Hb–C(8)), 2.77 (sept, 1H, ^3J=6.8 Hz, $(CH_3)_2$C*H*COO–C(3)), 2.60 (dd, 1H, ^2J=14.2 Hz, ^3J=5.6 Hz, Ha–C(6)), 2.24 (br d, 1H, ^2J=14.2 Hz, Hb–C(6)), 1.48 (d, 3H, ^3J=6.8 Hz, CH_3–C(2)), 1.46 (s, 3H, CH_3–C(4)), 1.40 (d, 3H, ^3J=6.8 Hz, H–C(2′)), 1.31 (2d, 6H, ^3J=7.4 Hz, (C*H*$_3$)$_2$CHCOO–C(3))). ^{13}C NMR ($CDCl_3$, 100.6 MHz, +60 °C): *δ* 174.1, 143.0, 139.5, 131.3, 130.0, 128.8, 128.0, 127.1, 126.5, 75.6, 75.4, 57.3, 54.9, 41.5, 34.2, 24.2, 19.0, 19.1, 18.4, 6.3. MALDI-HRMS: calcd for $C_{22}H_{30}O_5SNa^+$ 429.1712; found: 429.1712. Anal. Calcd for $C_{22}H_{30}O_5S$ (406.54): C, 65.00; H, 7.44; S, 7.89. Found: C, 65.05; H, 7.46; S 7.99.

4.4.8. (+)-(2*S*,5*S*)-2,4-dimethyl-7-methylene-1,1-dioxido-5-((1*R*)-1-phenylethoxy)-5,6,7,8-tetrahydro-2*H*-thiocin-3-yl benzoate ((+)-32a). Same procedure as that applied for the preparation of (±)-**32b** using (+)-**24a** (0.82 g, 2.54 mmol). Yield 0.45 g (41%). R_f=0.52, light petroleum ether/EtOAc 7:3), colorless oil. IR (film): *ν* 2970,

1735, 1450, 1315, 1270, 1220, 1140, 1120, 1080, 1020, 705, 620. ^{1}H NMR (C_6D_6, 400 MHz, +70 °C): δ 8.21 (d, 2H, ^3J=7.7 Hz, H–C(Bz)), 7.23 (d, 2H, ^3J=7.4 Hz, H–C(Ar)), 7.16–7.06 (m, 6H, H–C(Ar)), 5.56, 5.22 (2s, 2H, CH_2=C(7)), 5.39 (br s, 1H,((H–C(2)), 4.60 (q, 1H, ^3J= 6.2 Hz, H–C(1′)), 3.76 (d, 1H, AB syst, ^2J=14.2 Hz, Ha–C(8)), 3.61 (br s, 1H, H–C(5)), 3.45 (d, 1H, ^2J=14.2 Hz, AB syst, Hb–C(8)), 2.30 (dd, 1H, ^2J=14.2 Hz, ^3J=5.6 Hz, AB syst, Ha–C(6)), 1.82 (br d, 1H, ^2J=14.2 Hz, AB syst, Hb–C(6)), 1.51 (d, 3H, ^3J=6.8 Hz, CH_3–C(2)), 1.27 (s, 3H, CH_3–C(4)), 1.25 (d, 3H, ^3J=6.8 Hz, H–C(2′). ^{13}C NMR (C_6D_6, 400 MHz, +70 °C): δ 164.2, 143.4, 140.6, 133.6, 132.2, 130.6, 129.9, 129.7, 128.9, 128.8, 128.2, 126.8, 126.3, 76.7 (2C), 57.6, 55.6, 41.4, 24.1, 18.1, 6.5. MALDI-HRMS: calcd for $C_{25}H_{28}O_5SNa^+$ 463.1555; found: 463.1558. $[\alpha]_{589}^{25}$+76 (*c* 1.0 $CHCl_3$).

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Application of divergent multi-component reactions in the synthesis of a library of peptidomimetics based on γ-amino-α,β-cyclopropyl acids

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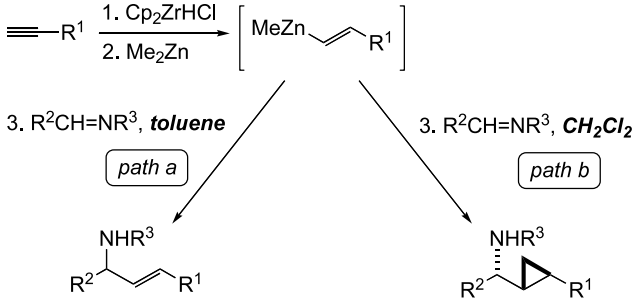
Abstract—The multi-component condensation of organozirconocene, aldimine and zinc carbenoid was applied to the stereoselective synthesis of cyclopropane amino acid derivatives. These compounds served as scaffolds for the preparation of a 46-member library. The C- and N-termini of the cyclopropane amino acid derivatives were diversified by condensations with ten amines and ten acylating agents, respectively. To improve yields and accelerate library synthesis, most products were prepared under microwave irradiation and purified by polymer-bound scavengers and SPE methodology. All compounds were analyzed by LC–MS and a representative selection was fully characterized.

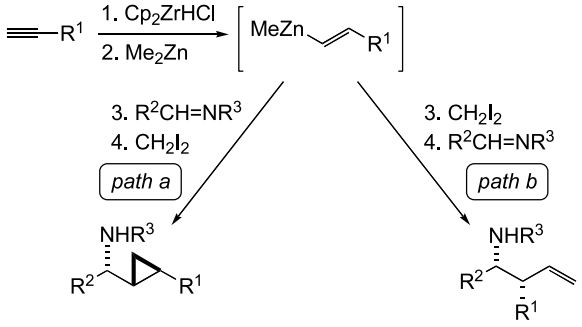
1. Introduction

Multi-component reactions such as the Ugi and Passerini reactions have had a significant influence on industrial structure–activity relationship (SAR) analyses and pharmaceutical library syntheses.[1] The Ugi four-component condensation provides amino acid analogs from readily available aldehydes, carboxylic acids, and amines, and less easily accessible isocyanides,[2] but only a single product structure is obtained from a given set of starting materials. We have recently introduced the concept of divergent multi-component reactions (DMCRs),[3] whereby reaction conditions such as the choice of solvent[4] or the order of addition of reagents[5] influence the reaction pathway and thus provide a rapid access to different scaffolds (Schemes 1 and 2).[6]

In addition to the discovery of new *C*,*C*-bond forming cascade reactions,[7] we have directed our DMCR methodology toward the synthesis of peptidomimetics[8] such as (*E*)-alkene peptide isosteres (ψ[RC=CH], δ-amino-β,γ-unsaturated amino acids, with R = alkyl, aryl, H, F, and CF_3),[9] cyclopropane dipeptide isosteres (ψ[RCp], δ-amino-β,γ-cyclopropyl amino acids),[9a,c] and, in an extension of the



Scheme 1. Choice of solvent influences product formation.



Scheme 2. Order of reagent addition influences product formation.

Keywords: Indexed library; Microwave irradiation; Polymer-bound scavengers.
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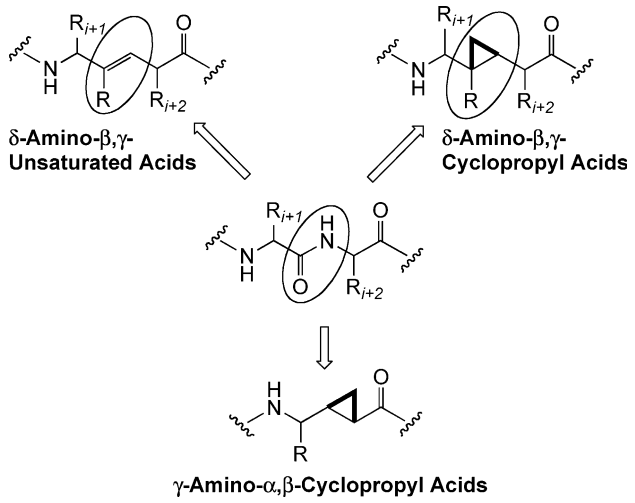


Figure 1. Peptidomimetics based on isosteric amide bond replacements or amino acid backbone chain extensions.

principle of vinylogy for α-amino acids,[10] backbone-modified γ-amino-α,β-cyclopropyl acids (Fig. 1).[11]

The scissile peptide bond is in part responsible for poor pharmacokinetic properties, low oral bioavailability and rapid proteolytic degradation of oligopeptides composed of natural amino acid residues. Peptidomimetics have the potential to provide increased metabolic stability and better oral bioavailability.[12] The replacement of peptide bonds with transition-state analogs such as hydroxyethylene,[13] hydroxyethylamine,[14] dihydroxyethylene[15] or ketomethylene[16] groups has produced chimeric molecules that combine improved pharmacokinetic properties and higher potency. Isosteric replacements such as (*E*)- or (*Z*)-alkenes,[17] (*E*)- or (*Z*)-methylalkenes,[9,18] (*Z*)-fluoroalkenes,[19] cyclopropyl rings[9,11,20] or larger ring systems[21] do not only prevent hydrolytic cleavage but also incorporate conformational constraints into the peptide backbone. This may allow for a tighter binding to a target enzyme or receptor leading to increased potency. We recently introduced the cyclopropane amino acid derivative ΔPhg (Fig. 2).[11] In contrast to alkenes which have the potential to undergo isomerization or oxidation, cyclopropanes display an increased chemical and metabolic stability.[22] X-ray and solution structural analyses have shown that cyclopropane-containing peptides occupy biologically relevant conformational space.[9,11]

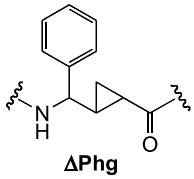


Figure 2. Phenylglycine derived cyclopropane amino acid residue; the Δ-prefix is used for amino acids that have a cyclopropane ring inserted into the backbone chain between carbonyl-C and α-C.

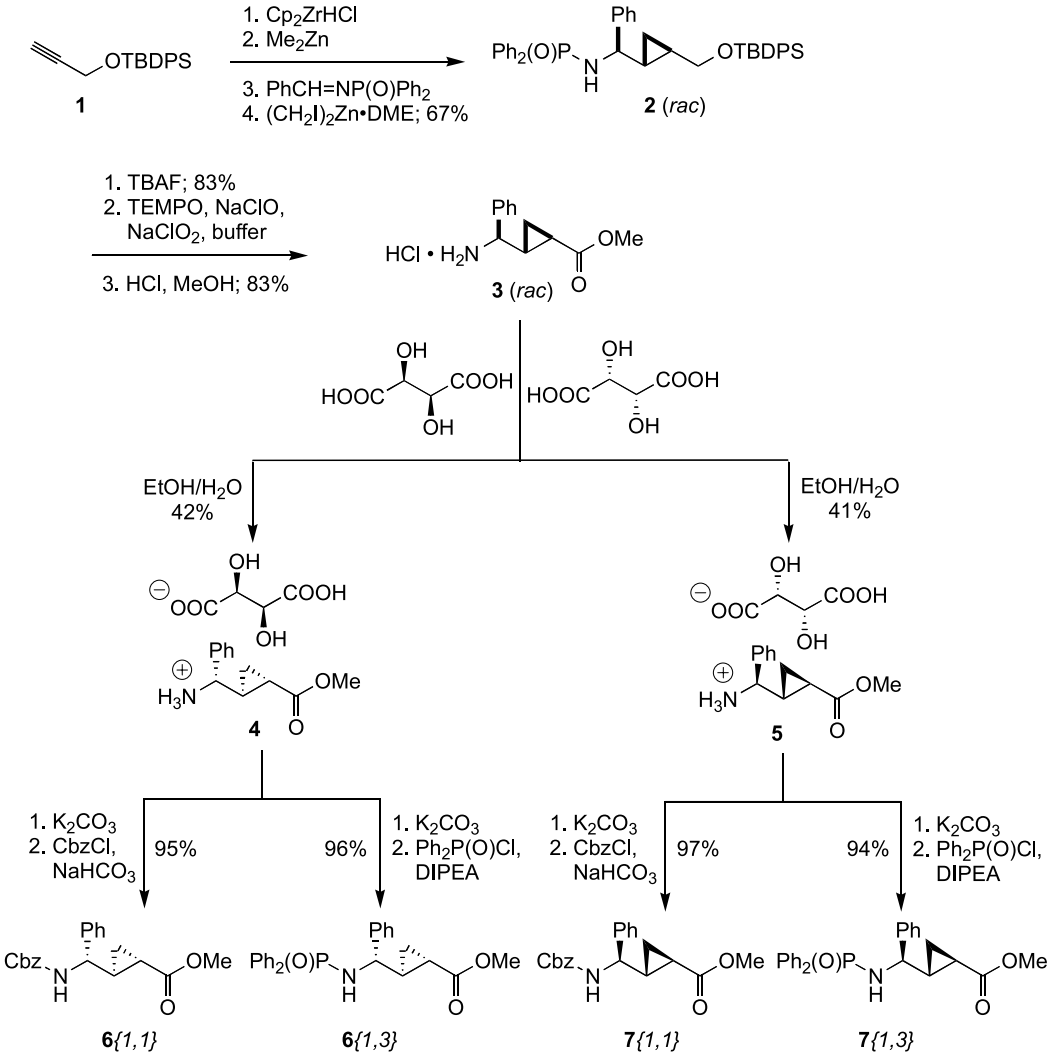
The ΔPhg residue can be accessed stereoselectively by the three component condensation of an alkenylzirconocene,[23] an aldimine and a dihalomethane-derived zinc carbenoid species. As a starting point for further investigation of the biological properties of these peptidomimetics,[4e] we now report a new, more expedient synthesis of ΔPhg as well as the synthesis of a 46-member library of ΔPhg derivatives.

2. Results and discussion

Synthetic methodology. In our recent approach to γ-amino-α,β-cyclopropyl acids,[11] we described a 9-step (including resolution) sequence relying upon sequential Grieco elimination–alkene oxidation to introduce the C-terminal carboxylate function. This strategy introduced several steps that complicated the scale up for preparative purposes. We have now been able to optimize this sequence to allow the multi-gram synthesis of the enantiomerically pure cyclopropyl amino acid derivatives **6** and **7** in a more efficient fashion (Scheme 3). Addition of Cp_2ZrHCl[24] to TBDPS-protected propargyl alcohol **1**, followed by sequential transmetallation to dimethylzinc, addition to *N*-diphenylphosphinylimine and treatment with bis(iodomethyl)-zinc·DME complex[25] afforded the desired amide **2** in an overall yield of 67% and in high diastereomeric ratio (>19:1). Removal of the TBDPS group with TBAF and oxidation of the resulting alcohol afforded the carboxylic acid which could be converted into the methyl ester hydrochloride salt **3** under acidic conditions (HCl in MeOH). The racemate **3** was resolved by formation of the diastereomeric salts with L- and D-tartaric acid. The hydrochloride salts **3** were first converted to the free amines that were co-crystallized with tartaric acid in an ethanol–water mixture affording **5**. The corresponding diastereomeric salt (recovered from the filtrate) was an amorphous solid, which was not easily crystallized. Formation of the D-tartaric acid salt facilitated its crystallization. Indeed, after only three crystallizations, over 80% of the initial amine could be recovered in the form of enantiomerically pure salts. Pure γ-amino-α,β-cyclopropyl acids (ee >95%) could be obtained by washing the crystalline salts **4** and **5** with an aqueous solution of K_2CO_3 at 0 °C in chloroform. X-ray structure analysis of a diastereomeric derivative was used to assign the absolute configuration of **4** and **5**.[11] The free amines were transformed into the Cbz-protected amino acid methyl esters **6**{*1,1*} and **7**{*1,1*} or the *N*-diphenylphosphinyl amides **6**{*1,3*} and **7**{*1,3*}.

Library design. For the generation of a focused library, both C- and N-termini of the cyclopropane peptidomimetics were modified. Instead of synthesizing a complete 12×12 matrix for **6** and **7**, i.e., 288 compounds, an indexed library design was chosen.[26] In an indexed library, only one substituent is varied at a time while all other substituents remain unchanged. Accordingly, a two-dimensional matrix is divided into two one-dimensional matrices (Fig. 3). In the present example, two 12×12 matrices were transformed into four 12×1 matrices, i.e., 48 compounds. Since two compounds appear in two matrices, only 46 compounds were synthesized to encompass a similar chemical space as two 12×12 matrices. If compounds **A**{*1,4*} and **A**{*3,1*} in Figure 3 show activity in an initial screen, compound **A**{*3,4*} can be synthesized and evaluated in a subsequent screen.

For an efficient library synthesis, polymer- or silica-bound



Scheme 3. Preparation of cyclopropane amino acid derivatives ΔPhg **6**{*1,1*}, **6**{*1,3*}, **7**{*1,1*} and **7**{*1,3*}.

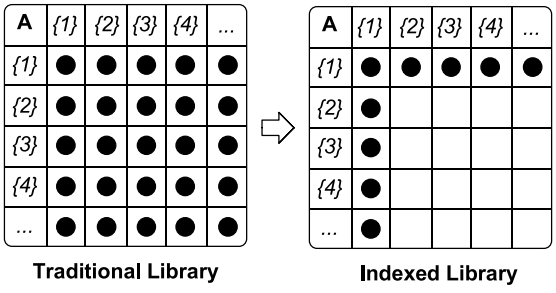


Figure 3. Traditional versus indexed library.

reagents and SPE scavenging and separation techniques were applied.[27] To further accelerate the library workflow, most reactions were carried out in an automated Emrys Optimizer single-mode microwave reactor.

C-Terminal functionalizations. The two esters **6**{*1,3*} and **7**{*1,3*} were hydrolyzed in parallel and the free acids were extracted using an ALLEXis system.[28] Each batch was divided into eleven parts; the free acid was added directly to the library, and the remaining 10 parts were transformed into amides. In order to obtain a broad distribution of

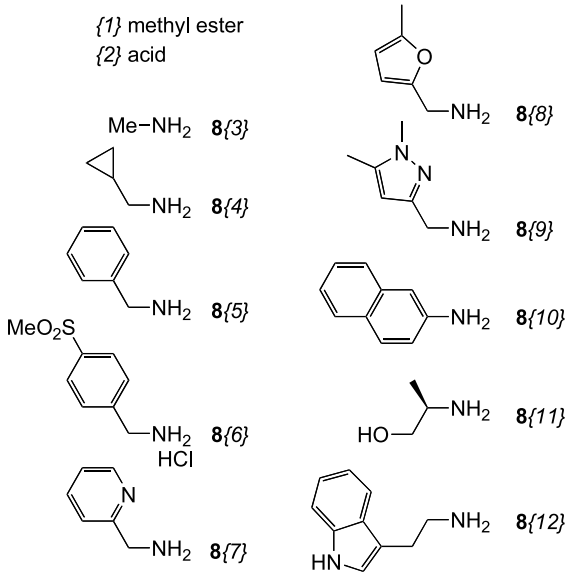
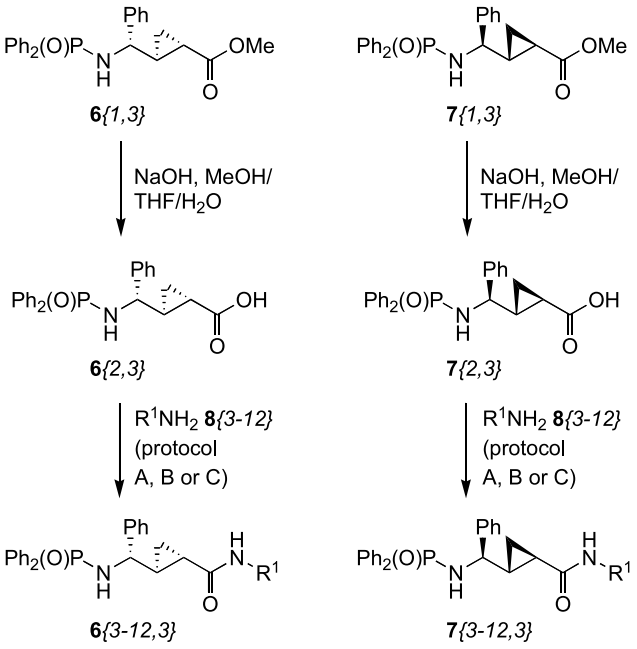


Figure 4. Building blocks **8**{*3–12*} for C-terminal functionalizations.

pharmacokinetic properties for the library,[29] a diverse set of 10 amines was chosen (Fig. 4). While methylamine (**8**{*3*}) was selected due to its small size, cyclopropanemethylamine (**8**{*4*}) was chosen due to its chain branching as well as its lipophilic character. Several aromatic and heteroaromatic amines (**8**{*5–10*}) that can act as hydrogen bond donors were also selected. Polar functions were represented by alaninol (**8**{*11*}) and tryptamine (**8**{*12*}).

The drawback of this diverse set of building blocks **8**{*3–12*} was that three different protocols for amide coupling were required (Scheme 4). The most efficient protocol (protocol A)[30] involved polymer-bound carbodiimide and 1-hydroxybenzotriazole as coupling reagents. These reagents were added in excess to a solution of the acid in chlorobenzene and stirred for 5 min before an equimolar amount of amine was added. Microwave irradiation at 100 °C for 5 min afforded the corresponding amides. In order to drive reactions to completion, volatile amines were added in excess and the reaction mixture was irradiated at 60 °C for



protocol A:
1. PS-DCC, HOBt
2. R^1NH_2, μW 100 °C, 5 min
workup: Si-CO_3^{2-} SPE
estimated time needed for 10 reactions: 2-3 h
scope: limited

protocol B:
1. EDCI, HOBt
2. R^1NH_2, r.t., 12 h
workup: ChemElut extraction and chromatography
estimated time needed for 10 reactions: ca. 15 h
scope: good

protocol C:
DEPBT, NEt_3, R^1NH_2, r.t., 12 h
workup: aq. extraction and chromatography
estimated time needed for 10 reactions: ca. 24 h
scope: broad

Scheme 4. C-Terminal functionalizations.

30 min. The reagents and polymer beads were removed by filtration of the reaction mixture through a silica-bound carbonate cartridge. This protocol was fast and allowed the synthesis of 10 library members in 2–3 h. Methylamine (**8**{*3*}), cyclopropanemethylamine (**8**{*4*}), benzylamine (**8**{*5*}), 4-methylsulfonylbenzylamine (**8**{*6*}), 2-aminomethylpyridine (**8**{*7*}), 5-methyl-2-furanmethanamine (**8**{*8*}) and (1,5-dimethyl-1*H*-pyrazol-3-yl)methylamine (**8**{*9*}) afforded the corresponding amides in moderate to good yields and high purities (Table 1). Subsequent purification was not necessary.

While protocol A worked well for most amines, for the syntheses of **6**{*10,3*} and **7**{*10,3*} the use of EDCI as the coupling reagent in the presence of HOBt was found to be advantageous, and the reaction mixture was stirred for 12 h at room temperature (protocol B). All water-soluble components were removed by ChemElut extraction. Since this extract contained a significant amount of impurities, automated parallel chromatography on SiO_2 with the ISCO Optix 10 system was necessary to afford the library members in high purity.

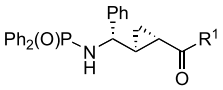
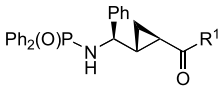
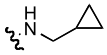
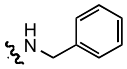
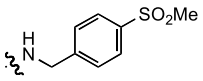
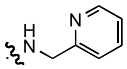
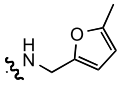
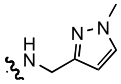
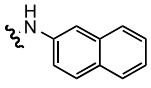
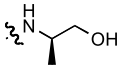
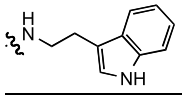
When the coupling protocols A or B were applied to the amidation with tryptamine (**8**{*12*}), the product was obtained in low yield, and with (*R*)-(−)-2-amino-1-propanol (**8**{*11*}) no product was formed. A more efficient coupling reagent such as 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT)[31] had to be used (protocol C). This method provided the desired amides in moderate yields and high purities, but it involved time-consuming additional aqueous extractions by the ALLEXis system and parallel chromatography on SiO_2 with the ISCO Optix 10 instrumentation.

Applying the three protocols A–C, a sublibrary of 20 C-terminal derivatized cyclopropyl carboxamides was successfully prepared. The use of polymer-bound reagents and scavenging techniques for most substrates significantly decreased the time needed for the library synthesis.

N-Terminal functionalizations. In addition to the C-terminal functionalizations of ΔPhg derivatives, *N*-phosphinylation, *N*-sulfonylation, *N*-carbamoylation and *N*-acylation further expanded the compound collection. The building blocks **6**{*1,2*} and **7**{*1,2*} were prepared by hydrogenolysis of **6**{*1,1*} and **7**{*1,1*}, followed by immediate conversion to the corresponding ammonium salts (Scheme 5). Compounds **6**{*1,2*} and **7**{*1,2*} were treated with 10 structurally diverse acylating reagents **9**{*3–12*} (Fig. 5), including one phosphinyl chloride, one chloroformate, two sulfonyl chlorides and six acyl chlorides to afford the 20 *N*-acyl derivatives **6**{*1,3–12*} and **7**{*1,3–12*}.

In a typical *N*-acylation procedure, microwave irradiation of a suspension of the ammonium salts **6**{*1,2*} or **7**{*1,2*} (1.0 equiv), PS-DMAP (1.2 equiv), triethylamine (2.0 equiv) and the corresponding acylating agent **9**{*3–12*} at 100 °C for 10 min in CH_2Cl_2 afforded the crude *N*-acylated products. Resin-bound scavengers were found to be ideal for purification because of ease, speed (avoiding chromatography) and the ability to proceed in parallel fashion. Upon cooling to room temperature, the reaction vial

Table 1. C-Terminal functionalizations, isolated yields (purity by LC–MS with ELS detection)

R^1	Protocol		
		**6**{*1*,*3*}, (95)	**7**{*1*,*3*}, (95)
		**6**{*2*,*3*}, (94)	**7**{*2*,*3*}, (94)
	**A**	**6**{*3*,*3*}, 23 (97)	**7**{*3*,*3*}, 30 (98)
	**A**	**6**{*4*,*3*}, 35 (91)	**7**{*4*,*3*}, 44 (>99)
	**A**	**6**{*5*,*3*}, 81 (92)	**7**{*5*,*3*}, 92 (98)
	**A**	**6**{*6*,*3*}, 82 (94)	**7**{*6*,*3*}, 98 (95)
	**A**	**6**{*7*,*3*}, 66 (>99)	**7**{*7*,*3*}, 77 (96)
	**A**	**6**{*8*,*3*},[a] 72 (94)	**7**{*8*,*3*},[a] 84 (91)
	**A**	**6**{*9*,*3*},[a] 73 (>99)	**7**{*9*,*3*},[a] 72 (98)
	**B**	**6**{*10*,*3*}, 69 (91)	**7**{*10*,*3*}, 72 (95)
	**C**	**6**{*11*,*3*}, 46 (98)	**7**{*11*,*3*}, 44 (97)
	**C**	**6**{*12*,*3*}, 53 (98)	**7**{*12*,*3*},[b] 68 (97)

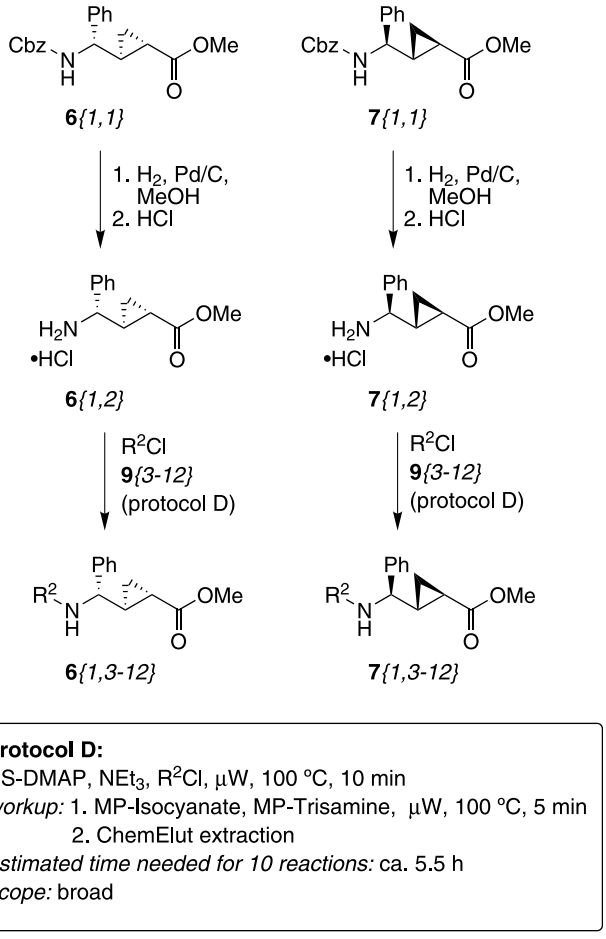
[a] Traces of amine were removed by product precipitation in diethylether.
[b] With protocol B, **7**{*12*,*3*} was obtained in 23% yield.

containing the crude product was charged with MP-trisamine[32,33] (1.0 equiv) and MP-isocyanate[33] (1.0 equiv), and microwave irradiation in the automated Emrys Optimizer microwave reactor was resumed at 100 °C for 5 min. Finally, the reaction mixture was subjected to an aqueous work-up by passage through a ChemElut SPE cartridge preconditioned with saturated aqueous $NaHCO_3$ solution to remove the resin-bound reagents and the triethylammonium chloride salt. The eluant was collected and concentrated to dryness using a centrifugal vacuum evaporator (Genevac HT-4) to provide the desired amides (Table 2).

Library analysis. The purity of all 46 library members was determined by reversed-phase HPLC with ELS and MS detection. Twelve library members (26%) were analyzed by ^{1}H NMR and five library members (11%) were fully characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR, MS, HRMS and mp. All library members were obtained in >85% purity by ELS detection and none had to be repurified by chromatography on SiO_2. The C-terminal functionalized amides **6**{*3–12*,*3*} and **7**{*3–12*,*3*} were isolated in an average yield of 64% and in an average purity of 96% (Table 1). The *N*-functionalized amides **6**{*1*,*3–12*} and **7**{*1*,*3–12*} were obtained in an average yield of 91% and in an average purity of 95% (Table 2).

3. Conclusions

We have optimized our DMCR approach to ΔPhg and applied it toward the preparation of a diverse indexed library of backbone-extended cyclopropane amino acid derivatives. Modern parallel synthesis techniques were used for the synthesis of 46 library members in an average purity of 95% after resin-based scavenging and SPE purification. Product yields varied depending on the reactant structure, but in most cases, the desired products were generated in good to excellent yields. The library members were obtained in an average yield of 78% and in an average amount of 24 mg. This study represents a further demonstration of the utility of multi-component reactions for diversity-oriented small molecule library synthesis.[34] Biological evaluation of this library will be reported in due course.



Scheme 5. N-Terminal functionalizations.

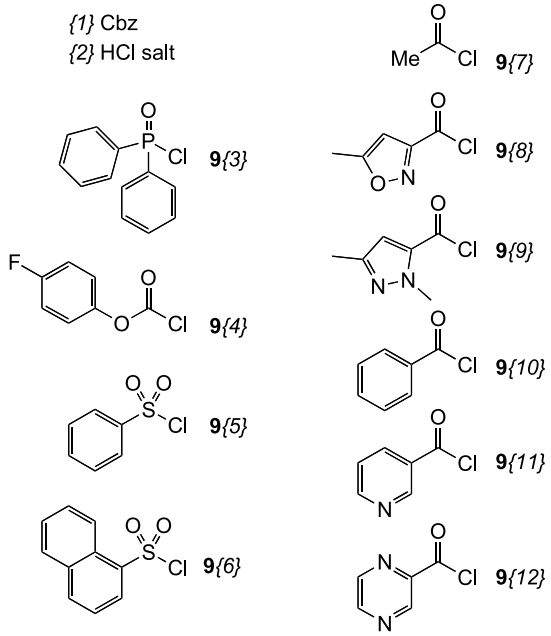


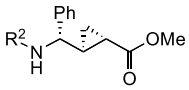
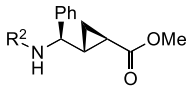
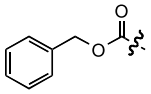
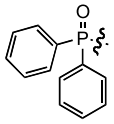
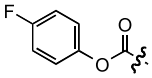
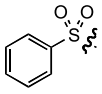
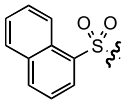
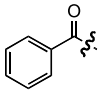
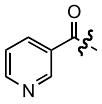
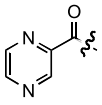
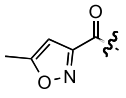
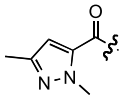
Figure 5. Building blocks **9**{*3–12*} for N-terminal functionalizations.

4. Experimental

4.1. General

All moisture-sensitive reactions were performed under an atmosphere of N_2 and glassware was flame dried under vacuum prior to use. DME and THF were dried by distillation over Na/benzophenone, Et_3N was dried by distillation over CaH_2. Toluene and CH_2Cl_2 were purified by filtration through activated alumina. Me_2Zn (2.0 M in toluene) and Et_2Zn (neat) were purchased from the Aldrich Chemical Company. Cp_2ZrHCl,[35] $PhCH{=}NP(O)Ph_2$[36] and alkyne **1**[37] were prepared according to literature protocols. PS-Carbodiimide, PS-DMAP, MP-isocyanate and MP-trisamine were purchased from Argonaut, silica-bound carbonate SPE cartridges from Silicycle and ChemElut 1003 cartridges from Varian. Unless stated otherwise, solvents or reagents were used without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040–0.055 mm, 230–400 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ and 0.20 g of $Ce(SO_4)_2$ in 100 mL of 3.5 N H_2SO_4 solution). NMR spectra were recorded in $CDCl_3$ (298 K) at either 300.1 MHz (^1H), 75.5 MHz (^{13}C) or 121.5 MHz (^{31}P) using a Bruker Avance 300 with XWIN-NMR software. Chemical shifts (δ) are reported in parts per million (ppm) with the

Table 2. N-Terminal functionalizations, isolated yields (purity by LC–MS with ELS detection)

R^2	Protocol		
		**6**{*1,1*}, (99)	**7**{*1,1*}, (>99)
HCl•H		**6**{*1,2*},[a] (93)	**7**{*1,2*},[a] (90)
	**D**	**6**{*1,3*}, 97 (96)	**7**{*1,3*}, >99 (90)
	**D**	**6**{*1,4*}, >99 (92)	**7**{*1,4*}, 98 (96)
	**D**	**6**{*1,5*}, >99 (96)	**7**{*1,5*}, >99 (>99)
	**D**	**6**{*1,6*}, >99 (99)	**7**{*1,6*}, 87 (93)
	**D**	**6**{*1,7*}, >99 (88)	**7**{*1,7*}, 97 (92)
	**D**	**6**{*1,8*}, 95 (>99)	**7**{*1,8*}, 92 (99)
	**D**	**6**{*1,9*}, >99 (92)	**7**{*1,9*}, >99 (99)
	**D**	**6**{*1,10*}, 89 (97)	**7**{*1,10*}, 83 (97)
	**D**	**6**{*1,11*}, 85 (97)	**7**{*1,11*}, 76 (95)
	**D**	**6**{*1,12*}, 52 (92)	**7**{*1,12*}, 97 (92)

[a] Purity by UV with detection at 240 nm.

residual solvent peak used as an internal standard. For ^{31}P NMR, Ph_3P (δ −5.5) was used as an external standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, bs=broad singlet, bd=broad dublet, bt=broad triplet, app.=apparent), coupling constants and integration. IR spectra were obtained on a Nicolet AVATAR 360 FTIR E.S.P. Spectrometer. Mass spectra were obtained on a Waters QTof API US. Melting points were obtained on a MelTemp melting point apparatus with digital temperature reading and are reported uncorrected. Optical rotations were obtained on a Perkin–Elmer 241 polarimeter. All microwave assisted reactions were performed in an Emrys Optimizer single mode microwave reactor (Biotage) using 2–5 mL Emrys process vials.

4.1.1. *N*-(*R)-(((1*R**,2*R**)-2-(*tert*-Butyldiphenylsilyloxymethyl)cyclopropyl)(phenyl)-methyl)-*P*,*P*-diphenylphosphinamide (2).** In a cooled flask (0 °C), Cp_2ZrHCl (12.7 g, 49.1 mmol) was suspended in dry CH_2Cl_2 (125 mL) and alkyne **1** (14.5 g, 49.1 mmol) was added immediately. The reaction mixture was warmed to room temperature, stirred for 30 min and the resultant light yellow solution was cooled to −78 °C and treated with Me_2Zn (24.6 mL, 49.1 mmol, 2.0 M in toluene). The reaction mixture was warmed to 0 °C and *N*-diphenylphosphinylimine (5.00 g, 16.4 mmol) was added. The mixture was heated under reflux for 30 h, cooled to 0 °C and treated with a solution of $(CH_2I)_2Zn\cdot DME$ (81.9 mmol) in CH_2Cl_2 (20.0 mL). This zinc carbenoid complex was prepared by dropwise addition of CH_2I_2 (13.2 mL, 164 mmol) to a solution of Et_2Zn (neat, 10.1 g,

81.9 mmol) in CH_2Cl_2 (20.0 mL) and DME (8.51 mL, 81.9 mmol) at −30 °C. After stirring for 10 min at −30 °C, the resultant solution was transferred via cannula. After warming to room temperature, the reaction mixture was stirred for 12 h, cooled to 0 °C, carefully quenched with satd NH_4Cl and extracted with EtOAc (3×). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on SiO_2 (hexanes/EtOAc 3/2) to give **2** (6.80 g, 67%) as a colorless foam: IR (neat) 3189, 3070, 3028, 2930, 2857, 1590, 1471, 1455, 1438, 1428, 1190, 1111 cm^{-1}; ^1H NMR δ 7.93–7.86 (m, 2H), 7.75–7.62 (m, 7H), 7.47–7.33 (m, 12H), 7.31–7.24 (m, 4H), 3.80 (dt, J=10.0, 7.9 Hz, 1H), 3.63 (dd, J=10.6, 5.4 Hz, 1H), 3.42 (dd, J=10.6, 6.2 Hz, 1H), 3.32–3.28 (m, 1H), 1.23–1.08 (m, 2H), 1.01 (s, 9H), 0.51 (dt, J=8.5, 5.1 Hz, 1H), 0.42 (dt, J=8.5, 5.2 Hz, 1H); ^{13}C NMR δ 143.32 (d, J_{CP}=4.5 Hz), 135.52 (d, J_{CP}=8.0 Hz), 133.82, 132.24 (d, J_{CP}=9.6 Hz), 131.91 (d, J_{CP}=9.3 Hz), 131.61 (d, J_{CP}=8.6 Hz), 131.41, 129.48, 128.37, 128.20, 128.13, 127.96, 127.53, 126.96, 126.79, 66.15, 58.16, 26.83, 24.72 (d, J_{CP}=5.7 Hz), 20.33, 19.09, 8.45; MS (ESI) *m/z* (intensity) 1253 ($[2M+Na]^+$, 23), 1231 ($[2M+H]^+$, 20), 638 ($[M+Na]^+$, 35), 616 ($[M+H]^+$, 100), 538 (29); HRMS (ESI) *m/z* calculated for $C_{39}H_{43}NO_2PSi$ (M+H) 616.2801, found 616.2799.

4.1.2. (1*R,2*R**)-2-((*R**)-1-Amino-1-phenylmethyl)cyclopropane carboxylic acid methyl ester hydrochloride salt (3).** Amide **2** (6.80 g, 11.0 mmol) was dissolved in THF (100 mL), cooled to 0 °C and treated with TBAF (13.8 mL, 13.8 mmol, 1.0 M in THF). The solution was warmed to room temperature, stirred for 10 h, quenched with sat. NH_4Cl and extracted with EtOAc (3×). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/acetone 2/3) to afford the corresponding alcohol (3.45 g, 83%) as a colorless solid. Mp 170.3–172.0 °C; IR (KBr) 3422, 3231, 2850, 1654, 1637, 1458, 1439 cm^{-1}; ^1H NMR δ 8.11–8.06 (m, 2H), 7.91–7.87 (m, 2H), 7.56–7.32 (m, 11H), 5.01 (bs, 1H), 4.08 (dd, J=11.1, 3.8 Hz, 1H), 3.53 (bs, 1H), 3.29 (bs, 1H), 2.86 (t, J=10.7 Hz, 1H), 1.44–1.32 (m, 1H), 1.10–0.99 (m, 1H), 0.41 (dt, J=8.5, 5.3 Hz, 1H), 0.26 (dt, J=8.7, 5.3 Hz, 1H); ^{13}C NMR δ 143.00 (d, J_{CP}=10.4 Hz), 133.67, 133.13 (d, J_{CP}=9.4 Hz), 131.69 (d, J_{CP}=9.4 Hz), 131.17, 129.43, 128.95, 128.84, 128.65, 128.48, 127.68, 126.67, 66.37, 61.43, 26.71, 23.04, 9.16; MS (EI) *m/z* (intensity) 377 (M^+, 3), 359 (4), 347 (6), 306 (67), 356 (10), 201 (100), 176 (9); HRMS (EI) *m/z* calculated for $C_{19}H_{12}NOP$ $[M-C_4H_7O]^+$306.1034, found 306.1048.

This alcohol (3.25 g, 8.61 mmol) was suspended in acetonitrile (100 mL) and pH 6.7 phosphate buffer (100 mL). The biphasic mixture was warmed to 45 °C and treated with TEMPO (135 mg, 0.861 mmol), $NaClO_2$ (1.95 g, 21.5 mmol) and NaClO (2.46 mL, 1.72 mmol, 0.7 M aqueous solution). After 12 h, the reaction mixture was cooled to room temperature, treated with methanol (5.0 mL), 10% HCl (300 mL) and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The resultant foam was dissolved in methanol (50.0 mL), cooled to 0 °C and HCl gas was bubbled through the solution for 5 min. After 6 h, the solution was poured into dry diethyl ether (350 mL), cooled to −20 °C and filtered to afford the methyl ester **3**[11] (1.72 g, 83%).

4.1.3. (1*S*,2*S*)-2-((*S*)-1-Amino-1-phenylmethyl)cyclopropane carboxylic acid methyl ester D-tartrate salt (4) and (1*R*,2*R*)-2-((*R*)-1-amino-1-phenylmethyl)cyclopropane carboxylic acid methyl ester L-tartrate salt (5). A solution of the methyl ester **3** (1.04 g, 4.30 mmol) in ice (10 g) and chloroform (75 mL) was treated with 1 M K_2CO_3 (25.0 mL). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (3×) and EtOAc (2×). The combined organic layers were dried (Na_2SO_4) and evaporated and the resulting free amine (850 mg, 96%) was dissolved in ethanol (15.0 mL) and treated with L-tartaric acid (622 mg, 4.14 mmol). The reaction mixture was heated at reflux for 10 min (white suspension formed), and water was added until the solid material dissolved. Ethanol (10.0 mL) was added and the mixture was allowed to stand for 24 h at room temperature. The mixture was filtered to give a colorless solid (725 mg) which was recrystallized from ethanol/water (20:1) to afford **5**[11] (604 mg, 41%) as a crystalline solid. The filtrates from two crystallizations were combined, concentrated and dissolved in water. Ice was added, followed by chloroform and 1 M K_2CO_3 (25.0 mL). The aqueous layer was extracted with $CHCl_3$ (3×) and EtOAc (2×) and the combined organic layers were dried and evaporated. The free amine was dissolved in a mixture of ethanol (10.0 mL) and water (1.5 mL) and D-tartaric acid (368 mg, 2.45 mmol) was added. The mixture was heated until all solid materials dissolved, treated with ethanol (10.0 mL), and slowly cooled to room temperature. Filtration afforded **4**[11] (614 mg, 42%) as a colorless crystalline solid.

4.1.4. (1*S*,2*S*)-2-((*S*)-(Benzyloxycarbonylamino)phenylmethyl)cyclopropane carboxylic acid methyl ester (6{*1,1*}) and (1*R*,2*R*)-2-((*R*)-(benzyloxycarbonylamino)-phenyl-methyl)cyclopropane carboxylic acid methyl ester (7{*1,1*}). The tartrate salt **4** (0.48 g, 1.34 mmol) was dissolved in EtOAc (5.0 mL) and water (5.0 mL), cooled to 0 °C followed by $NaHCO_3$ (0.56 g, 6.68 mmol) and benzyl chloroformate (0.22 mL, 1.60 mmol). The mixture was stirred at 0 °C for 2 h, diluted with water, extracted with CH_2Cl_2 (3×) and the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. Purification by chromatography on SiO_2 (hexanes/EtOAc 17/3) afforded **6**{*1,1*}[11] (0.43 g, 95%): $[\alpha]_D$+51.5 (*c* 1.1, $CHCl_3$). According to the same protocol, tartrate salt **5** (0.57 g, 1.60 mmol), $NaHCO_3$ (0.67 g, 8.00 mmol), benzyl chloroformate (0.28 mL, 1.92 mmol) in EtOAc (5.0 mL) and water (5.0 mL) afforded **7**{*1,1*}[11] (0.53 g, 97%): $[\alpha]_D$ −48.6 (*c* 1.0, $CHCl_3$).

4.1.5. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid methyl ester (6{*1,3*}) and (1*R*,2*R*)-2-((*R*)-(diphenylphosphinylamino)-phenylmethyl)cyclopropane carboxylic acid methyl ester (7{*1,3*}). The tartrate salt **4** (608 mg, 1.71 mmol) was dissolved in water (15.0 mL) and placed in a separatory funnel. Ice was added and the cold mixture was treated with 1 M K_2CO_3 solution (15.0 mL) and extracted with $CHCl_3$ (3×) and EtOAc (2×). The combined organic layers were

dried (Na_2SO_4) and evaporated to afford the free amine as a colorless oil. The residue was dissolved in dry CH_2Cl_2 (15.0 mL), cooled to 0 °C and treated with $Ph_2P(O)Cl$ (809 mg, 3.42 mmol) followed by DIPEA (1.18 mL, 6.75 mmol). The reaction mixture was warmed to room temperature, stirred for 10 h, diluted with EtOAc, washed with 10% HCl, water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/acetone 4/1, containing 1% v/v Et_3N) to afford **6**{*1*,*3*}[11] (664 mg, 96%) as a colorless solid: $[\alpha]_D+34.2$ (*c* 0.8, $CHCl_3$). According to the same protocol, **5** (600 mg, 1.69 mmol), $Ph_2P(O)Cl$ (800 mg, 3.38 mmol) and DIPEA (1.18 mL, 6.75 mmol) in dry CH_2Cl_2 (15.0 mL) afforded **7**{*1*,*3*}[11] (644 mg, 94%) as a colorless solid: $[\alpha]_D$ −34.8 (*c* 0.8, $CHCl_3$).

4.2. C-Terminal functionalizations

A solution of the cyclopropyl amino acid methyl esters **6**{*1*,*3*} and **7**{*1*,*3*} (0.935 mmol), respectively, in a mixture of methanol (10.0 mL) and THF (2.0 mL) was treated at room temperature with 1.0 M NaOH (10.0 mL). The resulting suspension was stirred until a clear solution was obtained (6 h). The resulting free acids **6**{*2*,*3*} and **7**{*2*,*3*} were extracted using an automated liquid–liquid extraction system (ALLEXis:[28] add 1.0 M HCl (20.0 mL), add EtOAc (20.0 mL), mix three times, extract lighter phase, add EtOAc (20.0 mL), mix three times, extract lighter phase, add EtOAc (20.0 mL), mix three times, extract lighter phase, add saturated aqueous NaCl solution (15.0 mL), mix three times, extract lighter phase). The organic phases were dried ($MgSO_4$) and all volatile components were removed in vacuo. The free acids were obtained in an average yield of 88% as colorless crystals (0.83 mmol). Each acid was dissolved in chlorobenzene (22.0 mL) and divided into eleven 2–5 mL Emrys process vials (0.0750 mmol each). Compounds **6**{*2*,*3*} and **7**{*2*,*3*} dissolved only upon heating to 60 °C in a water bath. Twenty vials (ten vials of each acid) were used to synthesize the corresponding amides according to the general protocols A–C, the remaining two vials contained the two free acids **6**{*2*,*3*} and **7**{*2*,*3*} as part of the desired library and all volatile components were removed in vacuo from these vials.

General protocol A.[30] PS-carbodiimide (loading 1.20 mmol/g, 125 mg, 0.150 mmol, 2 equiv) and 1-hydroxybenzotriazole (15.3 mg, 0.113 mmol, 1.5 equiv) were added to the acid in chlorobenzene. The reaction mixture was stirred for 5 min at room temperature before addition of the amine. Volatile amines such as methylamine (**8**{*3*}) (33 wt% in ethanol, 143 μL, 1.88 mmol, 25.0 equiv) and cyclopropanemethylamine (**8**{*4*}) (30.2 mg, 0.375 mmol, 5.0 equiv) were added in excess. Benzylamine (**8**{*5*}), 2-aminomethylpyridine (**8**{*7*}), 5-methyl-2-furanmethanamine (**8**{*8*}) and (1,5-dimethyl-1*H*-pyrazol-3-yl)methylamine (**8**{*9*}) were added as 0.4 M solution in chlorobenzene (188 μL, 0.0750 mmol, 1.0 equiv). 4-Methylsulfonylbenzylamine hydrochloride (**8**{*6*}) (8.9 mg, 0.075 mmol, 1.0 equiv) was added neat, followed by triethylamine (15.2 mg, 0.150 mmol, 2.0 equiv). After addition of the amines, the microwave tubes were sealed and irradiated for 5 min (hold time) at 100 °C (applying an initial power of 200 W). Reactions involving volatile amines (**8**{*3*} and **8**{*4*}) were irradiated for 30 min at 60 °C. After cooling to room temperature, the microwave tubes were uncapped and the reaction mixtures (including the resin) were loaded onto SPE-cartridges (prepacked with 500 mg silica-bound carbonate and preconditioned with CH_2Cl_2 (1.0 mL)). The SPE-cartridges were washed three times with CH_2Cl_2 (2.0 mL each). The eluants were collected via gravity filtration. Evaporation of all volatile components in a centrifugal vacuum evaporator (Genevac HT-4) provided the desired amides in yields of 23–98% (Table 1).

General protocol B. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (28.8 mg, 0.150 mmol, 2.0 equiv) and 1-hydroxybenzotriazole (15.3 mg, 0.113 mmol, 1.5 equiv) were added to a solution of the acid in chlorobenzene. The reaction mixture was stirred for 5 min at room temperature before 2-aminonaphthalene (**8**{*10*}) (188 μL of a 0.4 M solution in chlorobenzene, 0.075 mmol, 1.0 equiv) was added. The vials were sealed, purged with argon and stirred at room temperature for 12 h. The reaction mixtures were loaded onto ChemElut cartridges (3.0 mL cartridges, preconditioned for 5 min with 2.0 mL water) and washed with CH_2Cl_2 (2×2.0 mL). The eluants were collected via gravity filtration and all volatile components were removed in vacuo. Automated parallel chromatography on SiO_2 (ISCO Optix 10 System, 4 g cartridges, hexanes to hexanes/EtOAc, 1:1), followed by evaporation of all volatile components in a centrifugal vacuum evaporator (Genevac HT-4) provided the desired amides in yields of 69–72% (Table 1).

General protocol C.[31] 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (44.9 mg, 0.150 mmol, 2.0 equiv) and the corresponding amine were added to a solution of the acid in chlorobenzene. (*R*)-(−)-2-Amino-1-propanol (**8**{*11*}) was added as 0.4 M solution in chlorobenzene (281 μL, 0.113 mmol, 1.5 equiv), whereas tryptamine (**8**{*12*}) (18.1 mg, 0.113 mmol, 1.5 equiv) was added neat. After treating the reaction mixture with triethylamine (30.4 mg, 0.300 mmol, 4.0 equiv) the tube was sealed, purged with argon and stirred at room temperature for 12 h. The crude products were extracted using an automated liquid–liquid extraction system (ALLEXis:[28] add aqueous saturated NaCl solution (15.0 mL), add EtOAc (20.0 mL), mix three times, extract lighter phase, add EtOAc (20.0 mL), mix three times, extract lighter phase, add EtOAc (20.0 mL), mix three times, extract lighter phase, add aqueous 1 M HCl (15.0 mL), mix three times, extract lighter phase, add saturated $NaHCO_3$ solution (15.0 mL), mix three times, extract lighter phase, add saturated NaCl solution (15.0 mL), mix three times, extract lighter phase). The combined organic layers were dried ($MgSO_4$) and all volatile components were removed in vacuo. Automated parallel chromatography on SiO_2 (ISCO Optix 10 System, 4 g cartridges, hexanes to EtOAc), followed by evaporation of all volatile components in a centrifugal vacuum evaporator (Genevac HT-4) provided the desired amides in yields of 44–68% (Table 1).

4.2.1. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid cyclopropylmethyl amide (6{*4*,*3*}). According to the general protocol A,

(**6**{*4*,*3*}) (11.8 mg, 35%) was obtained as colorless crystals. Mp 198 °C; IR (KBr) 3400, 3151, 2859, 1645, 1529, 1436 cm^{-1}; ^1H NMR δ 7.92–7.78 (m, 4H), 7.55–7.26 (m, 12H), 3.54 (dd, $J=10.2$, 6.0 Hz, 1H), 3.39 (app. q, $J=$ 9.9 Hz, 1H), 3.20–3.02 (m, 2H), 2.04–1.96 (m, 1H), 1.65–1.55 (m, 1H), 1.38–1.32 (m, 1H), 1.05–0.97 (m, 1H), 0.72–0.66 (m, 1H), 0.53–0.47 (m, 2H), 0.27–0.22 (m, 2H); ^{13}C NMR δ 172.1, 142.6 (d, $J_{CP}=8.7$ Hz), 133.1 (d, $J_{CP}=$ 129.0 Hz), 132.7 (d, $J_{CP}=9.5$ Hz), 132.1 (2 signals overlapping), 131.7 (d, $J_{CP}=9.5$ Hz), 130.3, 128.8, 128.7, 128.5, 127.6, 126.3, 60.3, 44.3, 29.0, 23.5, 12.5, 10.8, 3.4, 3.3; ^{31}P NMR δ 22.9; MS (ESI) *m*/*z* (rel. intensity) 467 ($[M+Na]^+$, 100), 445 ($[M+H]^+$, 27); HRMS (ESI) *m*/*z* calculated for $C_{27}H_{30}N_2O_2P$ (M+H) 445.2045, found 445.2024.

4.2.2. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid 4-methanesulfonylbenzylamide (6{*6*,*3*}). According to the general protocol A, (**6**{*6*,*3*}) (34.4 mg, 82%) was obtained as colorless crystals: ^1H NMR δ 8.66 (app. t, $J=5.6$ Hz, 1H), 7.88–7.77 (m, 6H), 7.56 (d, $J=8.2$ Hz, 2H), 7.51–7.26 (m, 11H), 4.58 (dd, $J=15.9$, 6.7 Hz, 1H), 4.50–4.43 (m, 1H), 3.73 (dd, $J=10.8$, 6.1 Hz, 1H), 3.31 (app. q, $J=9.7$ Hz, 1H), 3.00 (s, 3H), 2.16–2.07 (m, 1H), 1.62–1.54 (m, 1H), 1.45–1.39 (m, 1H), 0.74–0.68 (m, 1H).

4.2.3. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid (pyridin-2-ylmethyl)amide (6{*7*,*3*}). According to the general protocol A (**6**{*7*,*3*}) (23.8 mg, 66%) was obtained as colorless crystals: ^1H NMR δ 8.53 (d, $J=4.2$ Hz, 1H), 8.13 (app. t, $J=5.3$ Hz, 1H), 7.89–7.77 (m, 4H), 7.60 (app. td, $J=7.7$, 1.6 Hz, 1H), 7.50–7.29 (m, 12H), 7.15 (dd, $J=6.6$, 5.3 Hz, 1H), 4.60, 4.56 (d of AB, $J=16.2$, 5.6 Hz, 2H), 3.63 (dd, $J=9.9$, 6.1 Hz, 1H), 3.46 (app. q, $J=9.7$ Hz, 1H), 2.10–2.04 (m, 1H), 1.74–1.65 (m, 1H), 1.41–1.34 (m, 1H), 0.77–0.71 (m, 1H).

4.2.4. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid naphthalen-2-ylamide (6{*10*,*3*}). According to the general protocol B (**6**{*10*,*3*}) (26.9 mg, 69%) was obtained as colorless crystals: ^1H NMR δ 10.74 (s, 1H), 8.41 (s, 1H), 7.99–7.95 (m, 4H), 7.81–7.76 (m, 4H), 7.60–7.33 (m, 13H), 3.54 (dd, $J=10.5$, 5.4 Hz, 1H), 3.37 (app. q, $J=9.4$ Hz, 1H), 2.30–2.20 (m, 1H), 1.70–1.50 (m, 2H), 1.80–1.74 (m, 1H).

4.2.5. (1*R*,2*R*)-2-((*R*)-(Diphenylphosphinylamino) phenylmethyl)cyclopropane carboxylic acid methylamide (7{*3*,*3*}). According to the general protocol A, (**7**{*3*,*3*}) (9.1 mg, 30%) was obtained as colorless crystals: ^1H NMR δ 7.91–7.77 (m, 4H), 7.54–7.30 (m, 12H), 3.62 (dd, $J=9.9$, 5.8 Hz, 1H), 3.34 (app. q, $J=9.6$ Hz, 1H), 2.78 (d, $J=4.7$ Hz, 3H), 1.98–1.88 (m, 1H), 1.65–1.57 (m, 1H), 1.39–1.33 (m, 1H), 0.68–0.62 (m, 1H).

4.2.6. (1*R*,2*R*)-2-((*R*)-(Diphenylphosphinylamino) (phenyl)methyl)cyclopropane carboxylic acid cyclopropylmethylamide (7{*4*,*3*}). According to the general protocol A, (**7**{*4*,*3*}) (14.7 mg, 44%) was obtained as colorless crystals: ^1H NMR δ 7.92–7.78 (m, 4H), 7.55–7.26 (m, 12H), 3.54 (dd, $J=10.2$, 6.1 Hz, 1H), 3.38 (app. q, $J=$ 9.9 Hz, 1H), 3.20–3.02 (m, 2H), 2.04–1.96 (m, 1H), 1.65–1.55 (m, 1H), 1.38–1.32 (m, 1H), 1.05–0.97 (m, 1H), 0.72–0.66 (m, 1H), 0.53–0.47 (m, 2H), 0.27–0.22 (m, 2H).

4.2.7. (1*R*,2*R*)-2-((*R*)-(Diphenylphosphinylamino)-phenylmethyl)cyclopropane carboxylic acid (5-methylfuran-2-ylmethyl)amide (7{*8*,*3*}). According to the general protocol A, (**7**{*8*,*3*}) (30.4 mg, 84%) was obtained as colorless crystals. Mp 170 °C; IR (KBr) 3165, 3058, 2920, 1653, 1541, 1437, 1186 cm^{-1}; ^1H NMR δ 7.86–7.78 (m, 4H), 7.71 (app. t, $J=4.1$ Hz, 1H), 7.51–7.28 (m, 11H), 6.14 (d, $J=2.6$ Hz, 1H), 5.88 (bs, 1H), 4.43–4.30 (m, 2H), 3.50 (dd, $J=10.1$, 4.1 Hz, 1H), 3.38 (app. q, $J=9.6$ Hz, 1H), 2.26 (s, 3H), 2.02–1.96 (m, 1H), 1.64–1.58 (m, 1H), 1.41–1.35 (m, 1H), 0.72–0.66 (m, 1H); ^{13}C NMR δ 172.0, 150.8 (d, $J_{CP}=87.7$ Hz), 142.5 (d, $J_{CP}=8.9$ Hz), 133.9, 132.7 (d, $J_{CP}=9.5$ Hz), 132.2 (d, $J_{CP}=7.0$ Hz), 132.0 (d, $J_{CP}=$ 2.8 Hz), 131.9 (d, $J_{CP}=2.8$ Hz), 131.6 (d, $J_{CP}=9.5$ Hz), 130.4, 128.7, 128.6 (d, $J_{CP}=4.7$ Hz), 128.5 (d, $J_{CP}=$ 4.5 Hz), 127.6, 126.3, 107.7, 106.1, 60.3, 36.8, 29.0, 23.5, 13.6, 12.5; ^{31}P NMR δ 22.9; MS (ESI) *m*/*z* (rel. intensity) 507 ($[M+Na]^+$, 100), 485 ($[M+H]^+$, 22); HRMS (ESI) *m*/*z* calculated for $C_{29}H_{29}N_2O_3PNa$ (M+Na) 507.1814, found 507.1798.

4.2.8. (1*R*,2*R*)-2-((*R*)-(Diphenylphosphinylamino)-phenylmethyl)cyclopropane carboxylic acid (1,5-dimethyl-1*H*-pyrazol-3-ylmethyl)amide (7{*9*,*3*}). According to the general protocol A, (**7**{*9*,*3*}) (26.0 mg, 72%) was obtained as colorless crystals: ^1H NMR δ 7.90–7.75 (m, 4H), 7.52–7.23 (m, 12H), 6.01 (s, 1H), 4.45 (dd, $J=15.1$, 5.6 Hz, 1H), 4.30 (dd, $J=15.1$, 5.3 Hz, 1H), 3.72 (s, 3H), 3.52 (dd, $J=5.8$, 3.8 Hz, 1H), 3.45 (app. q, $J=8.9$ Hz, 1H), 2.21 (s, 3H), 1.98–1.92 (m, 1H), 1.70–1.65 (m, 1H), 1.38–1.31 (m, 1H), 0.73–0.66 (m, 1H).

4.3. N-Terminal functionalizations

General protocol D. A 5 mL microwave tube was charged with PS-DMAP (loading 1.6 mmol/g, 0.046–0.13 mmol, 1.2 equiv), ammonium salt **6**{*1*,*2*} or **7**{*1*,*2*} (0.038–0.11 mmol, 1.0 equiv), respectively, and the solids were suspended in dry CH_2Cl_2 (0.75–2.0 mL). The suspension was treated with triethylamine (0.076–0.22 mmol, 2.0 equiv) and the acylating reagent **9**{*3–12*} (0.046–0.13 mmol, 1.2 equiv). The tube was capped and irradiated in the microwave for 10 min (hold time) at 100 °C (applying an initial power of 200 W). After cooling to room temperature, MP-trisamine[33] (loading 3.0 mmol/g, 0.038–0.11 mmol, 1.0 equiv) and MP-isocyanate[32,33] (loading 1.54 mmol/g, 0.038–0.11 mmol, 1.0 equiv) were added to the crude reaction mixture and the microwave irradiation was resumed for 5 min (hold time) at 100 °C (applying an initial power of 200 W). Upon cooling, the reaction mixture was transferred to a ChemElut SPE-cartridge (preconditioned with saturated aqueous $NaHCO_3$, 2.0 mL) and washed five times with CH_2Cl_2 (1.0 mL each). The CH_2Cl_2 eluant was collected and concentrated (Genevac HT-4) to afford the pure products.

4.3.1. (1*S*,2*S*)-2-((*S*)-(Diphenylphosphinylamino)phenylmethyl)cyclopropane carboxylic acid methyl ester (6{*1*,*3*}). According to the general protocol D, **6**{*1*,*2*}

(25 mg, 0.10 mmol), PS-DMAP (80 mg, 0.12 mmol), triethylamine (30 μL, 0.20 mmol), diphenyl phosphinic chloride (24 μL, 0.12 mmol), MP-isocyanate (70 mg, 0.10 mmol) and MP-trisamine (35 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) afforded **6**{*1,3*} (37 mg, 87%) as a colorless solid: ^{1}H NMR δ 7.94–7.87 (m, 2H), 7.75–7.68 (m, 2H), 7.56–7.42 (m, 5H), 7.36–7.30 (m, 6H), 3.88 (app. q, J=8.8 Hz, 1H), 3.62 (s, 3H), 3.34 (bt, J=7.7 Hz, 1H), 1.99–1.88 (m, 1H), 1.81–1.75 (m, 1H), 1.17–1.11 (m, 1H), 0.90–0.85 (m, 1H).

4.3.2. (1*S*,2*S*)-Methyl-2-((*S*)-phenyl(naphthalene-sulfonylamido)methyl)cyclopropanecarboxylate (6{*1,6*}). According to the general protocol D, **6**{*1,2*} (10 mg, 0.041 mmol), PS-DMAP (31 mg, 0.049 mmol), triethylamine (11 μL, 0.082 mmol), 1-naphthalene sulfonylchloride (12 mg, 0.049 mmol), MP-isocyanate (25 mg, 0.041 mmol) and MP-trisamine (13 mg, 0.041 mmol) in CH_2Cl_2 (1 mL) afforded **6**{*1,6*} (16 mg, 97%) as a pale yellow solid: ^{1}H NMR δ 8.55 (d, J=8.4 Hz, 1H), 8.02 (d, J=7.6 Hz, 1H), 7.95 (d, J=8.2 Hz, 1H), 7.88 (d, J=8.2 Hz, 1H), 7.66–7.55 (m, 2H), 7.35 (dd, J=7.8, 7.6 Hz, 1H), 7.03 (t, J=7.2 Hz, 1H), 6.95 (app. t, J=7.2 Hz, 2H), 6.86 (d, J=7.2 Hz, 2H), 5.25 (bd, J=6.2 Hz, 1H), 3.82 (app. t, J=6.4 Hz, 1H), 3.59 (s, 3H), 1.81–1.72 (m, 1H), 1.58–1.52 (m, 1H), 1.12–1.06 (m, 1H), 0.89–0.80 (m, 1H).

4.3.3. (1*S*,2*S*)-Methyl 2-((*S*)-(nicotinamido)(phenyl) methyl)cyclopropanecarboxylate (6{*1,9*}). According to the general protocol D, **6**{*1,2*} (25 mg, 0.10 mmol), PS-DMAP (80 mg, 0.12 mmol), triethylamine (30 μL, 0.20 mmol), 2-pyridinecarbonyl chloride (22 mg, 0.12 mmol), MP-isocyanate (70 mg, 0.10 mmol) and MP-trisamine (35 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) afforded **6**{*1,9*} (35 mg, >99%) as an off white solid. Mp 143–144 °C; IR (KBr) 3367, 3090, 3028, 3003, 2952, 1722, 1639 cm^{-1}; ^{1}H NMR δ 8.98 (d, J=1.8 Hz, 1H), 8.69 (dd, J=1.9, 4.8 Hz, 1H), 8.13 (ddd, J=1.8, 1.9, 8.1 Hz, 1H), 7.43–7.28 (m, 6H), 7.08 (bd, J=7.8 Hz, 1H), 4.78 (app. t, J=8.5 Hz, 1H), 3.64 (s, 3H), 2.05–1.84 (m, 2H), 1.36–1.30 (m, 1H), 1.08–1.02 (m, 1H); ^{13}C NMR δ 174.21, 164.93, 152.00, 147.91, 140.62, 135.48, 130.01, 128.67, 127.73, 126.64, 123.41, 56.02, 51.85, 26.80, 19.20, 14.46; MS (EI) *m/z* (rel. intensity) 310 (M^+, 3), 279 (9), 250 (11), 224 (70), 204 (74), 195 (23), 129 (31), 106 (87), 78 (100); HRMS (EI) *m/z* calculated for $C_{18}H_{18}N_2O_3$ (M) 310.1317, found 310.1306.

4.3.4. (1*S*,2*S*)-Methyl 2-((*S*)-(5-methylisoxazole-3-carboxamido)(phenyl)methyl)cyclopropanecarboxylate (6{*1,11*}). According to the general protocol D, **6**{*1,2*} (25 mg, 0.10 mmol), PS-DMAP (80 mg, 0.12 mmol), triethylamine (30 μL, 0.20 mmol), 5-methyl-isoxazole-3-carbonyl chloride (18 mg, 0.12 mmol), MP-isocyanate (70 mg, 0.10 mmol) and MP-trisamine (35 mg, 0.10 mmol) in CH_2Cl_2 (2.0 mL) afforded **6**{*1,11*} (30 mg, 95%) as an off white solid: ^{1}H NMR δ 7.44–7.31 (m, 5H), 7.21 (bd, J=7.7 Hz, 1H), 6.45 (s, 1H), 4.74 (app. t, J=8.6 Hz, 1H), 3.69 (s, 3H), 2.49 (s, 3H), 2.02–1.90 (m, 2H), 1.38–1.27 (m, 1H), 1.04–0.98 (m, 1H).

4.3.5. (1*R*,2*R*)-Methyl 2-((*R*)-phenyl(benzenesulfonyl-amido)methyl)cyclopropanecarboxylate (7{*1,5*}). According to the general protocol D, **7**{*1,2*} (15 mg, 0.062 mmol), PS-DMAP (50 mg, 0.074 mmol), triethylamine (20 μL, 0.12 mmol), benzenesulfonyl chloride (11 mg, 0.074 mmol), MP-isocyanate (40 mg, 0.062 mmol) and MP-trisamine (21 mg, 0.062 mmol) in CH_2Cl_2 (1.5 mL) afforded **7**{*1,5*} (23 mg, >99%) as a pale yellow solid: ^{1}H NMR δ 7.67 (d, J=7.7 Hz, 2H), 7.48 (t, J=7.5 Hz, 1H), 7.36 (dd, J=7.5, 7.7 Hz, 2H), 7.21–7.16 (m, 3H), 7.09–7.05 (m, 2H), 5.16 (bd, J=6.2 Hz, 1H), 3.92 (app. t, J=7.1 Hz, 1H), 3.66 (s, 3H), 1.87–1.78 (m, 1H), 1.72–1.66 (m, 1H), 1.19–1.13 (m, 1H), 0.93–0.87 (m, 1H).

4.3.6. (1*R*,2*R*)-Methyl 2-((*R*)-(benzamido)(phenyl) methyl)cyclopropanecarboxylate (7{*1,8*}). According to the general protocol D, **7**{*1,2*} (20 mg, 0.082 mmol), PS-DMAP (63 mg, 0.098 mmol), triethylamine (23 μL, 0.16 mmol), benzoylchloride (11 μL, 0.098 mmol), MP-isocyanate (55 mg, 0.082 mmol) and MP-trisamine (28 mg, 0.082 mmol) in CH_2Cl_2 (1.5 mL) afforded **7**{*1,8*} (24 mg, 92%) as a colorless solid. Mp 160–161 °C; IR (KBr) 3362, 3030, 2949, 1725, 1635 cm^{-1}; ^{1}H NMR δ 7.80–7.77 (m, 2H), 7.55–7.31 (m, 8H), 6.49 (bd, J=8.4 Hz, 1H), 4.85 (app. t, J=8.4 Hz, 1H), 3.69 (s, 3H), 2.04–1.93 (m, 2H), 1.37–1.31 (m, 1H), 1.08–1.01 (m, 1H); ^{13}C NMR δ 174.04, 166.71, 140.73, 134.27, 131.50, 128.71, 128.47, 127.71, 126.98, 126.70, 55.56, 51.75. 26.82, 18.99, 14.13; MS (EI) *m/z* (rel. intensity) 309 (M^+, 14), 278 (15), 222 (46), 204 (48), 129 (60), 105 (73), 77 (100); HRMS (EI) *m/z* calculated for $C_{19}H_{19}NO_3$ 309.1365, found 309.1368.

4.3.7. (1*R*,2*R*)-Methyl 2-((*R*)-(nicotinamido)(phenyl) methyl)cyclopropanecarboxylate (7{*1,9*}). According to the general protocol D, **7**{*1,2*} (15 mg, 0.062 mmol), PS-DMAP (50 mg, 0.074 mmol), triethylamine (20 μL, 0.12 mmol), nicotinoyl chloride (11 mg, 0.074 mmol), MP-isocyanate (40 mg, 0.062 mmol) and MP-trisamine (21 mg, 0.062 mmol) in CH_2Cl_2 (1.5 mL) afforded **7**{*1,9*} (20 mg, >99%) as an off white solid: ^{1}H NMR δ 8.99 (d, J=1.9 Hz, 1H), 8.71 (dd, J=4.8, 1.8 Hz, 1H), 8.13 (ddd, J=8.0, 1.9, 1.8 Hz, 1H), 7.44–7.29 (m, 6H), 6.87 (bd, J=7.5 Hz, 1H), 4.80 (app. t, J=8.4 Hz, 1H), 3.66 (s, 3H), 2.05–1.94 (m, 2H), 1.37–1.31 (m, 1H), 1.09–1.02 (m, 1H).

4.3.8. (1*R*,2*R*)-Methyl 2-((*R*)-phenyl(pyrazine-2-carboxamido)methyl)cyclopropanecarboxylate (7{*1,10*}). According to the general protocol D, **7**{*1,2*} (15 mg, 0.062 mmol), PS-DMAP (50 mg, 0.074 mmol), triethylamine (20 μL, 0.12 mmol), 2-pyrazinecarbonyl chloride (11 mg, 0.074 mmol), MP-isocyanate (40 mg, 0.062 mmol) and MP-trisamine (21 mg, 0.062 mmol) in CH_2Cl_2 (1.5 mL) afforded **7**{*1,10*} (15 mg, 76%) as an orange solid: ^{1}H NMR δ 9.42 (d, J=1.4 Hz, 1H), 8.77 (d, J=2.4 Hz, 1H), 8.54 (dd, J=2.4, 1.5 Hz, 1H), 8.23 (bd, J=4.9 Hz, 1H), 7.45–7.32 (m, 5H), 4.82 (app. t, J=8.8 Hz, 1H), 3.68 (s, 3H), 2.08–1.92 (m, 2H), 1.38–1.31 (m, 1H), 1.08–1.01 (m, 1H).

4.4. LC–MS analysis

LC–MS analysis was performed on a Thermo Finnigan octopole ion trap with APCI probe (positive ion detection mode), using a reversed-phase C_{18} column (acetonitrile/1% acetic acid in water 3/2, 1 mL/min). ELS detection was performed using split flow from the HPLC and a PL-ELS

2100 detector from Polymer Laboratories (nitrogen gas flow 1.25 SLM, evaporator 45 °C and nebulizer 45 °C).

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One-pot sequential four-component coupling via Cp*RuCl-catalyzed cyclotrimerization and Suzuki–Miyaura coupling

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Abstract—The catalytic intermolecular cyclotrimerization of alkynylboronates, propargyl alcohols, and terminal alkynes was accomplished by means of the ruthenium catalysis and the temporary tethering approach with the C–B–O linkage to give rise to highly substituted arylboronates with excellent selectivity. The resultant arylboronates were further converted to highly substituted biaryls via the Suzuki–Miyaura coupling with various aryl iodides using $Pd_2(dba)_3/PCy_3$ as a catalyst precursor in aqueous toluene. As a consequence, the four-component coupling approach to highly substituted biaryls was successfully established by combining these two operations into a sequential one-pot process.

1. Introduction

Transition-metal-catalyzed multi-component coupling cyclizations are powerful methods for assembling complex cyclic frameworks from inexpensive acyclic starting materials.[1] In particular, a sequential catalytic process that effects multiple reactions in a single-pot is highly desirable, because it would reduce wastes produced from the separation of intermediates.[2] Toward this end, each catalytic reaction should be refined as to be mutually compatible, and thus, a judicious choice of the catalyst combination as well as a substrate design play critical roles in the one-pot sequential catalytic process. In this context, we recently reported the one-pot sequential [2+2+2] cyclotrimerization/Suzuki–Miyaura coupling process, in which the catalytic cyclotrimerization of three different unsymmetrical alkynes was achieved regioselectively by means of a boron temporary tether, and the subsequent Suzuki–Miyaura coupling of the resultant cyclic arylboronates with aryl iodides successfully gave rise to the desired biaryls in reasonable yields.[3] Herein, we report the full detail of the study on the one-pot sequential four-component coupling synthesis of biaryls.

Keywords: Ruthenium catalysis; Cyclotrimerization; Suzuki–Miyaura coupling; Biaryl.
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2. Results and discussion

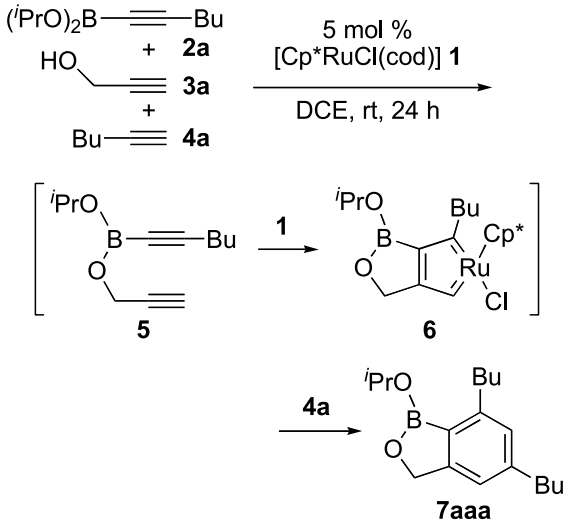
2.1. Exploratory study on the Cp*RuCl-catalyzed cyclotrimerization of three unsymmetrical alkynes by means of boron temporary tether

The transition-metal-catalyzed [2+2+2] alkyne cyclotrimerization has received continuous attention as a straightforward route to substituted benzenes.[4] Because of its atom-economical[5] and convergent nature, the cyclotrimerization approach to substituted benzene rings is considerably advantageous over conventional strategies requiring the sequential substitutions of a benzene ring by way of electrophilic aromatic substitutions or orthometalation techniques.[6] Although the selective cyclotrimerization of three different alkynes was accomplished using stoichiometric transition metal reagents,[7–9] the development of a catalytic protocol is highly desirable in terms of the atom-economy. In this context, intramolecular approach utilizing diynes or triynes have been explored as a promising tool to afford polycyclic arenes selectively.[10] However, additional synthetic operations are required, if the resultant polycyclic framework is not desirable. An unnecessary ring moiety needs to be cleaved and transformed into required side chains. Moreover, the preparation of polyalkyne substrates equipped with a cleavable tether as well as substituents or functional groups at appropriate positions can be troublesome.

One effective strategy to address these issues is the

temporary connecting of monoalkynes with a disposable tether group.[11] To realize the selective cyclotrimerization of three different alkynes through a temporary tether, Cp*RuCl(cod) **1** (Cp* = η^5-C_5Me_5, cod = 1,5-cyclooctadiene) is the desired catalyst precursor, because the previous density functional calculations revealed that the oxidative cyclization on the Cp*RuCl fragment yielding a key ruthenacycle intermediate is the rate-determining step, and, therefore, the ruthenium catalysis favors 1,6-diynes rather than monoalkynes.[12] In addition, the cycloaddition of unsymmetrical diyne with terminal monoalkynes proceeds with excellent regioselectivity at room temperature under the ruthenium catalysis.[12a] As a temporary tether, a C–B–O linkage is the better choice rather than widely prevalent C–Si–O or O–Si–O linkages,[13] because relatively long Si–C and Si–O bonds might cause deleterious effect on the formation of the ruthenacycle intermediate. Surprisingly, such boron tethers have remained less explored in transition-metal catalysis, while the boron temporary tethers were successfully applied to Diels–Alder reactions.[14] Various unsaturated organoboranes have been employed for transition-metal-catalyzed reactions,[15] but, to the best of our knowledge, the temporary boron tether approach has been confined to the ruthenium-catalyzed enyne metathesis using alkynyl- or allylboronates reported by Schreiber and Micalizio.[16]

With these in mind, we carried out the exploratory study on the cyclotrimerization of 1-hexynylboronate **2a**, propargyl alcohol **3a**, and 1-hexyne **4a** (Scheme 1). Propargyl alcohol **3a** (1.1 equiv) was added dropwise over 15 min to a solution of 5 mol% **1**, 1-hexynylboronate **2a**, and 1-hexyne **4a** (4 equiv) in 1,2-dichloroethane (DCE) at room temperature, and the solution was stirred for 24 h. In the ^{1}H NMR spectrum of the crude product mixture, the absorptions of aromatic and benzylic methylene protons were observed together with those of two *n*-butyl chains, indicative of the cyclotrimerization of the three alkyne components taking place via the expected diyne and ruthenacycle intermediates **5** and **6**. Unfortunately, the resultant arylboronate **7aaa** could not be purified at this stage, due to the facile exchange of the boronate ligands. Accordingly, we further attempted



Scheme 1.

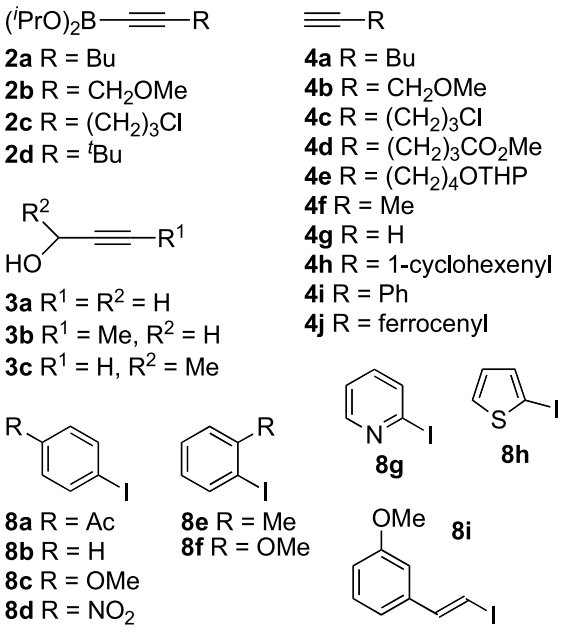
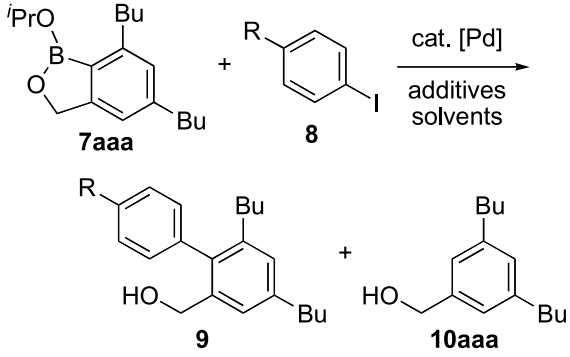


Figure 1. Starting materials used in this study.

the Suzuki–Miyaura coupling[17] of the crude **7aaa** without purification.

2.2. Suzuki–Miyaura coupling of cyclotrimerization product

The newly prepared **7aaa** was subjected to the Suzuki–Miyaura coupling with aryl iodides as shown in Scheme 2 and Table 1. Upon treatment with 5 mol% $Pd(PPh_3)_4$, *p*-iodoacetophenone **8a** (1.5 equiv), and K_2CO_3 in refluxing THF/H_2O for 24 h, the desired **9aaaa** was obtained in 32% yield together with a protodeboration product **10aaa** in 22% yield (entry 1). Significantly, both of these products were obtained as a single regioisomer. To minimize the unwanted protodeboration, the cross coupling conditions were optimized. In the absence of water, protodeboration was effectively suppressed and **9aaaa** was obtained exclusively in 68% yield (entry 2). Furthermore, we found that the reaction reached to completion within 2 h in heterogeneous solvent system toluene/H_2O at 70 °C to afford **9aaaa** in 71% yield (entry 3). The couplings with less reactive iodobenzene **8b** and *p*-iodoanisole **8c** required prolonged reaction time of 20 h otherwise under the same reaction conditions (entries 4 and 5). In addition, the desired product **9aaac** was



Scheme 2.

Table 1. Coupling of arylboronate **7aaa** and aryliodides **8**

Entry	ArI (**8**) (1.5 equiv)	Catalyst	Conditions	**9** Yield (%)	**10aaa** Yield (%)
1	*p*-AcC_6H_4I (**8a**)	5 mol% $Pd(PPh_3)_4$	THF/H_2O, reflux, 24 h	**9aaaa**, 32	22
2	**8a**	5 mol% $Pd(PPh_3)_4$	THF, reflux, 24 h	**9aaaa**, 68	—
3	**8a**	5 mol% $Pd(PPh_3)_4$	Toluene/H_2O, 70 °C, 2 h	**9aaaa**, 71	—
4	PhI (**8b**)	5 mol% $Pd(PPh_3)_4$	Toluene/H_2O, 70 °C, 20 h	**9aaab**, 71	—
5	*p*-$MeOC_6H_4I$ (**8c**)	5 mol% $Pd(PPh_3)_4$	Toluene/H_2O, 70 °C, 20 h	**9aaab**, 19/**9aaac**, 54	—
6	**8c**	2.5 mol% $Pd_2(dba)_3$ / 11 mol% PCy_3	Toluene/H_2O, 70 °C, 6 h	**9aaac**, 70	—

accompanied by the phenyl-substituted product **9aaab** as a result of the aryl-group interchange between the phosphorus-bound phenyl groups and the *p*-methoxyphenyl ligand.[18] When the combination of tricyclohexylphosphine, PCy_3, and $Pd_2(dba)_3$ was employed instead of $Pd(PPh_3)_4$, the reaction completed within 6 h and **9aaac** was successfully obtained as a sole product in 70% yield (entry 6).

2.3. Scope and limitations of one-pot cyclotrimerization/Suzuki–Miyaura coupling process

Having optimized the cross coupling conditions, the generality of the one-pot cyclotrimerization/Suzuki–Miyaura coupling was examined as summarized in Table 2 and Figure 1. With shorter reaction time of 5 h, the cyclotrimerization of **2a**, **3a**, and **4a** proceeded satisfactorily, and the biphenyl derivative **9aaaa** was obtained in 73% yield, after the Suzuki–Miyaura coupling with **8a** using the optimal catalyst precursors $Pd_2(dba)_3$/PCy_3 (entry 1). The less reactive iodides **8b** and **8c**, or nitro-substituted **8d** bearing a high coordinating ability underwent cross coupling with the arylboronate intermediate **9aaa** to furnish **9aaab**, **9aaac**, and **9aaad** in similar yields (entries 3–5). In contrast, sterically demanding *o*-substituted aryl iodides failed to undergo Suzuki–Miyaura coupling. To overcome such an inefficiency, 2-dicyclohexylphosphino-2′,6′-dimethoxy-biphenyl reported by Buchwald et al.[19] was used instead of tricyclohexylphosphine to furnish biaryls **9aaae** and **9aaaf** in 55 and 67% yields, respectively, (entries 5 and 6). In addition to the iodobenzenes, 2-iodopyridine **8g** and 2-iodothiophene **8h** can be used for the present one-pot coupling. Although longer reaction time of 24 h was required to ensure the cross coupling with these heterocyclic components, the desired hetero-biaryls **9aaag** and **9aaah** were obtained in 53 and 69% yields, respectively, (entries 7 and 8). Stilbene derivative **9aaai** was synthesized by way of the coupling with *trans*-*p*-methoxy-2-iodostyrene **8i** albeit in a moderate yield (entry 9).

With respect to the third alkyne components, methyl propargyl ether **4b**, 5-chloropent-1-yne **4c**, methyl 5-hexynoate **4d**, and *O*-protected 5-hexyn-1-ol **4e** can be employed for the boron-tethered cyclotrimerization (entries 10–13). After the cross coupling with **8a**, the desired biaryls bearing a chloroalkyl, an ester, or a protected alcohol functionality were obtained in 68–76% yields. These results indicate that the boron-tethered diyne intermediate was selectively formed with propargyl alcohol **3a**. In addition, gaseous propyne **4f** or acetylene **4g** were also incorporated into the final products **9aafa** and **9aaga** selectively (entries 14 and 15). On the other hand, conjugated alkynes showed diminished reactivity. Actually, employing ethynylcyclohexene **4h** resulted in the moderate-yield formation of the corresponding product **9aaha** (entry 16), and what is worse, protodeboration product **10aai** was exclusively formed in 59% yield, when ethynylbenzene **4i** was used. The inability of Suzuki–Miyaura coupling for the aromatic alkynes was improved by the filtration of the crude cyclotrimerization product through a silica gel short column prior to the cross coupling. In this way, the desired teraryl **9aaia** was obtained albeit in lower yield together with **10aai** (entry 17). Similarly, the four-component coupling involving ethynylferrocene **4j** furnished ferrocene-substituted **9aaja** in 56% yield (entry 18).

In place of propargyl alcohol **3a**, 2-butyn-1-ol **3b**, and 3-butyn-2-ol **3c** were allowed to react with the boronate **2a**, and acetylene **4g** or 1-hexyne **4a**, although these alkynols require reaction time of 72 h for cyclotrimerization and/or the catalyst loading of 10 mol% (entries 19 and 20). The corresponding biaryls **9abga** and **9acaa** were obtained in 55 and 49% yields, respectively. These results are in striking contrast to those with 2-methyl-3-butyn-2-ol or propargyl amines, which proved to be totally ineffective.

Finally, two more alkynylboronates **2b** and **2c** bearing an ether or a chloroalkyl functionality were subjected to the one-pot coupling (entries 21 and 22). Although the cyclotrimerization of these boronates with **3a** and **4a** requires prolonged reaction time compared to that of **2a**, Suzuki–Miyaura coupling of the resultant arylboronate intermediates with **8a** successfully gave rise to biaryls **9baaa** and **9caaa** in 63 and 66% yields, respectively. These products were the regioisomers of **9aaba** or **9aacab** (entry10 vs 21, and entry 11 vs 22). In contrast, 3,3-dimethyl-1-propynylboronate **2d** failed to undergo cyclotrimerization with propargyl alcohol **3a** and 1-hexyne **4a**.

2.4. Extension to partially intramolecular reactions

The present ruthenium-catalyzed intermolecular alkyne cyclotrimerization with the boron temporary tether was further extended to the partially intramolecular versions of diynylboronate **11** or diynol **14**. The 1,6-octadiynylboronate **11** and 2-butyn-1-ol **3b** (2 equiv) were treated with 5 mol% **1** in DCE at room temperature for 24 h. The resultant cyclic boronate **12** was then allowed to react with *p*-iodoacetophenone **8a** under the optimal conditions to afford **13** in 72% yield with excellent regioselectivity (Scheme 3). In a similar way, 1-hexynylboronate **2a** and 2,8-heptadiyne-1-ol **14** (1.1 equiv) were converted to **16** in 60% yield via the corresponding tricyclic boronate intermediate **15** (Scheme 4). These partially intramolecular cyclotrimerizations proceeded with definite regioselectivity via temporarily connected triyne intermediates.

Table 2. One-pot four-component couplings

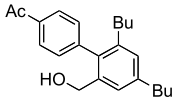
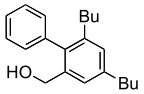
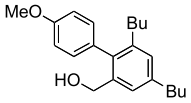
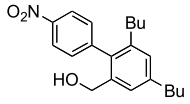
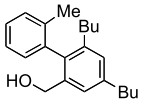
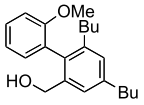
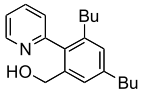
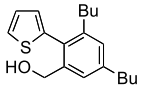
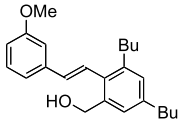
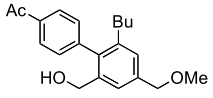
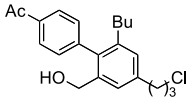
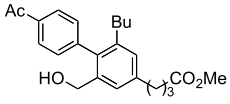
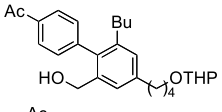
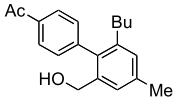
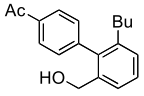
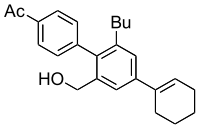
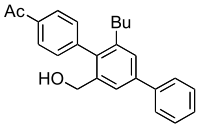
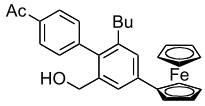
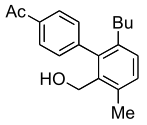
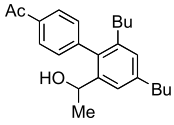
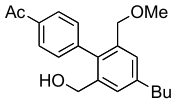
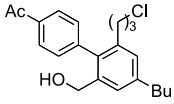
Entry	Cyclotrimerization alkynes/time (h)[a]	Suzuki–Miyaura coupling aryliodides/time (h)[b]	Products	Yield (%)
1	**2a**, **3a**, **4a**/5	**8a**/3		**9aaaa**, 73
2	**2a**, **3a**, **4a**/5	**8b**/6		**9aaab**, 71
3	**2a**, **3a**, **4a**/5	**8c**/6		**9aaac**, 70
4	**2a**, **3a**, **4a**/5	**8d**/4		**9aaad**, 71
5	**2a**, **3a**, **4a**/5	**8e**/5[c]		**9aaae**, 55
6	**2a**, **3a**, **4a**/5	**8f**/5[c]		**9aaaf**, 67
7	**2a**, **3a**, **4a**/5	**8g**/24		**9aaag**, 53
8	**2a**, **3a**, **4a**/5	**8h**/24		**9aaah**, 69
9	**2a**, **3a**, **4a**/5	**8i**/20		**9aaai**, 51
10	**2a**, **3a**, **4b**/5	**8a**/3		**9aaba**, 69
11	**2a**, **3a**, **4c**/5	**8a**/3		**9aaca**, 76
12	**2a**, **3a**, **4d**/5	**8a**/4		**9aada**, 73
13	**2a**, **3a**, **4e**/24	**8a**/6		**9aaea**, 68
14	**2a**, **3a**, **4f**/24[d]	**8a**/5		**9aafa**, 70
15	**2a**, **3a**, **4g**/24[d]	**8a**/4		**9aaga**, 67
16	**2a**, **3a**, **4h**/24	**8a**/6		**9aaha**, 56
17	**2a**, **3a**, **4i**/24	**8a**/24[e]		**9aaia**, 34

Table 2 (*continued*)

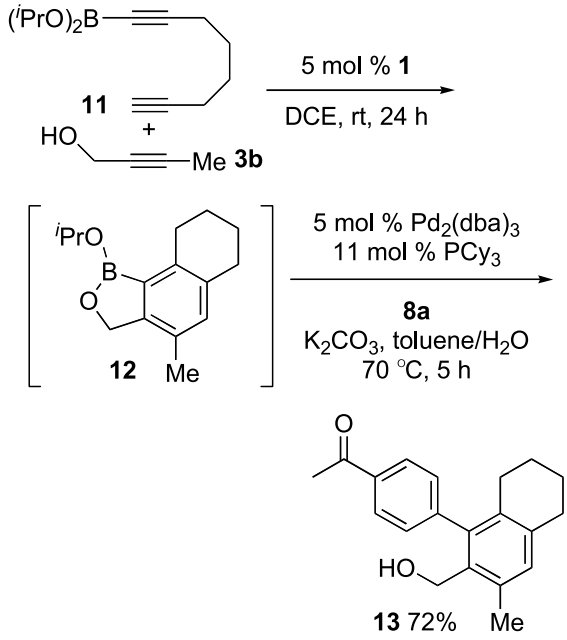
Entry	Cyclotrimerization alkynes/time (h)[a]	Suzuki–Miyaura coupling aryliodides/time (h)[b]	Products	Yield (%)
18	**2a**, **3a**, **4j**/24	**8a**/24[e]		**9aaja**, 56
19	**2a**, **3b**, **4g**/72[d]	**8a**/5		**9abga**, 55
20	**2a**, **3c**, **4a**/24	**8a**/4		**9acaa**, 49
21	**2b**, **3a**, **4a**/24	**8a**/4		**9baaa**, 63
22	**2c**, **3a**, **4a**/24	**8a**/4		**9caaa**, 66

[a] In 1,2-dichloroethane (4 mL), **2**, **3** (1.1 equiv), and **4** (4 equiv) were treated with 5 mol% **1** (10 mol% for entries 19 and 20) under Ar atmosphere at room temperature.
[b] Crude arylboronates were treated with **8** (1.5 equiv) in toluene/H_2O at 70 °C in the presence of 2.5 mol% $Pd_2(dba)_3$ and 11 mol% PCy_3.
[c] 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl was used instead of tricyclohexylphosphine.
[d] Under 1 atm propyne or acetylene.
[e] Crude arylboronates were filtered through a silica gel short column before Suzuki–Miyaura coupling. The protodeboration product **10aai** was also obtained in 28% yield for entry 17.

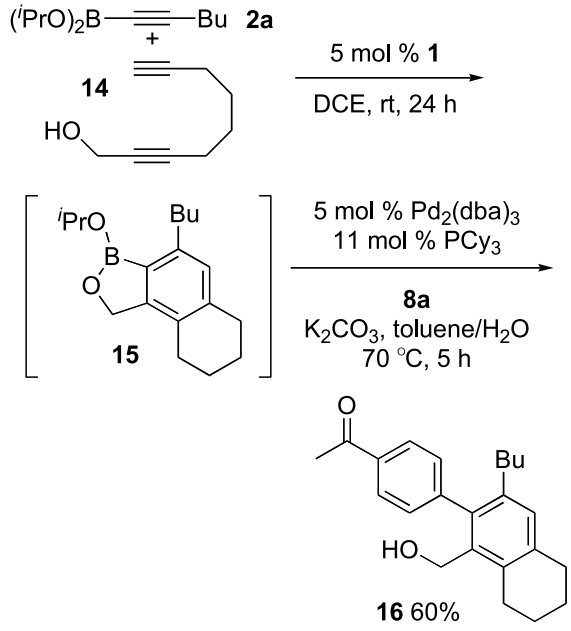
3. Conclusion

In conclusion, the catalytic intermolecular cyclotrimerization of three different unsymmetrical alkynes was accomplished by means of the ruthenium catalysis and the temporary tethering approach with the C–B–O linkage. The crude arylboronates were further applied to the Suzuki–Miyaura coupling with various aryl iodides using $Pd_2(dba)_3$/$2PCy_3$ as a catalyst precursor in aqueous toluene to afford biaryls. As a result, the novel four-component coupling approach to highly substituted biaryls was successfully established by combining these two operations into a sequential one-pot process.

The partially intramolecular versions of the temporary tethering cyclotrimerization were also realized using the diynylboronate or the diynol.



Scheme 3.



Scheme 4.

4. Experimental

4.1. General

Flash chromatography was performed with a silica gel column (Cica silica gel 60N) eluted with mixed solvents [hexane/AcOEt]. TLC analyses were performed with Merck TLC plate silica gel 60 F254. ^{1}H and ^{13}C NMR spectra were measured on a Varian Mercury 300 NMR spectrometer as $CDCl_3$ solutions at 25 °C. ^{1}H NMR chemical shifts are reported in terms of chemical shift (δ, ppm) relative to the singlet at 7.26 ppm for chloroform. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; sext, sextet; sept, septet; m, multiplet. Coupling constants are reported in Hz. ^{13}C NMR spectra were fully decoupled and are reported in terms of chemical shift (δ, ppm) relative to the triplet at $\delta=77.0$ ppm for $CDCl_3$. Infrared spectra were recorded on a JASCO FT/IR-230. Mass spectra were recorded on a JEOL JMS 700 mass spectrometer. Elemental analyses were performed at the Microanalytical Center of Kyoto University or Instrumental Analysis Facility of Nagoya University. Melting points were obtained by a Büchi Melting Point B-540 and are uncorrected. 1,2-Dichloroethane was distilled from CaH_2, and degassed before use. Cp*RuCl(cod),[20] $Pd_2(dba)_3\cdot CHCl_3$,[21] and alkynylboronates[22] were prepared according to the literature procedures. Commercially available diisopropyl 3,3-dimethyl-1-propynylboronate and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl were purchased and used without further purifications.

4.1.1. Representative procedure for one-pot cyclotrimerization/Suzuki–Miyaura coupling: synthesis of biphenyl 9aaaa from 1-hexynylboronate 2a, propargyl alcohol 3,1-hexyne 4a, and *p*-iodoacetophenone 8a. To a solution of Cp*RuCl(cod) (**1**) (9.5 mg, 0.025 mmol), 1-hexynylboronate **2a** (105.1 mg, 0.50 mmol), and 1-hexyne **4a** (164.3 mg, 2.0 mmol) in dry degassed 1,2-dichloroethane (1 mL) was added a solution of propargyl alcohol **3a** (30.8 mg, 0.55 mmol) in dry degassed 1,2-dichloroethane (3 mL) over 15 min at room temperature under Ar atmosphere. The solution was stirred at room temperature under Ar atmosphere for 5 h, and then, the solvent was removed under reduced pressure. To the residue were added $Pd_2(dba)_3\cdot CHCl_3$ (13.0 mg, 0.0125 mmol), PCy_3 (15.9 mg, 0.055 mmol), *p*-iodoacetophenone **8a** (184.5 mg, 0.75 mmol), toluene (3.5 mL), and 2 M aq K_2CO_3 (1.5 mL), and the reaction mixture was degassed at −78 °C under reduced pressure. After heating at 70 °C under Ar atmosphere for 3 h, the resultant solution was extracted with AcOEt (3 mL×3) and the organic layer was dried with $MgSO_4$. The solvent was evaporated and the crude product was purified by silica gel flash column chromatography (hexane/AcOEt 6:1) to give biphenyl **9aaaa** (123.4 mg, 73%) as pale yellow oil (R_f 0.2, hexane/AcOEt 3:1); IR (neat) 3424, 1682, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (t, $J=7.2$ Hz, 3H), 0.96 (t, $J=7.2$ Hz, 3H), 1.15 (sext, $J=7.5$ Hz, 2H), 1.32–1.47 (m, 4H), 1.60–1.70 (m, 2H), 1.85–2.00 (br s, 1H), 2.29 (t, $J=8.1$ Hz, 2H), 2.64 (t, $J=8.1$ Hz, 2H), 2.64 (s, 3H), 4.28 (s, 2H), 7.06 (d, $J=1.5$ Hz, 1H), 7.21 (d, $J=1.5$ Hz, 1H), 7.29 (dd, $J=8.5$, 2.1 Hz, 2H), 8.00 (dd, $J=8.5$, 2.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.82, 14.02, 22.50, 22.54, 26.60, 33.00, 33.54, 33.62, 35.51, 63.32, 125.05, 128.04, 128.27, 129.89, 135.53, 136.28, 138.04, 140.35, 142.50, 144.71, 197.69; MS (EI): *m/z* (%): 338 (100) [M$^+$], 323 (18) [M$^+$−Me], 295 (50) [M$^+$−COMe], 277 (70) [M$^+$−COMe–H_2O], 265 (25) [M$^+$−COMe–HCHO]; EA calcd (%) for $C_{23}H_{30}O_2$ (338.48): C, 81.61; H, 8.93; found: C, 81.51; H, 9.03.

4.1.2. Compound 9aaab. Yield 71%; oil (R_f 0.45, hexane/AcOEt 3.5:1); IR (neat) 3315, 1609 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (t, $J=7.5$ Hz, 3H), 0.98 (t, $J=7.5$ Hz, 3H), 1.18 (sext, $J=7.5$ Hz, 2H), 1.34–1.49 (m, 4H), 1.58 (br s, 1H), 1.62–1.73 (m, 2H), 2.32 (t, $J=7.8$ Hz, 2H), 2.66 (t, $J=7.8$ Hz, 2H), 4.33 (s, 2H), 7.07 (s, 1H), 7.16–7.22 (m, 3H), 7.33–7.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.87, 14.10, 22.59, 22.66, 33.06, 33.64, 33.72, 35.58, 63.80, 125.05, 126.83, 128.10, 128.26, 129.48, 137.52, 138.45, 139.15, 140.91, 142.05; MS (EI): *m/z* (%): 296 (100) [M$^+$], 278 (11) [M$^+$−H_2O], 253 (40) [M$^+$−$(CH_2)_2CH_3$], 235 (90) [M$^+$−$(CH_2)_2CH_3$–H_2O], 220 (35) [M$^+$−C_6H_4]; EA calcd (%) for $C_{21}H_{28}O$ (296.45): C, 85.08; H, 9.52; found: C, 85.04; H, 9.55.

4.1.3. Compound 9aaac. Yield 70%; oil (R_f 0.3, hexane/AcOEt 3:1); IR (neat) 3326, 1607 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (t, $J=7.2$ Hz, 3H), 0.98 (t, $J=7.5$ Hz, 3H), 1.20 (sext, $J=7.5$ Hz, 2H), 1.36–1.49 (m, 4H), 1.62–1.75 (m, 3H), 2.35 (t, $J=8.0$ Hz, 2H), 2.66 (t, $J=7.8$ Hz, 2H), 3.86 (s, 3H), 4.34 (s, 2H), 6.96 (d, $J=8.4$ Hz, 2H), 7.06 (d, $J=1.5$ Hz, 1H), 7.11 (d, $J=8.4$ Hz, 2H), 7.18 (d, $J=1.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.91, 14.07, 22.60, 22.63, 33.09, 33.64, 33.71, 35.55, 55.18, 63.79, 113.52, 124.97, 128.17, 130.45, 131.24, 137.13, 138.86, 141.32, 141.86, 158.26; MS (EI): *m/z* (%): 326 (100) [M$^+$], 308 (5) [M$^+$−H_2O], 283 (40) [M$^+$−$(CH_2)_2CH_3$], 265 (90) [M$^+$−$(CH_2)_2CH_3$–H_2O]; EA calcd (%) for $C_{22}H_{30}O_2$ (326.47): C, 80.94; H, 9.26; found: C, 80.96; H, 9.24.

4.1.4. Compound 9aaad. Yield 71%; oil (R_f 0.3, hexane/AcOEt 3:1); IR (neat) 3328, 1598, 1518, 1464, 1347 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (t, $J=7.2$ Hz, 3H), 0.96 (t, $J=7.5$ Hz, 3H), 1.16 (t, $J=7.2$ Hz, 2H), 1.31–1.47 (m, 4H), 1.50 (br s, 1H), 1.60–1.71 (m, 2H), 2.25 (t, $J=7.8$ Hz, 2H), 2.65 (t, $J=7.5$ Hz, 2H), 4.29 (s, 2H), 7.08 (d, $J=1.5$ Hz, 1H), 7.21 (d, $J=1.5$ Hz, 1H), 7.39 (d, $J=8.7$ Hz, 2H), 8.28 (d, $J=8.7$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.84, 14.05, 22.52, 22.57, 33.05, 33.54, 33.64, 35.53, 63.33, 123.19, 125.38, 128.57, 130.71, 135.32, 137.77, 140.32, 143.13, 146.72, 146.79; MS (EI): *m/z* (%): 341 (100) [M$^+$], 298 (71) [M$^+$−$(CH_2)_2CH_3$], 280 (46) [M$^+$−$(CH_2)_2CH_3$–H_2O]; EA calcd (%) for $C_{21}H_{27}NO_3$ (341.44): C, 73.87; H, 7.97; N, 4.10; found: C, 73.78; H, 7.96; N, 4.01.

4.1.5. Compound 9aaae. Yield 55%; oil (R_f 0.4, hexane/AcOEt 3:1); IR (neat) 3300 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (t, $J=7.5$ Hz, 3H), 0.98 (t, $J=7.5$ Hz, 3H), 1.12–1.24 (m, 2H), 1.34–1.49 (m, 4H), 1.57 (br s, 1H), 1.63–1.73 (m, 2H), 1.98 (s, 3H), 2.17 (dt, $J=13.5$, 7.8 Hz, 1H), 2.29 (dt, $J=13.5$, 7.8 Hz, 1H), 2.67 (t, $J=7.5$ Hz, 2H), 4.25 (s, 2H), 7.06–7.10 (m, 2H), 7.20 (d, $J=1.8$ Hz, 1H), 7.21–7.29 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.89, 14.11, 19.92, 22.61, 22.66, 32.77, 33.08, 33.70, 35.62, 63.70,

124.89, 125.58, 127.22, 128.13, 129.61, 129.83, 136.12, 136.38, 138.07, 138.55, 140.47, 141.85; MS (EI): *m/z* (%): 310 (41) [M^+], 292 (100) [M^+-H_2O], 267 (11) [M^+-COCH_3], 249 (43) [$M^+-COCH_3-H_2O$]; EA calcd (%) for $C_{22}H_{30}O$ (310.47): C, 85.11; H, 9.74; found: C, 85.24; H, 9.84.

4.1.6. Compound 9aaaf. Yield 67%; oil (R_f 0.25, hexane/AcOEt 3:1); IR (neat) 3389 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.76 (t, $J=7.5$ Hz, 3H), 0.98 (t, $J=7.5$ Hz, 3H), 1.17 (sext, $J=7.5$ Hz, 2H), 1.32–1.50 (m, 4H), 1.64–1.74 (m, 2H), 2.03 (br s, 1H), 2.20–2.40 (m, 2H), 2.67 (t, $J=7.5$ Hz, 2H), 3.74 (s, 3H), 4.26 (d, $J=12.0$ Hz, 1H), 4.31 (d, $J=12.0$ Hz, 1H), 6.99–7.10 (m, 4H), 7.20 (d, $J=1.8$ Hz, 1H), 7.36 (ddd, $J=8.4$, 7.2, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.90, 14.11, 22.53, 22.70, 33.14, 33.24, 33.58, 35.57, 55.35, 64.37, 110.80, 120.64, 125.77, 127.85, 128.50, 128.66, 131.28, 133.72, 138.92, 141.27, 142.07, 156.50; MS (EI): *m/z* (%): 326 (100) [M^+], 308 (36) [M^+-H_2O], 265 (12) [$M^+-COCH_3-H_2O$]; EA calcd (%) for $C_{22}H_{30}O_2$ (326.47): C, 80.94; H, 9.26; found: C, 80.92; H, 9.36.

4.1.7. Compound 9aaag. Yield 53%; oil (R_f 0.15, hexane/AcOEt 2:1); IR (neat) 3362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.76 (t, $J=7.5$ Hz, 3H), 0.95 (t, $J=7.5$ Hz, 3H), 1.17 (sext, $J=7.5$ Hz, 2H), 1.32–1.46 (m, 4H), 1.59–1.69 (m, 2H), 2.47 (t, $J=7.8$ Hz, 2H), 2.63 (t, $J=7.8$ Hz, 2H), 4.18 (s, 2H), 4.45 (br s, 1H), 7.08 (d, $J=1.8$ Hz, 1H), 7.14 (d, $J=1.8$ Hz, 1H), 7.30 (ddd, $J=7.5$, 4.8, 1.2 Hz, 1H), 7.37 (dt, $J=7.5$, 1.0 Hz, 1H), 7.77 (dt, $J=7.5$, 1.8 Hz, 1H), 8.65 (ddd, $J=4.8$, 1.8, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.83, 14.07, 22.55 (2 C), 33.13, 33.56, 33.65, 35.47, 64.56, 121.92, 125.33, 127.41, 129.05, 136.06, 136.91, 139.78, 140.68, 143.26, 148.67, 158.53; MS (EI): *m/z* (%): 297 (100) [M^+], 279 (49) [M^+-H_2O], 268 (21) [$M^+-CH_2CH_3$], 250 (96) [$M^+-H_2O-CH_2CH_3$]; EA calcd (%) for $C_{20}H_{27}NO$ (297.43): C, 80.76; H, 9.15; N, 4.71; found: C, 80.39; H, 9.29; N, 4.40.

4.1.8. Compound 9aaah. Yield 69%; oil (R_f 0.35, hexane/AcOEt 3:1); IR (neat) 3330 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, $J=7.5$ Hz, 3H), 0.97 (t, $J=7.5$ Hz, 3H), 1.25 (sext, $J=7.5$ Hz, 2H), 1.36–1.53 (m, 4H), 1.60–1.71 (m, 2H), 1.74 (br s, 1H), 2.43 (t, $J=7.8$ Hz, 2H), 2.65 (t, $J=7.8$ Hz, 2H), 4.45 (s, 2H), 6.89 (dd, $J=3.3$, 1.2 Hz, 1H), 7.07 (s, 1H), 7.10 (dd, $J=5.1$, 3.3 Hz, 1H), 7.20 (s, 1H), 7.38 (dd, $J=5.1$, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.94, 14.07, 22.60, 22.69, 33.23, 33.63, 34.12, 35.59, 63.74, 125.22, 125.56, 126.84, 127.36, 128.30, 129.19, 139.21, 140.64, 143.27, 143.33; MS (EI): *m/z* (%): 302 (100) [M^+], 284 (11) [M^+-H_2O], 269 (20) [$M^+-H_2O-CH_3$], 255 (42) [$M^+-H_2O-CH_2CH_3$], 241 (30) [$M^+-H_2O-CH_2CH_2CH_3$]; EA calcd (%) for $C_{19}H_{26}OS$ (302.48): C, 75.45; H, 8.66; found: C, 75.54; H, 8.47.

4.1.9. Compound 9aaai. Yield 51%; oil (R_f 0.35, hexane/AcOEt 3:1); IR (neat) 3363 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, $J=7.5$ Hz, 3H), 0.97 (t, $J=7.5$ Hz, 3H), 1.39 (sept, $J=7.5$ Hz, 4H), 1.54–1.69 (m, 4H), 1.81 (br s, 1H), 2.62 (t, $J=7.5$ Hz, 2H), 2.69 (t, $J=7.5$ Hz, 2H), 3.89 (s, 3H), 4.74 (s, 2H), 6.66 (d, $J=16.5$ Hz, 1H), 6.86 (ddd, $J=8.1$, 2.7, 0.6 Hz, 1H), 7.02–7.06 (m, 2H), 7.12 (d, $J=7.8$ Hz, 1H), 7.18 (s, 1H), 7.21 (d, $J=16.5$ Hz, 1H), 7.29 (dd, $J=15.5$, 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.08, 14.10, 22.57, 22.76, 33.26, 33.51, 33.71, 35.48, 55.26, 63.93, 111.76, 112.97, 118.92, 125.69, 125.97, 128.75, 129.52, 133.19, 134.06, 138.37, 138.75, 141.34, 141.81, 159.68; MS (EI): *m/z* (%): 352 (100) [M^+], 334 (27) [M^+-H_2O], 321 (13) [M^+-OCH_3], 291 (12) [$M^+-H_2O-COCH_3$]; EA calcd (%) for $C_{24}H_{32}O_2$ (352.51): C, 81.77; H, 9.15; found: C, 81.97; H, 9.17.

4.1.10. Compound 9aaba. Yield 69%; oil (R_f 0.3, hexane/AcOEt 2:1); IR (neat) 3384, 1681, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.74 (t, $J=7.5$ Hz, 3H), 1.14 (sext, $J=7.2$ Hz, 2H), 1.32–1.42 (m, 2H), 2.02 (br s, 1H), 2.30 (t, $J=7.5$ Hz, 2H), 2.64 (s, 3H), 3.43 (s, 3H), 4.28 (s, 2H), 4.48 (s, 2H), 7.21 (d, $J=1.8$ Hz, 1H), 7.27 (d, $J=8.1$ Hz, 2H), 7.35 (d, $J=1.8$ Hz, 1H), 8.00 (d, $J=8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.82, 22.51, 26.66, 33.00, 33.46, 58.32, 63.20, 74.53, 124.30, 127.48, 128.13, 129.71, 135.73, 137.76, 138.33, 138.46, 140.80, 144.33, 197.66; MS (EI): *m/z* (%): 326 (100) [M^+], 311 (20) [M^+-CH_3], 295 (88) [M^+-OCH_3], 281 (14) [$M^+-CH_2OCH_3$], 265 (69) [$M^+-OCH_3-CH_2O$]; EA calcd (%) for $C_{21}H_{26}O_3$ (326.43): C, 77.27; H, 8.03; found: C, 77.11; H, 8.19.

4.1.11. Compound 9aaca. Yield 76%; oil (R_f 0.3, hexane/AcOEt 2:1); IR (neat) 3435, 1681, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.75 (t, $J=7.5$ Hz, 3H), 1.15 (sext, $J=7.2$ Hz, 2H), 1.31–1.41 (m, 2H), 1.56 (br s, 1H), 2.09–2.19 (m, 2H), 2.29 (t, $J=7.8$ Hz, 2H), 2.66 (s, 3H), 2.82 (t, $J=7.8$ Hz, 2H), 3.59 (t, $J=6.5$ Hz, 2H), 4.31 (s, 2H), 7.08 (d, $J=1.6$ Hz, 1H), 7.21 (d, $J=1.6$ Hz, 1H), 7.30 (d, $J=8.4$ Hz, 2H), 8.02 (d, $J=8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.85, 22.52, 26.68, 32.70, 33.02, 33.55, 35.99, 44.35, 63.33, 125.14, 128.14, 128.48, 129.84, 135.72, 136.91, 138.36, 140.38, 140.79, 144.45, 197.66; MS (EI): *m/z* (%): 358 (100) [M^+], 343 (24) [M^+-CH_3], 297 (58) [MH^+-CH_2CHCl], 255 (64) [$MH^+-CH_2CHCl-CH_2CHCH_3$]; EA calcd (%) for $C_{22}H_{27}ClO_2$ (358.90): C, 73.62; H, 7.58; found: C, 73.54; H, 7.68.

4.1.12. Compound 9aada. Yield 73%; oil (R_f 0.3, hexane/AcOEt 1:1); IR (neat) 3448, 1736, 1683, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.75 (t, $J=7.5$ Hz, 3H), 1.14 (sext, $J=7.5$ Hz, 2H), 1.30–1.41 (m, 2H), 1.65 (br s, 1H), 2.01 (q, $J=7.5$ Hz, 2H), 2.28 (t, $J=7.8$ Hz, 2H), 2.38 (t, $J=7.2$ Hz, 2H), 2.65 (s, 3H), 2.69 (t, $J=7.5$ Hz, 2H), 3.68 (s, 3H), 4.29 (s, 2H), 7.05 (d, $J=1.8$ Hz, 1H), 7.20 (d, $J=1.8$ Hz, 1H), 7.30 (d, $J=8.1$ Hz, 2H), 8.01 (d, $J=8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.86, 22.55, 26.48, 26.69, 33.05, 33.57 (2 C), 35.01, 51.58, 63.40, 125.20, 128.13, 128.44, 129.87, 135.70, 136.81, 138.27, 140.70, 141.25, 144.53, 173.76, 197.66; MS (EI): *m/z* (%): 382 (5) [M^+], 364 (81) [M^+-H_2O], 333 (10) [$M^+-H_2O-OCH_3$], 321 (100) [$M^+-H_2O-CH_2CH_2CH_3$], 291 (72) [$M^+-H_2O-CH_2CO_2CH_3$]; EA calcd (%) for $C_{24}H_{30}O_4$ (382.49): C, 75.36; H, 7.91; found: C, 75.28; H, 7.99.

4.1.13. Compound 9aaea. Yield 68%; oil (R_f 0.4, hexane/AcOEt 1:1); IR (neat) 3444, 1682, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.75 (t, $J=7.5$ Hz, 3H), 1.15 (sext, $J=7.2$ Hz, 2H), 1.31–1.41 (m, 2H), 1.49–1.88 (m, 11H), 2.28 (t, $J=7.8$ Hz, 2H), 2.65 (s, 3H), 2.68 (t, $J=7.2$ Hz,

2H), 3.40–3.54 (m, 2H), 3.75–3.91 (m, 2H), 4.29 (s, 2H), 4.57–4.59 (m, 1H), 7.06 (d, J=1.2 Hz, 1H), 7.20 (d, J=1.2 Hz, 1H), 7.30 (d, J=8.1 Hz, 2H), 8.01 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.86, 19.74, 22.54, 25.53, 26.69, 28.08, 29.50, 30.80, 33.05, 33.58, 35.58, 62.38, 63.45, 67.41, 98.82, 125.19, 128.10, 128.41, 129.91, 135.65, 136.52, 138.11, 140.53, 142.15, 144.67, 197.69; MS (EI): m/z (%): 438 (5) [M^+], 420 (6) [M^+-H_2O], 354 (100) [M^+−H–THP], 336 (61) [M^+−H–OTHP]; EA calcd (%) for $C_{28}H_{38}O_4$ (438.60): C, 76.68; H, 8.73; found: C, 76.54; H, 8.87.

4.1.14. Compound 9aafa. Yield 70%; oil (R_f 0.3, hexane/AcOEt 2:1); IR (neat) 3798, 1682, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (t, J=7.5 Hz, 3H), 1.15 (sext, J=7.2 Hz, 2H), 1.32–1.42 (m, 2H), 1.84 (br s, 1H), 2.28 (t, J=7.8 Hz, 2H), 2.34 (s, 3H), 2.64 (s, 3H), 4.28 (s, 2H), 7.07 (s, 1H), 7.20 (s, 1H), 7.29 (d, J=8.4 Hz, 2H), 8.00 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.85, 21.30, 22.54, 26.66, 32.97, 33.57, 63.33, 125.83, 128.10, 128.99, 129.92, 135.62, 136.21, 137.54, 138.10, 140.54, 144.61, 197.69; MS (EI): m/z (%): 296 (85) [M+], 281 (20) [M^+-CH_3], 254 (22) [M^+-CH_2CO], 235 (50) [$M^+-COCH_3-H_2O$], 220 (25) [$M^+-COCH_3-H_2O-CH_3$], 205 (100) [$M^+-COCH_3-H_2O-2CH_3$]; EA calcd (%) for $C_{20}H_{24}O_2$ (296.40): C, 81.04; H, 8.16; found: C, 80.96; H, 8.24.

4.1.15. Compound 9aaga. Yield 67%; oil (R_f 0.2, hexane/AcOEt 2:1); IR (neat) 3420, 1682, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (t, J=7.5 Hz, 3H), 1.15 (sext, J=7.5 Hz, 2H), 1.32–1.42 (m, 2H), 1.76 (br s, 1H), 2.31 (t, J=7.5 Hz, 2H), 2.65 (s, 3H), 4.31 (s, 2H), 7.25 (dd, J=6.9, 2.1 Hz, 1H), 7.31 (d, J=8.7 Hz, 2H), 7.34–7.40 (m, 2H), 8.01 (d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.86, 22.49, 26.70, 33.02, 33.49, 63.38, 125.05, 127.95, 128.16, 128.35, 129.70, 135.76, 138.23, 139.03, 140.62, 144.45, 197.68; MS (EI): m/z (%): 282 (100) [M^+], 267 (22) [M^+-CH_3], 221 (64) [$M^+-COCH_3-H_2O$]; EA calcd (%) for $C_{19}H_{22}O_2$ (282.38): C, 80.82; H, 7.85; found: C, 80.44; H, 8.02.

4.1.16. Compound 9aaha. Yield 56%; mp 110.9–111.3 °C (R_f 0.35, hexane/AcOEt 2:1); IR (neat) 3421, 1678, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (t, J=7.5 Hz, 3H), 1.16 (sext, J=7.5 Hz, 2H), 1.33–1.45 (m, 3H), 1.64–1.72 (m, 2H), 1.77–1.85 (m, 2H), 2.20–2.27 (m, 2H), 2.31 (t, J=7.5 Hz, 2H), 2.44–2.48 (m, 2H), 2.66 (s, 3H), 4.32 (d, J=6.0 Hz, 2H), 6.19 (sept, J=1.5 Hz, 1H), 7.26 (d, J=2.1 Hz, 1H), 7.31 (d, J=8.4 Hz, 2H), 7.39 (d, J=2.1 Hz, 1H), 8.02 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.90, 22.25, 22.60, 23.15, 25.99, 26.73, 27.54, 33.27, 33.66, 63.72, 121.96, 125.02, 125.11, 128.15, 129.89, 135.77, 136.17, 137.42, 138.05, 140.57, 142.39, 144.58, 197.63; MS (EI): m/z (%): 362 (100) [M^+], 331 (32) [M^+-CH_3OH], 301 (16) [$M^+-COCH_3-H_2O$]; EA calcd (%) for $C_{25}H_{30}O_2$ (362.50): C, 82.83; H, 8.34; found: C, 82.70; H, 8.37.

4.1.17. Compound 9aaia. Yield 34%; oil (R_f 0.3, hexane/AcOEt 2:1); IR (neat) 3422, 1682, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (t, J=7.5 Hz, 3H), 1.19 (sext, J=7.5 Hz, 2H), 1.38–1.48 (m, 2H), 1.64 (br s, 1H), 2.39 (t, J=7.5 Hz, 2H), 2.67 (s, 3H), 4.39 (d, J=5.4 Hz, 2H), 7.33–7.50 (m, 6H), 7.63–7.68 (m, 3H), 8.04 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.91, 22.57, 26.75, 33.22, 33.59, 63.52, 123.88, 127.03, 127.08, 127.31, 128.23, 128.67, 129.79, 135.84, 138.07, 138.77, 140.65, 140.82, 141.22, 144.24, 197.64; MS (EI): m/z (%): 358 (100) [M^+], 297 (28) [$M^+-COCH_3-H_2O$], 255 (68) [$M^+-COCH_3-H_2O-CH_2$=$CHCH_3$], 241 (68) [$M^+-COCH_3-H_2O-CH_2$=$CHCH_2CH_3$]; EA calcd (%) for $C_{25}H_{26}O_2$ (358.47): C, 83.76; H, 7.31; found: C, 83.61; H, 7.46.

4.1.18. Compound 9aaja. Yield 56%; mp 161.8–162.4 °C (R_f 0.2, hexane/AcOEt 2:1); IR (KBr) 3366, 1680, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (t, J=7.5 Hz, 3H), 1.20 (sext, J=7.5 Hz, 2H), 1.36–1.46 (m, 2H), 1.76 (br s, 1H), 2.34 (t, J=7.5 Hz, 2H), 2.65 (s, 3H), 4.09 (s, 5H), 4.33 (t, J=1.5 Hz, 2H), 4.34 (d, J=1.5 Hz, 2H), 4.68 (t, J=1.5 Hz, 2H), 7.33 (d, J=8.4 Hz, 2H), 7.36 (d, J=1.8 Hz, 1H), 7.55 (d, J=1.8 Hz, 1H), 8.02 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.91, 22.47, 26.70, 33.05, 33.52, 63.45, 66.65, 68.90, 69.56, 85.21, 122.89, 126.15, 128.14, 129.83, 135.66, 136.66, 138.12, 138.90, 140.42, 144.57, 197.67; MS (EI): m/z (%): 466 (100) [M^+], 410 (15) [M^+-CH_2=$CHCH_2CH_3$], 368 (27) [$M^+-COCH_3-CH_2$=$CHCH_2CH_3$]; EA calcd (%) for $C_{29}H_{30}FeO_2$ (466.39): C, 74.68; H, 6.48; found: C, 74.64; H, 6.41.

4.1.19. Compound 9abga. Yield 55%; oil (R_f 0.3, hexane/AcOEt 2:1); IR (neat) 3422, 1684, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (t, J=7.5 Hz, 3H), 1.14 (sext, J=7.5 Hz, 2H), 1.25–1.42 (m, 2H), 1.59 (br s, 1H), 2.25 (t, J=7.8 Hz, 2H), 2.46 (s, 3H), 2.64 (s, 3H), 4.31 (s, 2H), 7.15 (d, J=8.1 Hz, 1H), 7.19 (d, J=8.1 Hz, 1H), 7.32 (d, J=8.4 Hz, 2H), 8.00 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.82, 19.19, 22.44, 26.64, 33.08, 33.45, 60.03, 127.92, 128.59, 129.82, 130.02, 134.93, 135.56, 135.73, 138.21, 140.72, 145.28, 197.64; MS (EI): m/z (%): 296 (75) [M^+], 278 (33) [M^+-H_2O], 235 (100) [$M^+-H_2O-COCH_3$], 193 (69) [$M^+-H_2O-COCH_3-CH_2$=$CHCH_3$]; EA calcd (%) for $C_{20}H_{24}O_2$ (296.40): C, 81.04; H, 8.16; found: C, 80.85; H, 8.27.

4.1.20. Compound 9acaa. Yield 49%; oil (R_f 0.45, hexane/AcOEt 2:1); IR (neat) 3436, 1684, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (t, J=7.5 Hz, 3H), 0.96 (t, J=7.5 Hz, 3H), 1.14 (sext, J=7.5 Hz, 2H), 1.29 (d, J=6.3 Hz, 3H), 1.321.48 (m, 4H), 1.61–1.71 (m, 2H), 1.80 (br s, 1H), 2.24 (t, J=7.8 Hz, 2H), 2.65 (s, 3H), 4.52 (q, J=6.3 Hz, 3H), 7.03 (d, J=1.8 Hz, 1H), 7.23–7.26 (m, 1H), 7.30–7.34 (m, 2H), 8.00 (d, J=7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.86, 14.08, 22.57, 22.65, 24.95, 26.69, 33.26, 33.59, 33.69, 35.72, 67.00, 122.18, 127.93, 128.01, 128.15, 129.80, 130.35, 135.37, 135.56, 140.14, 142.78, 143.19, 144.94, 197.66; MS (EI): m/z (%): 352 (100) [M^+], 337 (77) [M^+-CH_3], 309 (39) [M^+-COCH_3], 291 (45) [$M^+-H_2O-COCH_3$], 277 (84) [$M^+-H_2O-(CH_2)_3CH_3$]; EA calcd (%) for $C_{24}H_{32}O_2$ (352.51): C, 81.77; H, 9.15; found: C, 81.54; H, 9.22.

4.1.21. Compound 9baaa. Yield 53%; oil (R_f 0.1, hexane/AcOEt 3:1); IR (neat) 3431, 1683, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, J=7.5 Hz, 3H), 1.39 (sext, J=7.5 Hz, 2H), 1.59–1.70 (m, 2H), 2.05 (br s, 1H), 2.63 (s,

3H), 2.66 (t, $J=7.8$ Hz, 2H), 3.20 (s, 3H), 4.05 (s, 2H), 4.30 (s, 2H), 7.28 (s, 1H), 7.29–7.33 (m, 3H), 7.99 (d, $J=8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.01, 22.52, 26.63, 33.57, 35.49, 58.15, 62.95, 72.34, 127.05, 127.56, 128.01, 129.74, 135.60, 137.78, 136.15, 138.16, 142.86, 143.46, 197.66; MS (EI): *m/z* (%): 326 (30) [M^+], 308 (22) [M^+-H_2O], 293 (41) [$M^+-H_2O-CH_3$], 277 (10) [$M^+-H_2O-OCH_3$], 265 (100) [$M^+-OCH_3-CH_2O$]; EA calcd (%) for $C_{21}H_{26}O_3$ (326.43): C, 77.27; H, 8.03; found: C, 77.07; H, 8.15.

4.1.22. Compound 9caaa. Yield 63%; oil (R_f 0.3, hexane/AcOEt 2:1); IR (neat) 3429, 1682, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, $J=7.5$ Hz, 3H), 1.40 (sext, $J=7.2$ Hz, 2H), 1.60–1.70 (m, 2H), 1.73 (br s, 1H), 1.77–1.86 (m, 2H), 2.47 (t, $J=7.8$ Hz, 2H), 2.64 (s, 3H), 2.64 (t, $J=7.2$ Hz, 2H), 3.35 (t, $J=6.6$ Hz, 2H), 4.29 (s, 2H), 7.07 (d, $J=1.2$ Hz, 1H), 7.24 (d, $J=1.2$ Hz, 1H), 7.30 (d, $J=8.4$ Hz, 2H), 8.01 (d, $J=8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.05, 22.56, 26.69, 30.53, 33.65, 33.80, 35.50, 44.30, 63.35, 125.71, 128.26, 128.49, 129.83, 135.81, 136.55, 138.33 (2 C), 142.88, 144.21, 197.59; MS (EI): *m/z* (%): 358 (100) [M^+], 343 (31) [M^+-CH_3], 315 (69) [$M^+-CH_2CH_2CH_3$], 297 (45) [$M^+-H_2O-CH_2CH_2CH_3$]; EA calcd (%) for $C_{22}H_{27}ClO_2$ (358.90): C, 73.62; H, 7.58; found: C, 73.52; H, 7.71.

4.1.23. Compound 10aaa. Yield 22%; oil (R_f 0.4, hexane/AcOEt 3.5:1); IR (neat) 3329, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, $J=7.2$ Hz, 6H), 1.37 (sext, $J=7.2$ Hz, 4H), 1.55–1.65 (m, 4H), 1.72 (br s, 1H), 2.59 (t, $J=7.8$ Hz, 4H), 4.64 (s, 2H), 6.94 (s, 1H), 7.00 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.05, 22.54, 33.76, 35.65, 65.52, 124.29, 127.85, 140.54, 143.05; MS (EI): *m/z* (%): 220 (69) [M^+], 203 (3) [M^+-OH], 191 (12) [M^+-CHO], 177 (68) [$M^+-CH_2CH_2CH_3$], 160 (100) [$M^+-OH-CH_2CH_2CH_3$]; EA calcd (%) for $C_{15}H_{24}O$ (220.35): C, 81.76; H, 10.98; found: C, 81.90; H, 11.26.

4.1.24. Compound 10aai. Yield 28%; mp 41.9–42.3 °C (R_f 0.3, hexane/AcOEt 3:1); IR (neat) 3320, 1600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, $J=7.2$ Hz, 3H), 1.40 (sext, $J=7.2$ Hz, 2H), 1.60–1.71 (m, 2H), 1.77 (br s, 1H), 2.69 (t, $J=7.5$ Hz, 2H), 4.74 (s, 2H), 7.19 (s, 1H), 7.31–7.47 (s, 5H), 7.58–7.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.09, 22.53, 33.77, 35.77, 65.50, 123.11, 125.93, 126.62, 127.08, 127.15, 128.59, 141.01, 141.13, 141.38, 143.69; MS (EI): *m/z* (%): 240 (100) [M^+], 197 (35) [$M^+-(CH_2)_2CH_3$], 180 (28) [$M^+-CH_2{=}CHCH_3-H_2O$]; EA calcd (%) for $C_{17}H_{20}O$ (240.34): C, 84.96; H, 8.39; found: C, 84.83; H, 8.53.

4.1.25. Compound 13. Yield 72%; mp 158.1–158.8 °C (R_f 0.2, hexane/AcOEt 3:1); IR (neat) 3409, 1665, 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (br s, 1H), 1.61–1.77 (m, 4H), 2.21 (t, $J=6.0$ Hz, 2H), 2.44 (s, 3H), 2.65 (s, 3H), 2.79 (t, $J=6.0$ Hz, 2H), 4.32 (s, 2H), 7.01 (s, 1H), 7.29 (d, $J=8.4$ Hz, 2H), 8.02 (d, $J=8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.08, 22.76, 23.42, 26.72, 28.37, 29.84, 59.99, 128.29, 129.52, 131.07, 132.35, 133.31, 134.49, 135.59, 137.23, 141.20, 145.62, 197.60; MS (EI): *m/z* (%): 294 (37) [M^+], 276 (12) [M^+-H_2O], 233 (100) [$M^+-H_2O-COCH_3$]; EA calcd (%) for $C_{20}H_{22}O_2$ (294.39): C, 81.60; H, 7.53; found: C, 81.65; H, 7.52.

4.1.26. Compound 16. Yield 60%; oil (R_f 0.35, hexane/AcOEt 2:1); IR (neat) 3417, 1678, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (t, $J=7.5$ Hz, 3H), 1.15 (sext, $J=7.5$ Hz, 2H), 1.24–1.43 (m, 2H), 1.70 (br s, 1H), 1.77–1.91 (m, 4H), 2.24 (t, $J=7.8$ Hz, 2H), 2.65 (s, 3H), 2.83 (t, $J=5.7$ Hz, 2H), 2.93 (t, $J=5.7$ Hz, 2H), 4.30 (s, 2H), 7.01 (s, 1H), 7.33 (d, $J=8.4$ Hz, 2H), 8.01 (d, $J=8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.80, 22.49, 22.78, 23.38, 25.87, 26.60, 30.02, 32.99, 33.49, 59.50, 127.87, 129.67, 129.97, 133.86, 135.37, 135.47, 137.15, 137.49, 138.42, 145.46, 197.65; MS (EI): *m/z* (%): 336 (49) [M^+], 318 (89) [M^+-H_2O], 275 (100) [$M^+-H_2O-COCH_3$]; EA calcd (%) for $C_{23}H_{28}O_2$ (336.47): C, 82.10; H, 8.39; found: C, 81.73; H 8.76.

Acknowledgements

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Multicomponent synthesis of epoxy-tetrahydronaphthyridine and structural diversification by subsequent fragmentation

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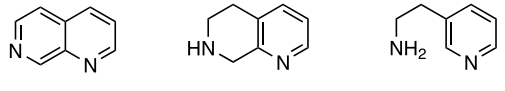
Abstract—Three-component reaction of an α-isocyanoacetamide **7**, an homoallylamine **8** and an aldehyde **9** in methanol at room temperature provides oxa-bridged tricycle **4** in good to excellent yield as a mixture of two separable diastereoisomers. In this one-pot multicomponent process, one C–N, one C–O and three C–C bonds are formed with concomitant creation of five asymmetric centers and three rings. Fragmentation of epoxy-tetrahydronaphthyridine **4** affords differentially substituted 5,6,7,8-tetrahydro-1,7-naphthyridine (**5**, **6**) depending on the reaction conditions, providing thus additional structural diversity. A one-pot three-component synthesis of 5,6,7,8-tetrahydro-1,7-naphthyridine (**6**) from **7**, **8** and **9** is also documented.

1. Introduction

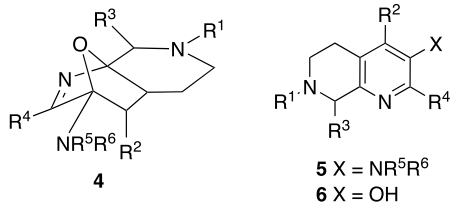
1,7-Naphthyridine (**1**) is an important heterocycle that is found in the structure of a great number of bioactive compounds.[1] On the other hand, the biological profile of the 5,6,7,8-tetrahydro-1,7-naphthyridine or 8-azatetrahydro-isoquinoline (**2**, Fig. 1) is poorly defined and only a few syntheses have been reported. Besides the partial reduction of 1,7-naphthyridine,[2] mainly two strategies have been developed for the access to the bicyclic heterocycles (**2**). One is the annulation of a piperidine ring onto a functionalized pyridine[3] and the other is the elaboration of a pyridine ring from a preformed piperidine derivative.[4] Both synthetic routes suffer from the linearity and the ability to introduce significant molecular complexity in each step.



1 **2** **3**

Figure 1. Structure of 1,7-naphthyridine (**1**), 5,6,7,8-tetrahydro-1,7-naphthyridine (**2**) and 2-(3-pyridyl)ethylamine (**3**).

The 2-(3-pyridyl)ethylamine (**3**) is known to bind to members of the dopaminergic and cholinergic receptors.[5] Structurally, 5,6,7,8-tetrahydro-1,7-naphthyridine (**2**) can be considered as the ring constrained analogue of **3**; consequently it would be interesting to develop a more efficient and flexible route to **2** in order to fully exploit its potential biological functions. Impelled by an interest in providing a rapid construction of polyheterocyclic scaffolds, we report herein a multicomponent reaction[6,7] for the synthesis of oxa-bridged tricyclic compound **4** and its subsequent fragmentation to 5,6,7,8-tetrahydro-1,7-naphthyridine (**5**, **6**, Fig. 2).



4 **5** X = NR^5R^6, **6** X = OH

Figure 2. Polysubstituted epoxy-tetrahydronaphthyridine (**4**) and 5,6,7,8-tetrahydro-1,7-naphthyridine (**5**, **6**).

2. Results and discussion

2.1. Reaction sequence design

Based on the unique reactivity of α-isocyanoacetamide **7**, an efficient three-component synthesis of 5-aminooxazole has been developed in our laboratory.[8] Taking advantage of the chemical reactivity of 5-aminooxazole and by fine tuning the structure of the starting materials, several new multi-component reactions have subsequently been devised for

Keywords: Multicomponent reaction (MCR); Isonitrile; Isocyanoacetamide; Heterocycle; Naphthyridine; High throughput synthesis; Diversity-oriented synthesis.
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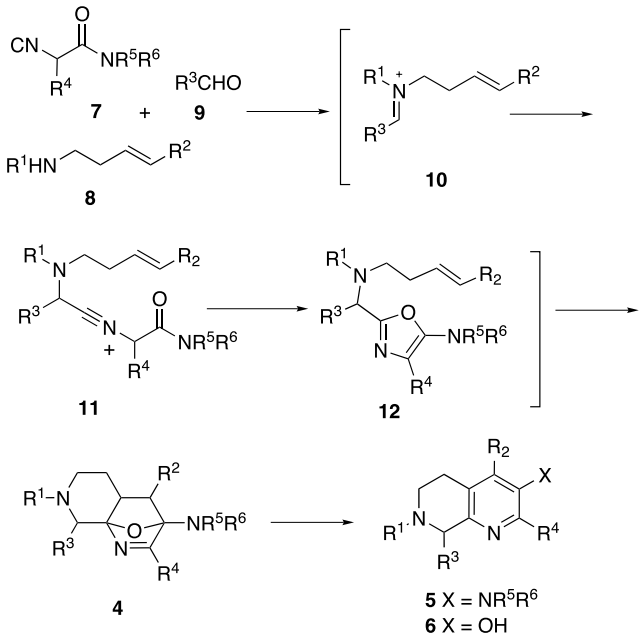
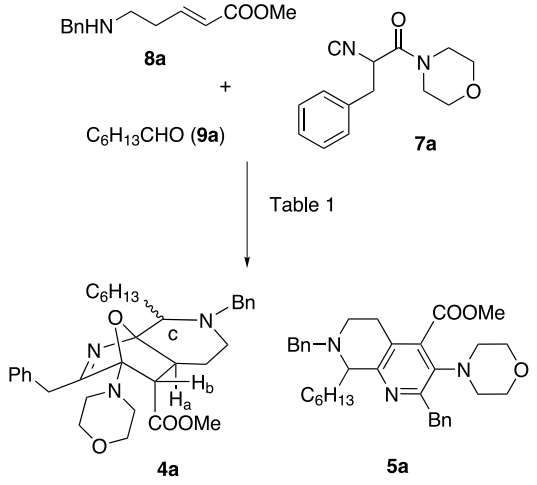


Scheme 1. Sequence of event of three-component synthesis of compounds **4**, **5** and **6**, a working hypothesis.



Scheme 2. Three-component reaction of **7a**, **8a** and **9a**.

the syntheses of a number of polyheterocycles[6h,9] and macrocycles.[10] As a continuation of our work in this field, a three-component synthesis of **4**, **5**, and **6** from α-isocyanoacetamide **7**, homoallylamine **8** and aldehyde **9** was envisaged according to the sequence of events shown in Scheme 1. Thus, condensation of an amine **8** and an aldehyde **9** should give the Schiff base **10**, which would react with isonitrile **7** to produce the nitrilium intermediate **11**. This latter intermediate, after tautomerization would cyclize to produce the oxazole **12**. Intramolecular Diels–Alder cycloaddition of **12** between oxazole and the tethered dienophile would furnish the epoxy-tetrahydronaphthyridine **4**,[11] which under appropriate conditions, would undergo fragmentation to provide 5,6,7,8-tetrahydro-1,7-naphthyridine (**5** or **6**).

2.2. Three-component synthesis of the epoxy-tetrahydronaphthyridine 4. Using isocyanoacetamide **7a**, 5-benzylamino pentanoate (**8a**), an heptanal (**9a**) as test substrates (Scheme 2), we performed a survey of reaction conditions; the results are summarized in Table 1. When the reaction was carried out in methanol (MeOH) at room temperature, the oxa-bridged tricyclic compound (**4**) was isolated in 71% yield as a mixture of two separable diastereomers (entry 1). The stereoselectivity was time-dependant indicating the reversibility of the final cycloaddition process (entry 2). Addition of ammonium chloride (entry 3) was detrimental to the reaction,[12] while the presence of camphorsulfonic acid (entry 4) or silica gel (entry 5) lowered the product yield.[13] Performing the reaction at higher temperature under otherwise identical conditions decreased the yield of the desired product (entries 6, 7). The high substrate concentration is favorable to the overall reaction sequence (entries 1 vs 8). Performing the reaction in toluene at room temperature in the presence of lithium bromide[14] afforded **4a** in only 26% yield (entry 9). Forcing the reaction conditions led to the formation of compound **5a**, resulting from the fragementation of **4a**, in moderate yield (entries 10, 11). Interestingly, dichloromethane turned out to be a good solvent producing **4a** in 69% yield (entry 12). Overall, under optimized conditions (MeOH, 0.4 M, room temperature), we were able to produce

Table 1. Three-component synthesis of **4a**, a survey of reaction conditions[a]

Entry	Solvent	Time (h)	*T* (°C)	Additive	**4a** (**5a**) (%)
1	MeOH	20	25	—	71[b]
2	MeOH	3	25	—	66[c]
3	MeOH	20	25	NH_4Cl[d]	—
4	MeOH	20	25	CSA[e]	33
5	MeOH	20	25	SiO_2[d]	55
6	MeOH	5	Reflux	—	55
7	MeOH[f]	8	Reflux	—	51
8	MeOH[g]	15	25	—	44
9	Toluene	20	25	LiBr	26
10	Toluene[f]	20	80	—	0 (23)
11	Toluene[g]	20	Reflux	—	0 (25)
12	CH_2Cl_2	15	25	—	69

Abbreviations: LiBr, lithium bromide; NH_4Cl, ammonium chloride, SiO_2, silica gel.
[a] General conditions: mole ratio: **7a/8a/9a**=1/1.2/1.2, *C*=0.4 M.
[b] Diastereomeric ratio 2/1.
[c] Diastereomeric ratio 1/1.
[d] 1.0 equiv.
[e] 0.1 equiv.
[f] *C*=0.2 M.
[g] *C*=0.1 M.

4a in 71% yield from readily accessible starting materials. Neither external reagent, nor heating was required to trigger the reaction sequence and simply mixing three inputs together, a highly ordered and complex reaction sequence took place to afford **4a** with the creation of five chemical bonds and three rings. The coupling constant of 3.7 Hz between protons H_a and H_b indicated their *gauche* relationship in compound **4a**. Since H_a has to be *endo*-oriented for the inherent ring strain imposed by the connecting bridge,[15] the observed coupling constant indicated an *exo* position of the H_b, hence, an *endo* position of the methyl ester group. This mode of ring formation is indicative of a concerted rather than a stepwise process, since one could expect the presence of *exo*, *exo* diastereomers if the latter mechanism was operating. The face selectivity for the cycloaddition is controlled solely by the substituent at C_c and is apparently inefficient in the present case since the observed selectivity (dr=2/1) was low and reflected the thermodynamic controlled process (entries 1 vs 2). It is noteworthy that the intramolecular Diels–Alder reaction of 5-amino oxazole and the tethered dienophile occurred at room temperature[16–19] in the absence of any promoters.

The scope of this novel domino 3CR/IMDA reaction was examined using three amines, three aldehydes and five isocyanoacetamides as inputs (Fig. 3). Tricyclic compounds synthesized by this multicomponent process (MeOH, room temperature) were listed in Figure 4. Most of these heterocycles (**4**) were isolated with good to excellent yield. However, when isobutyaldehyde **9c** was used as input, **4g** was isolated in only 21% yield together with

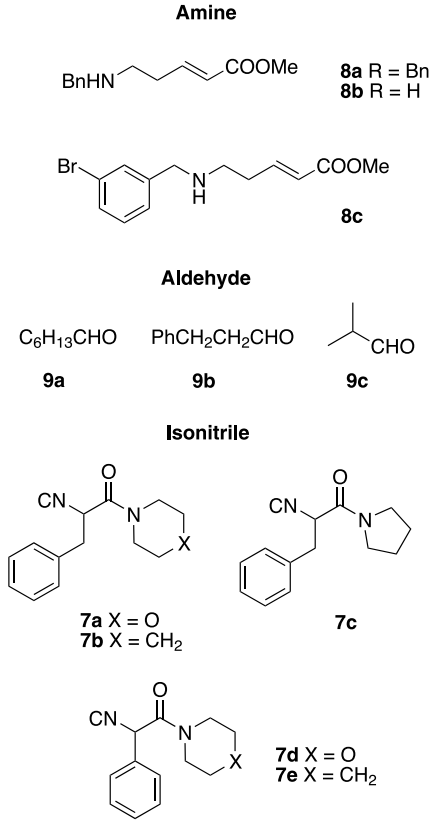


Figure 3. Structure of the starting materials.

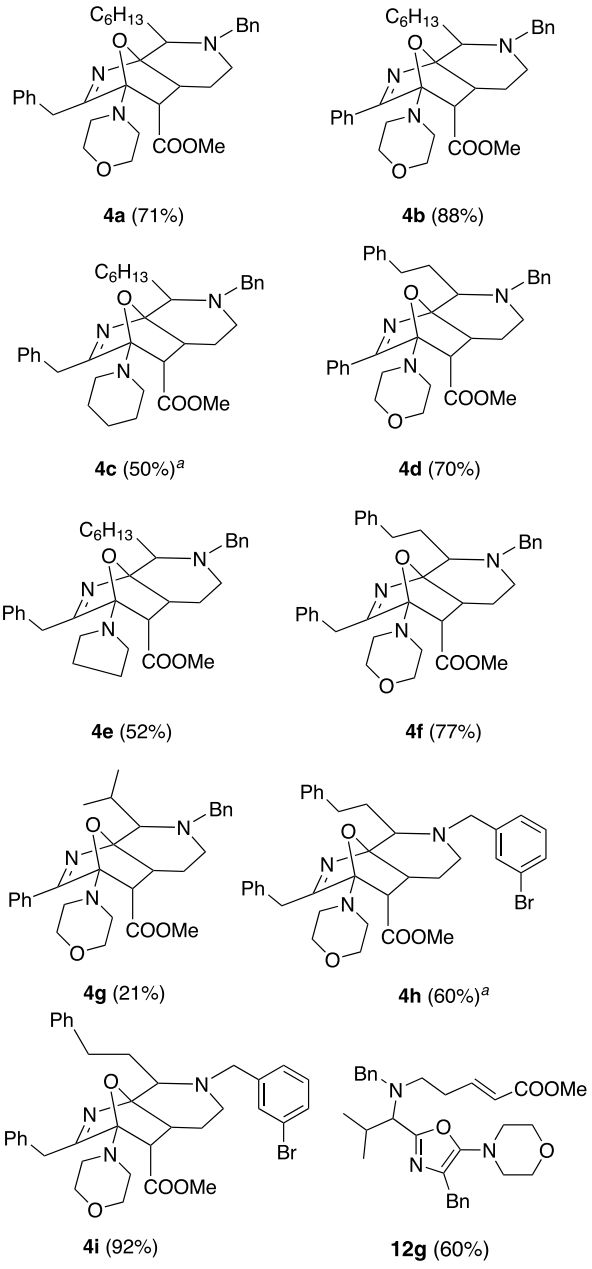
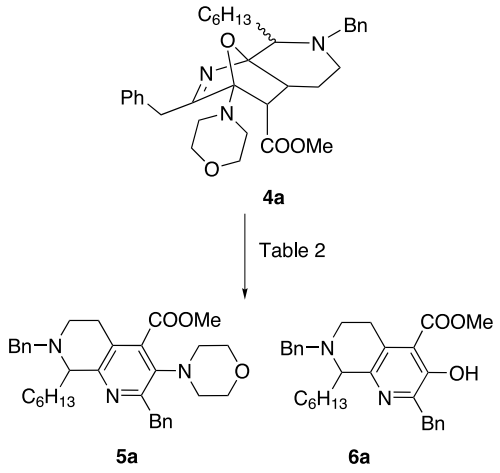


Figure 4. Representative structure of epoxy-tetrahydronaphthyridine, dr= 2/1; [a]only one diastereoisomer was isolated.

oxazole **12g** (60%). Heating to reflux was required to complete the reaction sequence when isonitriles **7d** and **7e**, derived from phenylglycine, were used. The presence of phenyl substituent at the C-4 position of the 5-aminooxazole may reduce the electron density of the diene unit, decreasing consequently its reactivity towards the electron-poor dienophile. Curiously, the primary amine **8b** did not participate in this reaction, although we have previously demonstrated that simpler primary amine is an efficient reaction partner in the three-component synthesis of oxazole.[8]

2.3. Fragmentation of epoxy-tetrahydronaphthyridine 4 and three component synthesis of 6. Using **4a** as model compound, conditions for performing the fragmentation of bridged α-amino ether function (Scheme 3) were surveyed



Scheme 3. Acid-mediated fragmentation of epoxy-tetrahydronaphthyridine **4a**.

varying solvents (MeOH, toluene), acids (TFA, *p*-TsOH, TMSCl, TMSOTf) and temperatures (room temperature, 0, −30, −78 °C). The results are summarized in Table 2. As is seen, the fragmentation pathway depended on the reaction conditions and both compounds **5a** and **6a** can be prepared by combination of a suitable acid and a solvent. While TMSCl in MeOH promoted the formation of **5a** (entry 4), TMSOTf in MeOH afforded both **5a** and **6a** in yields of 27 and 28%, respectively (entry 3). Interestingly, in dichloromethane and in the presence of trifluoroacetic acid (TFA), compound **5a** was isolated in 68% yield (entry 2), while in methanol and in the presence of *p*-toluenesulfonic acid, an alternative fragmentation occurred leading to compound **6a** as the only isolable product in 65% yield (entry 5). Figure 5 summarized the 5,6,7,8-tetrahydro-1,7-naphthyridine (**5**, **6**) synthesized by applying these two conditions [$^{a}CH_2Cl_2$, TFA, room temperature; ^{b}MeOH, *p*-TsOH, room temperature] to the respective epoxy-tetrahydronaphthyridine. Fragmentation of **4b** with a phenyl substituent at the C-2 position was found to be more difficult and **5b** was isolated in only moderate yield under both conditions.

Table 2. Fragmentation of **4a**, a survey of reaction conditions

Entry	Solvent	*T* (°C)	Acid (equiv)	**5a** (**6a**) (%)[a]
1	MeOH	−78 to Room temperature	TFA (7)	31
2	CH_2Cl_2	Room temperature	TFA (10)	68
3	MeOH	Room temperature	TMSOTf (3)	28 (27)
4	MeOH	Room temperature	TMSCl (1)	21
5	MeOH	Room temperature	TsOH (5)	(65)

Abbreviations: TFA, trifluoroacetic acid; TMSOTf, trimethylsilyl trifluoromethanesulfonate; TMSCl, trimethylsilyl chloride; TsOH=*para*-toluenesulfonic acid.
[a] Refers to isolated yield.

While the formation of **5** can be rationalized based on an assumption that the fragmentation of amino ether was assisted by the lone-pair electron of nitrogen, the fragmentation of **4** leading to **6** (*p*-TsOH in MeOH) is more intriguing. A possible reaction sequence that accounted for the formation of **6** was advanced in Scheme 4. The nucleophilic addition of methanol (or water) onto the imine would trigger the fragmentation to afford the ketone

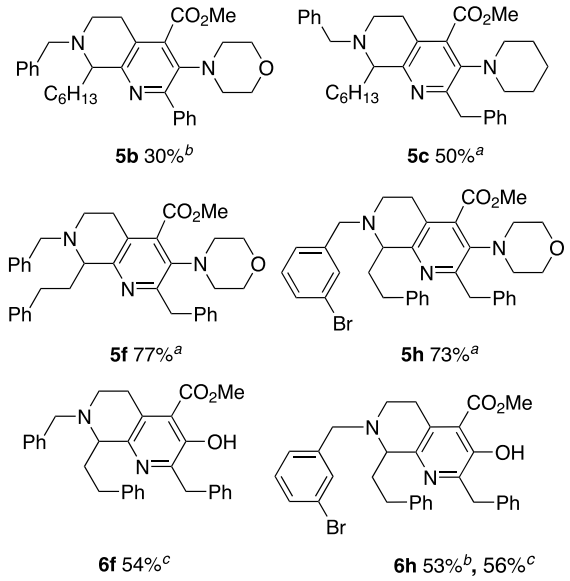
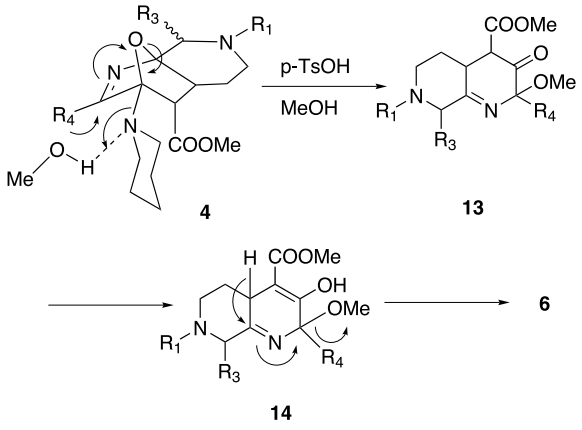


Figure 5. Fragmentation of epoxy-tetrahydronaphthyridine to 5,6,7,8-tetrahydro-1,7-naphthyridine; [a]CH_2Cl_2, TFA, room temperature; [b]MeOH, *p*-TsOH, room temperature; [c]one-pot three-component synthesis.



Scheme 4. Mechanistic hypothesis for the formation of naphthyridine **6**.

13 which, after tautomerization and ejection of methanol would provide compound **6**.

It is evident that conditions for the three-component synthesis of *oxa*-bridged tricycle **4** and its subsequent fragmentation to **6** are compatible. This consideration prompted us to examine the one-pot synthesis of **6**. In the event, stirring a solution of isocyanoacetamide **7a**, amine **8a** and aldehyde **9a** at room temperature for 2 h followed by addition of *p*-TsOH provided directly the 5,6,7,8-tetrahydro-1,7-naphthyridine **6a** in 48% yield. Compounds **6f** and **6h** were similarly prepared by this one-pot procedure in yields of 54 and 56%, respectively (Fig. 5).

3. Conclusion

In conclusion, we have developed a novel three-component synthesis of epoxy-tetrahydro naphthyridine (**4**) starting from easily available isocyanoacetamide (**7**), homoallylamine (**8**) and aldehyde (**9**). It is worthy noting that neither

external reagent nor heating (or cooling) was required to promote this rather complex transformation that leads to the formation of five chemical bonds and three rings.

The process is also atom economic and ecologically benign since only molecular water was lost in this multicomponent process. Subsequent studies revealed that compound **4** can undergo two types of fragmentation leading to differently substituted 5,6,7,8-tetrahydro-1,7-naphthyridines (**5**, **6**) depending on the choice of the acid and reaction medium. Thus, from the same starting materials, three different heterocycles are readily synthesized by simply modifying the workup procedure. The operational simplicity and good to excellent chemical yield made these novel heterocycle syntheses highly attractive in diversity-oriented synthesis program.[20]

4. Experimental

4.1. General procedure for the synthesis of isonitrile

α-Substituted-α-isocyano acetamides were obtained by dehydration of the corresponding *N*-formyl derivatives.[9] Synthesis of **7a** is typical: a stirred solution of morpholinyl amide of *N*-formyl phenylalanine (10.0 mmol) and triethylamine (50.0 mmol) in dry dichloromethane (50.0 mL) was cooled to −20 to −30 °C. Phosphorus oxychloride (15.0 mmol) was added dropwise and the reaction mixture was stirred for 2 h at −20 to −30 °C. An aqueous solution of sodium bicarbonate was introduced dropwise so that the temperature of mixture was maintained at −20 to −30 °C. The mixture was stirred for 0.5 h and raised to room temperature. The aqueous layer was separated and extracted with dichloromethane. The organic extracts were combined, washed with brine and dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel to provide the isocyanide **7a**.

4.1.1. Compound 7a. (Yield: 95%; eluent: heptane/EtOAc=2:1); white solid, mp 79–81 °C; IR ($CHCl_3$) ν 2928, 2863, 2142, 1668, 1496, 1456, 1116 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 3.13–3.78 (m, 10H), 4.55 (t, 1H, J=7.3 Hz), 7.22–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 39.1, 42.9, 46.2, 55.0, 65.9, 66.4, 127.7, 128.8 (2CH), 129.4 (2CH), 135.0, 159.8, 163.5; MS (EI): *m/z* 244. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.71; H, 6.54; N, 11.47.

4.1.2. Compound 7b. Mp 75–78 °C; IR ($CHCl_3$) ν 2949, 2862, 2142 (N≡C), 1659, 1453, 1271, 1137, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81–1.66 (m, 6H), 3.15–3.68 (m, 6H), 4.56 (dd, J=8.2, 6.3 Hz, 1H), 7.24–7.36 (m, 5H); RMN ^{13}C ($CDCl_3$, 75 MHz) δ 23.6, 24.8, 25.3, 38.6, 43.3, 46.4, 54.7, 128.2, 127.0, 127.8, 128.9, 129.3, 134.9, 158.6, 162.6; MS (IE) *m/z* 216 $[M-NC]^+$, 242 $[M]^+$.

4.1.3. Compound 7c. Mp 85–87 °C; IR ($CHCl_3$) ν 3032, 3011, 2982, 2956, 2882, 2146 (N≡C), 1659, 1440, 1343, 1232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70–1.87 (m, 4H), 2.95–3.03 (m, 1H), 3.11 (dd, J=13.7, 7.8 Hz, 1H), 3.22 (dd, J=13.7, 6.8 Hz, 1H), 3.32–3.49 (m, 3H), 4.34 (dd, J=7.8, 6.8 Hz, 1H), 7.18–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.9, 26.0, 39.0, 46.6, 46.7, 57.2, 127.6, 127.6, 128.7, 129.4, 135.2, 159.3, 163.0; MS (IE) *m/z* 202 $[M-NC]^+$, 242 $[M]^+$.

4.1.4. Compound 7d. Mp 89–90 °C; IR ($CHCl_3$) ν 3499, 3011, 2926, 2863, 2146 (N≡C), 1664, 1497, 1439, 1361, 1302, 1273, 1234, 1115, 1069, 1000, 958, 859 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.33 (m, 4H), 3.62 (m, 4H), 5.55 (s, 1H), 7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 43.1, 46.2, 60.1, 65.7, 66.4, 126.2, 129.4, 131.9, 163.1; MS (IE) *m/z* 230 $[M]^+$.

4.2. General procedure for the three-component synthesis of epoxy-tetrahydronaphthyridine (4)

A solution of homoallylamine (**8**, 1.2 equiv) and aldehyde (**9**, 1.2 equiv) in dry MeOH (0.4 M) was stirred at room temperature for 1 h. α-Isocyanoacetamide (**7**, 1.0 equiv) was added. After being stirred at room temperature for additional 20 h, the reaction mixture was diluted with water; the volatile was removed under reduce pressure and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the crude product by either preparative TLC (silica gel, eluent heptane/AcOEt) or flash chromatography (silica gel, eluent heptane/AcOEt) afforded the title compound.

4.2.1. Compound 4a. Yield: 71%, dr=2/1. *Major isomer*. Yellow oil; IR ($CHCl_3$) ν 2956, 2929, 2859, 1732, 1635, 1495, 1453, 1347, 1271, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J=6.5 Hz, 3H), 1.27 (m, 8H), 1.45–1.86 (m, 4H), 2.12 (m, 1H), 2.24 (td, J=13.0, 1.6 Hz, 1H), 2.59–2.65 (m, 2H), 2.81 (d, J=5.3 Hz, 1H), 2.82 (m, 1H), 2.96–3.04 (m, 2H), 3.34 (t, J=5.3 Hz, 1H), 3.40 (d, J=13.7 Hz, 1H), 3.62 (s, 2H), 3.67–3.75 (m, 4H), 3.70 (s, 3H), 3.97 (d, J=13.7 Hz, 1H), 7.22–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.9, 27.8, 28.4, 29.9, 31.8, 35.3, 44.5, 48.4 (2C), 49.6, 49.9, 52.1, 54.3, 63.1, 67.0 (2C), 98.3, 107.1, 126.7, 126.8, 128.4 (2C), 128.7, 128.9 (2C), 129.1 (2C), 129.7 (2C), 135.9, 170.8, 176.1; MS (EI) *m/z* 474 $[M-C_6H_{13}]^+$, 528 $[M-OMe]^+$, 559 $[M]^+$, 560 $[M+H]^+$; MS (ESI) *m/z* 560 $[M+H]^+$; HRMS *m/z* calcd for: $[C_{34}H_{45}N_3O_4+H]^+$ 560.3488, *m/z* found: 560.3502. *Minor isomer*. Yellow oil; IR ($CHCl_3$) ν 2956, 2930, 2859, 1729, 1656, 1495, 1443, 1330, 1262, 1174, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.27–1.79 (m, 11H), 2.09 (m, 1H), 2.26 (m, 1H), 2.54–2.65 (m, 3H), 2.82–2.90 (m, 1H), 2.83 (d, J=3.3 Hz, 1H), 2.97–3.06 (m, 3H), 3.53 (d, J=15.7 Hz, 1H), 3.66–3.76 (m, 5H), 3.67 (s, 3H), 3.88 (m, 2H), 7.30 (m, 10H); MS (IE) *m/z* 474 $[M-C_6H_{13}]^+$, 559 $[M]^+$; MS (ESI) *m/z* 560 $[M+H]^+$; HRMS *m/z* calcd for: $[C_{34}H_{45}N_3O_4+H\ ]^+$ 560.3488, *m/z* found: 560.3495.

4.2.2. Compound 4b. Yield: 88%, dr=2/1. *Major isomer*. Yellow oil; IR ($CHCl_3$) ν 2956, 2928, 2859, 1736, 1722, 1601, 1571, 1494, 1452, 1436, 1366, 1302, 1271, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (m, 3H), 1.30 (m, 8H), 1.57–1.96 (m, 4H), 2.27–2.35 (m, 2H), 2.78–2.87 (m, 3H), 3.00 (d, J=3.5 Hz, 1H), 3.17–3.24 (m, 2H), 3.33 (s, 3H), 3.46 (m, 1H), 3.48 (d, J=13.8 Hz, 1H), 3.76 (m, 4H), 3.99

(d, J=13.8 Hz, 1H), 7.26–7.44 (m, 8H), 8.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 25.9, 27.8, 27.9, 29.8, 31.8, 43.8, 48.1, 49.5, 49.9, 51.7, 53.8, 53.9, 63.0, 66.9 (2C), 97.2, 107.3, 126.8, 127.0 (2C), 128.2 (2C), 128.3 (2C), 129.1 (2C), 131.0, 131.9, 139.6, 169.8, 170.0; MS (IE) *m/z*; MS (ESI) *m/z* 546 $[M+H]^+$; HRMS *m/z* calcd for: $[C_{33}H_{43}N_3O_4+H]^+$ 546.3332, *m/z* found: 546.3305. *Minor isomer*. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (m, 3H), 1.32 (m, 8H), 1.76 (m, 2H), 1.90 (m, 1H), 2.26 (m, 1H), 2.44 (m, 1H), 2.63 (m, 1H), 2.79–2.85 (m, 2H), 2.95 (m, 1H), 3.03 (d, J=3.5 Hz, 1H), 3.14 (m, 1H), 3.17–3.24 (m, 2H), 3.35 (s, 3H), 3.77–3.80 (m, 4H), 3.92 (d, J=13.4 Hz, 1H), 4.00 (d, J=13.4 Hz, 1H), 7.24–7.44 (m, 8H), 8.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 22.8, 26.7, 27.2, 28.3, 29.2, 32.1, 40.5, 42.5, 48.3, 50.8, 51.8, 58.0, 58.7, 67.0 (2C), 98.0, 106.8, 126.7, 127.1 (2C), 128.0 (2C), 128.2 (2C), 129.1 (2C), 130.9, 132.0, 140.4, 170.3, 170.4; MS (ESI) *m/z* 546 $[M+H]^+$; HRMS *m/z* calcd for: $[C_{33}H_{43}N_3O_4+H]^+$ 546.3332, *m/z* found: 546.3323.

4.2.3. Compound 4c. Yield: 50%, 1 diastereomer. Yellow oil; IR ($CHCl_3$) ν 3023, 2937, 2858, 1728, 1602, 1453, 1438, 1275, 1254 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (m, 3H), 1.27 (m, 8H), 1.54–1.84 (m, 9H), 2.09 (m, 1H), 2.23 (m, 2H), 2.60–2.64 (m, 2H), 2.80 (m, 1H), 2.87 (d, J=3.6 Hz, 1H), 2.94–3.01 (m, 2H), 3.32 (t, J=5.3 Hz, 1H), 3.40 (d, J=13.6 Hz, 1H), 3.64 (s, 2H), 3.69 (s, 3H), 3.97 (d, J=13.6 Hz, 1H), 7.23–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.8, 24.7, 26.0, 26.2 (2C), 29.1, 29.8, 31.9, 35.3, 44.7, 49.2 (2C), 49.8, 51.5, 63.4, 98.0, 108.2, 126.5, 126.9, 128.4 (2C), 128.9 (2C), 129.1 (2C), 129.5, 129.9 (2C), 136.5, 171.2, 177.1; MS (ESI) *m/z* 558 $[M+H]^+$, 580 $[M+Na]^+$.

4.2.4. Compound 4d. Yield: 70%, dr=2/1. *Major isomer*. Yellow oil; IR ($CHCl_3$) ν 3065, 3003, 2954, 2859, 1736, 1722, 1601, 1495, 1452, 1436, 1365, 1302, 1271, 1255, 1169, 1119 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (td, J=12.6, 3.2 Hz, 1H), 1.85 (m, 1H), 2.07–2.28 (m, 2H), 2.30–2.40 (m, 3H), 2.79–2.93 (m, 3H), 2.98–3.08 (m, 1H), 3.03 (d, J=3.5 Hz, 1H), 3.22 (m, 2H), 3.34 (s, 3H), 3.54 (m, 2H), 3.77 (m, 4H), 4.07 (d, J=13.9 Hz, 1H), 7.09–7.37 (m, 13H), 8.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 29.3, 29.8, 31.7, 43.8, 48.1, 49.6, 49.8, 51.8, 53.7, 53.8, 62.4, 66.93, 97.9, 107.4, 125.6, 126.9, 127.0 (2C), 128.3 (4C), 128.4 (4C), 128.8 (2C), 131.1, 131.7, 139.5, 143.1, 170.0. *Minor isomer*. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (m, 2H), 2.16 (m, 1H), 2.45 (m, 1H), 2.60 (m, 1H), 2.70 (m, 1H), 2.74–2.84 (m, 2H), 2.90–3.00 (m, 3H), 3.02 (d, J=3.2 Hz, 1H), 3.18–3.24 (m, 3H), 3.32 (s, 3H), 3.77 (m, 4H), 3.96 (m, 2H), 7.24–7.43 (m, 13H), 8.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 29.3, 30.5, 33.6, 40.6, 42.4, 48.3, 50.7, 51.8, 58.0, 58.7, 67.0 (2C), 97.7, 106.9, 125.5, 126.8, 127.0 (2C), 128.1 (2C), 128.2 (4C), 128.6 (2C), 129.1 (2C), 130.9, 131.9, 140.2, 143.2, 170.2.

4.2.5. Compound 4e. Yield: 52%, dr=3/2. *Major isomer*. Yellow oil; IR ($CHCl_3$) ν 3065, 2954, 2873, 1722, 1605, 1453, 1368, 1341, 1262, 1171 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.26–1.51 (m, 8H), 1.62–1.77 (m, 4H), 1.88–2.00 (m, 3H), 2.29 (m, 1H), 2.64–2.98 (m, 3H), 3.13 (m, 1H), 3.19 (d, J=13.4 Hz, 1H), 3.16–3.34 (m, 2H), 3.39–3.54 (m, 3H), 3.61 (d, J=13.4 Hz, 1H), 3.70 (d, J=13.4 Hz, 1H), 3.80 (s, 3H), 3.90 (d, J=13.4 Hz, 1H), 7.12–7.35 (m, 10H); MS (ESI) *m/z* 544 $[M+H]^+$, 566 $[M+Na]^+$. *Minor isomer*. Yellow oil; IR ($CHCl_3$) ν 3000, 2955, 2931, 2874, 1728, 1614, 1495, 1454, 1437, 1341, 1264, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (m, 3H), 1.07 (m, 1H), 1.27–1.49 (m, 8H), 1.65 (m, 1H), 1.76 (m, 2H), 1.83–2.04 (m, 3H), 2.41 (m, 1H), 2.64–2.73 (m, 1H), 3.07 (m, 1H), 3.18–3.32 (m, 4H), 3.31 (d, J=13.4 Hz, 1H), 3.42 (m, 1H), 3.51 (s, 2H), 3.59 (m, 1H), 3.80 (s, 3H), 3.80 (d, J=13.4 Hz, 1H), 4.02 (m, 1H), 7.17–7.38 (m, 10H); MS (ESI) *m/z* 544 $[M+H]^+$, 566 $[M+Na]^+$.

4.2.6. Compound 4f. Yield: 77%, dr=2/1. *Major isomer*. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71–1.58 (m, 1H), 1.87 (m, 1H), 2.02–2.20 (m, 4H), 2.28 (m, 1H), 2.60–2.68 (m, 2H), 2.75–2.96 (m, 2H), 2.84 (d, J=3.6 Hz, 1H), 2.98–3.05 (m, 2H), 3.44 (t, J=5.3 Hz, 1H), 3.47 (d, J=13.8 Hz, 1H), 3.64 (s, 2H), 3.71 (s, 3H), 3.66–3.77 (m, 4H), 4.06 (d, J=13.8 Hz, 1H), 7.18–7.43 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.3 (2C), 30.9, 33.0, 36.5, 45.5, 49.5 (2C), 50.8, 53.2, 54.8, 63.6, 68.0 (2C), 99.3, 108.3, 126.5, 127.8, 129.2 (2C), 129.3 (2C), 129.3 (2C), 129.4 (2C), 129.5 (2C), 129.6 (2C), 129.9, 130.4, 136.9, 144.2, 171.7, 177.5; MS (ESI) *m/z* 580 $[M+H]^+$. *Minor isomer*. Yellow oil; IR ($CHCl_3$) ν 3086, 3002, 2954, 2924, 2860, 1733, 1706, 1632, 1602, 1495, 1454, 1364, 1270, 1118 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70–1.83 (m, 2H), 2.02–2.13 (m, 1H), 2.25–2.32 (m, 1H), 2.35–2.47 (m, 1H), 2.59–2.93 (m, 6H), 2.85 (d, J=3.2 Hz, 1H), 2.99–3.07 (m, 2H), 3.12 (m, 1H), 3.54 (d, J=16.1 Hz, 1H), 3.69 (s, 3H), 3.64–3.78 (m, 5H), 3.88 (m, 2H), 7.16–7.40 (m, 15H); MS (ESI) *m/z* 580 $[M+H]^+$.

4.2.7. Compound 4g. Yield: 21%, 1 diastereomer. Yellow oil; IR ($CHCl_3$) ν 3021, 2964, 2859, 1735, 1722, 1494, 1451, 1369, 1302, 1271, 1118 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J=6.9 Hz, 3H), 1.21 (d, J=6.9 Hz, 3H), 1.65 (m, 1H), 1.78 (m, 1H), 2.22–2.41 (m, 3H), 2.76–2.88 (m, 3H), 2.98 (d, J=3.6 Hz, 1H), 3.18–3.22 (m, 2H), 3.33 (m, 1H), 3.34 (s, 3H), 3.42 (d, J=13.8 Hz, 1H), 3.78 (m, 4H), 4.08 (d, J=13.8 Hz, 1H), 7.26–7.44 (m, 8H), 8.11 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 21.7, 27.8, 28.4, 29.3, 44.5, 48.1, 49.6, 49.7, 51.8, 54.8, 66.9, 68.0 (2C), 98.3, 107.0, 126.7, 126.9 (2C), 128.3 (2C), 128.5 (4C), 130.9, 132.0, 140.0, 167.6, 170.1; MS (ESI) *m/z* 504 $[M+H]^+$, 526 $[M+Na]^+$.

4.2.8. Compound 4h. Yield: 60%, 1 diastereomer. Yellow oil; IR ($CHCl_3$) ν 3003, 2943, 2860, 1726, 1604, 1495, 1453, 1437, 1365, 1266, 1252, 1176, 1127 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58–1.72 (m, 6H), 1.89 (m, 1H), 1.96–2.21 (m, 3H), 2.32 (m, 1H), 2.65–2.73 (m, 3H), 2.75–2.90 (m, 2H), 2.94 (d, J=3.5 Hz, 1H), 2.93–3.05 (m, 3H), 3.42–3.48 (m, 2H), 3.69 (s, 2H), 3.73 (s, 3H), 4.03 (d, J=14.2 Hz, 1H), 7.13–7.44 (m, 13H), 7.60 (s, 1H); MS (ESI) *m/z* 656 $[^{79}BrM+H]^+$, 658 $[^{81}BrM+H]^+$, 678 $[^{79}BrM+Na]^+$, 680 $[^{81}BrM+Na]^+$; HRMS *m/z* calcd for: $[C_{36}H_{40}BrN_3O_4+H]^+$ 656.2488, 658.2467, *m/z* found: 656.2522, 658.2510.

4.2.9. Compound 4i. Yield: 92%, dr=2/1. *Major isomer*. Yellow oil; IR ($CHCl_3$) ν 3066, 3036, 3021, 3014, 2954, 2860, 1729, 1657, 1641, 1632, 1602, 1495, 1453, 1438,

1271, 1170, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51–1.65 (m, 2H), 1.83 (m, 1H), 1.90–2.16 (m, 3H), 2.27 (m, 1H), 2.56–2.63 (m, 2H), 2.66–2.91 (m, 2H), 2.80 (d, J= 3.7 Hz, 1H), 2.93–3.00 (m, 2H), 3.38 (t, J=5.4 Hz, 1H), 3.43 (d, J=14.6 Hz, 1H), 3.58 (s, 2H), 3.63–3.72 (m, 4H), 3.67 (s, 3H), 3.95 (d, J=14.6 Hz, 1H), 7.03–7.36 (m, 13H), 7.52 (s, 1H); MS (ESI) *m/z* 658 $[^{79}BrM+H]^+$, 660 $[^{81}BrM+H]^+$. *Minor isomer*. Yellow oil; IR ($CHCl_3$) ν 3064, 3043, 3036, 3011, 2953, 1728, 1602, 1453, 1438, 1272, 1191, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.63–1.86 (m, 2H), 2.00–2.12 (m, 1H), 2.29 (m, 3H), 2.45 (m, 1H), 2.57–2.72 (m, 2H), 2.74–2.90 (m, 2H), 2.86 (d, J= 3.7 Hz, 1H), 2.97–3.11 (m, 3H), 3.55 (d, J=16.1 Hz, 1H), 3.69 (s, 3H), 3.65–3.78 (m, 5H), 3.85 (s, 2H), 7.15–7.39 (m, 13H), 7.56 (s, 1H); MS (ESI) *m/z* 658 $[^{79}BrM+H]^+$, 660 $[^{81}BrM+H]^+$.

4.2.10. Compound 12g. Yellow oil; yield: 60%; IR ($CHCl_3$) ν 3065, 2964, 2924, 2859, 1719, 1657, 1640, 1602, 1496, 1448, 1438, 1373, 1272, 1177, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, J=6.5 Hz, 3H), 1.11 (d, J= 6.5 Hz, 3H), 2.29–2.49 (m, 3H), 2.85 (m, 2H), 3.14 (t, J= 5.6 Hz, 4H), 3.26 (d, J=13.9 Hz, 1H), 3.35 (d, J=10.8 Hz, 1H), 3.74 (s, 3H), 3.90 (d, J=5.6 Hz, 4H), 4.02 (d, J= 13.9 Hz, 1H), 5.84 (d, J=15.5 Hz, 1H), 6.95 (m, 1H), 7.46–7.27 (m, 8H), 8.01 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 20.3, 28.5, 31.2, 49.1, 50.5 (2C), 51.4, 55.2, 64.7, 67.0 (2C), 121.8, 123.6, 126.0 (2C), 126.9, 127.0, 128.3 (2C), 128.4 (2C), 128.9 (2C), 132.0, 139.5, 147.8, 150.6, 156.0, 166.9; MS (ESI) *m/z* 504 $[M+H]^+$, 526 $[M+Na]^+$.

4.3. General procedure for the synthesis of tetrahydronaphthyridines (5)

To a solution of epoxy-naphthyridine **4** in dry CH_2Cl_2 (0.2 M), TFA (10.0 equiv) was added and the reaction mixture was stirred at room temperature, the reaction was monitored by TLC (typically 30–60 min). After completion of the reaction, the mixture was diluted with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of crude product by either preparative TLC (silica gel, eluent heptane/AcOEt) or flash chromatography (silica gel, eluent heptane/AcOEt) afforded the tetrahydronaphthyridines **5**.

4.3.1. Compound 5a. Yellow oil; yield: 68%; IR ($CHCl_3$) ν 3017, 2955, 2858, 1731, 1453, 1437, 1415, 1263, 1235, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J= 6.6 Hz, 3H), 1.23–1.28 (m, 7H), 1.41–1.48 (m, 1H), 1.79–2.04 (m, 2H), 2.46–2.56 (m, 1H), 2.61–2.76 (m, 2H), 2.90 (m, 4H), 3.11 (m, 1H), 3.61 (d, J=13.6 Hz, 1H), 3.64–3.71 (m, 5H), 3.91 (d, J=13.6 Hz, 1H), 3.94 (s, 3H), 4.14 (d, J= 14.4 Hz, 1H), 4.34 (d, J=14.4 Hz, 1H), 7.19–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.5, 22.9, 25.8, 29.6, 32.1, 33.6, 40.4, 43.5, 51.3, 52.5, 58.0, 64.0, 67.9 (2C), 125.3, 126.1, 127.1, 128.3 (2C), 128.4 (2C), 128.8 (2C), 128.9 (2C), 139.3, 139.6, 140.2, 155.7, 157.3, 168.8; MS (EI) *m/z* 91 $[CH_2Ph]^+$, 455 $[M-C_4H_8NO]^+$, 456 $[M-C_6H_{13}]^+$, 510 $[M-OMe]^+$; MS (ESI) *m/z* 542 $[M+H]^+$.

4.3.2. Compound 5b. Yellow oil; yield: 30%; IR ($CHCl_3$) ν 3018, 2954, 2930, 2858, 1730, 1602, 1450, 1436, 1415, 1224, 1208, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (t, J=6.7 Hz, 3H), 1.18 (m, 7H), 1.36 (m, 1H), 1.75–1.82 (m, 2H), 2.34–2.42 (m, 1H), 2.64–2.86 (m, 2H), 2.75 (m, 4H), 3.05–3.13 (m, 1H), 3.45 (m, 4H), 3.62 (d, J= 13.6 Hz, 1H), 3.65 (m, 1H), 3.77 (d, J=13.6 Hz, 1H), 3.89 (s, 3H), 7.16–7.39 (m, 8H), 7.47–7.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 21.6, 22.7, 26.1, 29.4, 31.9, 33.9, 42.3, 51.4 (2C), 52.5, 57.7, 63.5, 67.3 (2C), 125.6, 126.9, 128.11 (3C), 128.2 (2C), 128.8 (2C), 129.1 (2C), 139.3 (2C), 139.4, 140.1, 154.9, 155.3, 168.7; MS (ESI) *m/z* 528 $[M+H]^+$.

4.3.3. Compound 5c. Yellow oil; yield: 50%; IR ($CHCl_3$) ν 2935, 2857, 1730, 1602, 1493, 1453, 1437, 1414, 1348, 1274, 1175, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J=6.6 Hz, 3H), 1.22–1.60 (m, 14H), 1.76–2.02 (m, 2H), 2.45–2.73 (m, 3H), 2.84 (m, 4H), 3.09 (m, 1H), 3.59 (d, J=13.5 Hz, 1H), 3.67 (m, 1H), 3.90 (d, J=13.5 Hz, 1H), 3.91 (s, 3H), 4.08 (d, J=14.3 Hz, 1H), 4.33 (d, J=14.3 Hz, 1H), 7.19–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.4, 22.7, 24.2, 25.6, 26.8 (3C), 29.5, 31.9, 33.4, 39.9, 43.5, 52.2 (2C), 57.9, 63.9, 124.7, 125.7, 126.9, 128.0 (2C), 128.2 (2C), 128.7 (2C), 128.8 (2C), 139.1, 139.6, 140.4, 140.9, 154.3, 157.2, 168.9; MS (ESI) *m/z* 540 $[M+H]^+$, 562 $[M+Na]^+$.

4.3.4. Compound 5f. Yellow oil; yield: 77%; IR ($CHCl_3$) ν 3065, 3004, 1731, 1602, 1495, 1453, 1437, 1414, 1299, 1263, 1176, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.13–2.42 (m, 2H), 2.53–2.83 (m, 5H), 2.92 (m, 4H), 3.10–3.19 (m, 1H), 3.62 (d, J=13.6 Hz, 1H), 3.68 (m, 4H), 3.78 (t, J=5.4 Hz, 1H), 3.94 (s, 3H), 3.98 (d, J=13.6 Hz, 1H), 4.15 (d, J=14.4 Hz, 1H), 4.35 (d, J=14.4 Hz, 1H), 7.08–7.03 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 29.4, 31.9, 35.2, 40.3, 43.9, 51.3, 52.6, 58.1, 63.8, 67.9 (2C), 125.5, 125.6, 126.1, 127.2, 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.6 (2C), 128.8 (2C), 128.9 (2C), 139.3, 139.4, 140.2, 143.2, 155.0, 157.5, 168.7; MS (ESI) *m/z* 562 $[M+H]^+$, 584 $[M+Na]^+$, 600 $[M+K]^+$; HRMS *m/z* calcd for: $[C_{36}H_{39}N_3O_3+H]^+$ 562.3070, *m/z* found: 562.3076.

4.3.5. Compound 5h. Yellow oil; yield: 73%; ^1H NMR (300 MHz, $CDCl_3$) δ 2.12–2.41 (m, 2H), 2.55–2.82 (m, 5H), 2.94 (m, 4H), 3.16 (m, 1H), 3.63 (d, J=13.9 Hz, 1H), 3.70 (m, 4H), 3.77 (m, 1H), 3.93 (s, 3H), 3.97 (d, J=13.9 Hz, 1H), 4.16 (d, J=14.4 Hz, 1H), 4.37 (d, J=14.4 Hz, 1H), 7.10–7.41 (m, 12H), 7.44 (d, J=8.0 Hz, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 29.3, 31.8, 35.1, 40.2, 43.8, 51.2, 52.5, 57.4, 63.6, 67.7 (2C), 122.5, 125.1, 125.5, 126.0, 127.3, 128.2 (2C), 128.3 (2C), 128.4 (2C), 128.7 (2C), 129.9, 130.1, 131.6, 139.3, 139.9 (2C), 141.8, 142.7, 154, 6, 157.5, 168.5; MS (ESI) *m/z* 640 $[^{79}BrM+H]^+$, 642 $[^{81}BrM+H]^+$; HRMS *m/z* calcd for: $[C_{36}H_{38}BrN_3O_3+H]^+$ 640.2175, 642.2154, *m/z* found: 640.2217, 642.2212.

4.4. General procedure for the synthesis of tetrahydronaphthyridines (6)

To a solution of epoxy-naphthyridine **4** in dry MeOH (0.4 M), TsOH (5.0 equiv) was added and the reaction mixture was stirred at room temperature, the reaction was

monitored by TLC (typically 30–60 min). After completion of the reaction, the mixture was diluted with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of crude product by either preparative TLC (silica gel, eluent heptane/AcOEt) or flash chromatography (silica gel, eluent heptane/AcOEt) afforded the tetrahydronaphthyridine **6**.

4.5. Three-component synthesis of of tetrahydronaphthyridines (6)

A solution of homoallylamine (**8**, 1.2 equiv) and aldehyde (**9**, 1.2 equiv) in dry MeOH (0.4 M) was stirred at room temperature for 1 h. α-Isocyanoacetamide (**7**, 1.0 equiv) was added. After being stirred at room temperature for 20 h, TsOH (5 equiv) was added and the reaction mixture was stirred at room temperature for additional 30–60 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution, and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of crude product by either preparative TLC (silica gel, eluent heptane/AcOEt) or flash chromatography (silica gel, eluent heptane/AcOEt) afforded the tetrahydronaphthyridine **6**.

4.5.1. Compound 6a. Yellow oil; yield: 65% (two-steps); 47% (one-pot three component); IR ($CHCl_3$) ν 2957, 2931, 2858, 1674, 1601, 1535, 1441, 1408, 1344, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.09–1.30 (m, 7H), 1.46 (m, 1H), 1.83–2.10 (m, 2H), 2.50 (m, 1H), 2.83–3.08 (m, 3H), 3.51 (d, $J=13.5$ Hz, 1H), 3.70 (t, $J=4.9$ Hz, 1H), 3.95 (s, 3H), 3.98 (d, $J=13.5$ Hz, 1H), 4.11 (d, $J=13.6$ Hz, 1H), 4.30 (d, $J=13.6$ Hz, 1H), 7.17–7.40 (m, 10H), 10.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 25.1, 26.3, 29.6, 31.9, 33.4, 38.9, 44.6, 52.6, 58.1, 64.3, 116.8, 126.0, 126.9, 127.9, 128.1 (2C), 128.2 (2C), 128.8 (2C), 129.0 (2C), 139.3, 139.6, 148.6, 148.9, 152.2, 171.2; MS (EI) *m/z* 91 $[CH_2Ph]^+$, 387 $[M-C_6H_{13}]^+$; MS (ESI) *m/z* 473 $[M+H]^+$; HRMS *m/z* calcd for: $[C_{30}H_{36}N_2O_3+H]^+$ 473. 2804, *m/z* found: 473.2768.

4.5.2. Compound 6f. Yellow oil; yield: 54% (one-pot three component); IR ($CHCl_3$) ν 3693, 2959, 1667, 1603, 1441, 1347, 1262, 1176 1098, 1012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.09–2.19 (m, 1H), 2.32–2.43 (m, 3H), 2.53–3.02 (m, 4H), 3.43 (d, $J=13.6$ Hz, 1H), 3.71 (m, 1H), 3.86 (s, 3H), 3.95 (d, $J=13.6$ Hz, 1H), 4.01 (d, $J=13.7$ Hz, 1H), 4.24 (d, $J=13.7$ Hz, 1H), 6.97–7.36 (m, 15H), 10.7 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 31.3, 35.1, 38.8, 45.1, 52.6, 58.2, 64.1, 116.8, 125.3, 126.0, 126.7, 128.0, 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.4 (2C), 128.5 (2C), 128.8 (2C), 129.1, 139.5, 143.1, 148.0, 149.2, 152.3, 171.1; MS (ESI) *m/z* 493 $[M+H]^+$.

4.5.3. Compound 6h. Yellow oil; yield: 53% (two-step), 56% (one-pot three component); IR ($CHCl_3$) ν 3025, 2957, 1675, 1533, 1495, 1441, 1342, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.16–2.28 (m, 1H), 2.35–2.60 (m, 3H), 2.73–2.83 (m, 1H), 2.93–3.13 (m, 3H), 3.53 (d, $J=13.7$ Hz, 1H), 3.80 (t, $J=4.6$ Hz, 1H), 3.99 (s, 3H), 4.01 (d, $J=13.7$ Hz, 1H), 4.13 (d, $J=13.7$ Hz, 1H), 4.35 (d, $J=13.7$ Hz, 1H), 7.09–7.46 (m, 13H), 7.62 (s, 1H), 10.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 31.4, 35.2, 38.8, 45.1, 52.7, 57.6, 64.1, 116.7, 122.5, 125.4, 126.1, 127.3, 127.9, 128.1 (2C), 128.2 (2C), 128.5 (2C), 129.1 (2C), 129.9, 130.1, 131.7, 139.3, 142.0, 142.9, 147.7, 149.3, 152.4, 171.1; MS (ESI) *m/z* 551 $[^{79}BrM+H]^+$, 573 $[^{81}BrM+H]^+$; HRMS *m/z* calcd for: $[C_{32}H_{31}BrN_2O_3+H]^+$: 571.1596, *m/z* found: 571.1610.

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