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The first one-pot Alder-ene-reductive amination sequence

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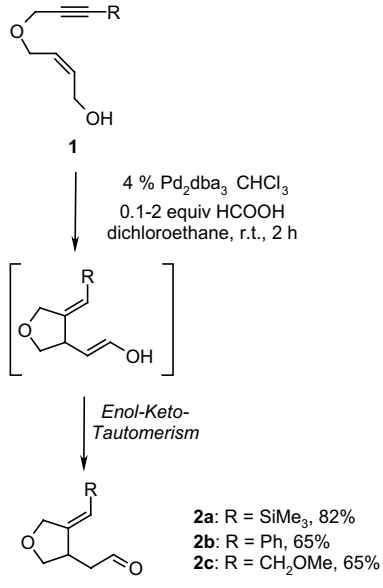
Abstract—Alkyne allyl alcohols **1** are cycloisomerized under Pd catalysis to give (4-alkylidene tetrahydrofuran-3-yl) acetaldehydes **2** in good yields. These mild reaction conditions are fully compatible with a subsequent reductive amination with secondary amines and formic acid. Thus, the cycloisomerization-reductive amination sequence of yne allyl alcohols **1** and secondary amines **3** furnishes β-amino ethyl alkylidene tetrahydrofurans **4** in moderate to good yields in a one-pot fashion.

Sequential transformations and multicomponent processes have recently gained a considerable and steadily increasing academic, economic, and ecological interest since they address the very fundamental principles of synthetic efficiency and reaction design.[1] Besides, the prospect of extending one-pot reactions into combinatorial and solid phase application[1c,2] promises manifold opportunities for developing novel lead structures of pharmaceuticals, catalysts, and even novel molecule-based materials. Therefore, transition metal catalyzed reactions under exceptionally mild reaction conditions significantly enhance synthetic efficiency if they can be directed in a domino fashion generating a suitable reactive functionality en route.[3] In particular, the intramolecular transition metal catalyzed Alder-ene reaction,[4] that is, the cycloisomerization of a 1,6-enyne to a 1,3-diene, opens an intriguing starting point for the development of novel sequential one-pot transformation. As part of our program directed to initiate new one-pot sequences and domino processes based upon transition metal catalyzed in situ activation of alkynes,[5] here we communicate first palladium catalyzed cycloisomerization-reductive amination sequences of yne allyl alcohols and secondary amines to give a rapid access to β-amino ethyl alkylidene furans.

A suitable model reaction for the *en route* generation of a reactive aldehyde functionality by a palladium catalyzed Alder-ene cycloisomerization[4a–c,6] is the hitherto undeveloped transformation of yne allyl alcohols to γ,δ-enals. Therefore, we have designed an Alder-ene sequence of alkyne allyl alcohol substrates **1**[7] in the presence of a catalytic amount of Pd_2dba_3 complex and 0.1–2 equiv of formic acid in dichloroethane at room temperature to furnish the cycloisomerized γ,δ-enal **2** in good yields (Scheme 1).[8,9] As a consequence of the instantaneous enol-aldehyde tautomerism the initially formed 1,4-dienol is transformed into an aldehyde functionality in the course of this domino reaction.



Scheme 1. Palladium catalyzed cycloisomerization of yne allyl alcohols **1** to (4-alkylidene tetrahydrofuran-3-yl) acetaldehydes **2**.

Keywords: Alkynes; Amination; Catalysis; Domino reactions; Ene reactions.

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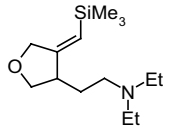
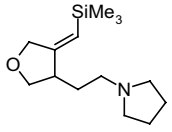
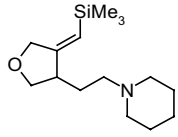
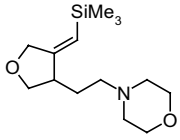
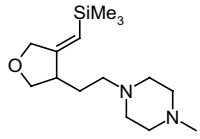
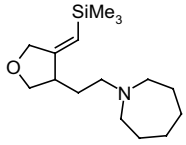
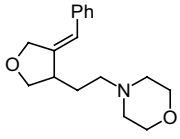
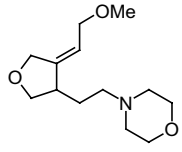
Table 1. Cycloisomerization-reductive amination sequence of yne allyl alcohols **1** to β-amino ethyl alkylidene tetrahydrofurans **4**[a]

Entry	Yne allyl alcohol **1**	Amine **3**	β-Amino ethyl alkylidene tetrahydrofurans **4** (yield)[b]
1	**1a**: $R^1 = SiMe_3$	**3a**: diethylamine	 **4a** (61%)
2	**1a**	**3b**: pyrrolidine	 **4b** (87%)
3	**1a**	**3c**: piperidine	 **4c** (80%)
4	**1a**	**3d**: morpholine	 **4d** (88%)
5	**1a**	**3e**: *N*-methyl piperazine	 **4e** (73%)
6	**1a**	**3f**: azepane	 **4f** (89%)
7	**1b**: $R^1 = Ph$	**3d**	 **4g** (44%)
8	**1c**: $R^1 = CH_2OCH_3$	**3d**	 **4h** (64%)

[a] Reaction conditions: 1.0 equiv of the yne allyl alcohol **1**, 2 equiv of HCOOH, 0.04 equiv of $Pd_2(dba)_3{\cdot}CHCl_3$, 4 equiv of amine **3**, and 8 equiv of HCOOH (0.1 M in dichloroethane).

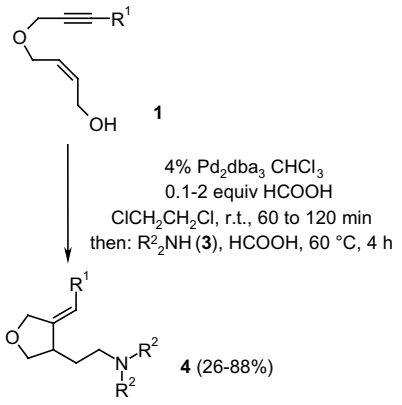
[b] Yields refer to isolated yields of compounds **4** after flash chromatography on basic alumina to be $\geqslant 95\%$ pure as determined by NMR spectroscopy and elemental analysis and/or HRMS.

The structures of the alkylidene tetrahydrofuranyl acetaldehydes **2** were unambiguously supported by ^1H, ^{13}C and DEPT, COSY, NOESY, HETCOR and HMBC NMR experiments, IR, UV/Vis, mass spectrometry,

and/or combustion analyses. Most characteristically for the furan derivatives **2** bearing a stereogenic center at C4, all methylene protons are diastereotopic and appear in the ^{1}H spectra as well resolved discrete signals with the dominant geminal ($J = 18$ Hz) and vicinal coupling constants. Characteristically, the aldehyde methine resonances can be found between δ 9.7 and 9.9 whereas the olefinic protons of the exocyclic double bonds can be detected between δ 5.3 and 6.3, depending on the steric and electronic nature of the adjacent substituent. The *Z*-configuration can be unambiguously deduced from the appearance of significant cross-peaks (olefinic methine signals and the methylene proton resonances in α-position to the aldehyde) in the NOESY spectra. Accordingly, the suggested structures are supported by ^{13}C NMR and mass spectra and the molecular composition is confirmed either by HRMS or elemental analysis. In the IR spectra the dominant carbonyl valence vibration at 1720 cm^{-1} is most characteristic for aliphatic aldehydes.

Now the stage is set for a sequential one-pot transformation that is compatible with the reaction medium of the initial Pd-catalyzed process. Taking into account the presence of formic acid in the reaction medium, now the newly formed aldehyde functionality is perfectly suited for a subsequent reductive amination under Leuckart–Wallach conditions[10] in a sequential one-pot reaction. Thus, the reaction of alkyne allyl alcohols **1** in the presence of a catalytic amount of Pd_2dba_3 complex and 2 equiv of formic acid in dichloroethane at room temperature and, after subsequent addition, with various secondary amines **3** and formic acid at 60 °C gives rise to the formation of β-amino ethyl alkylidene tetrahydrofurans **4** in moderate to excellent yields (Scheme 2, Table 1).[9,11] Surprisingly, the silyl group can be carried through the sequence without desilylation (entries 1–6). However, the reactions with bulky secondary amines such as diisopropylamine or primary amines to furnish secondary amination products were met by failure under standard reaction conditions.

The structures of the β-amino ethyl alkylidene tetrahydrofurans **4** were unambiguously supported by ^{1}H, ^{13}C and DEPT, COSY, NOESY, HETCOR and HMBC



Scheme 2. A cycloisomerization-reductive amination sequence of yne allyl alcohols **1** to β-amino ethyl alkylidene tetrahydrofurans **4**.

NMR experiments, IR, UV/Vis, mass spectrometry, and/or combustion analyses. The *Z*-configuration of the *exo* double bond is retained under the reaction conditions and can be deduced from the appearance of significant cross-peaks (olefinic methine signals and the allylic methylene proton resonances) in the NOESY spectra. As indicated above, all methylene protons are diastereotopic and appear in the ^{1}H spectra in many cases as well-resolved discrete signals with the dominant geminal ($J = 18$ Hz) and vicinal coupling constants. Additionally, the ^{13}C NMR and mass spectra support the structures of the compounds **4** and their molecular composition is confirmed either by HRMS or elemental analysis.

In conclusion, starting from a palladium catalyzed Alder-ene cycloisomerization of yne allyl alcohols **1** to (4-alkylidene tetrahydrofuran-3-yl) acetaldehydes **2** we have developed a novel one-pot cycloisomerization-reductive amination sequence to β-ethyl amino alkylidene tetrahydrofurans **4**. Studies addressing the scope of this novel sequence to enhance molecular diversity in pharmaceutically interesting targets are currently underway and will be reported in due course.

Acknowledgements

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3. For recent excellent reviews on transition metal assisted sequential transformations and domino processes, see for example: (a) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111; (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671–2681; (c) Negishi, E.-I.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393; (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
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7. The synthesis of yne allyl alcohol substrates were performed according to Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981–13996, The detailed protocols will be described elsewhere.
8. Typical procedure for **2a**: To a solution of 62 mg (0.06 mmol) of $Pd_2(dba)_3{\cdot}CHCl_3$ in 15 mL of dichloroethane were added 0.298 g (1.50 mmol) of **1a** and 7 mg (0.15 mmol) of formic acid. The reaction mixture was stirred at room temperature for 30 min and then diluted with 150 mL of diethylether. After filtration the solvents were evaporated in vacuo and the residue was chromatographed on silica gel to give 0.244 g (82%) of **2a** as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.09 (s, 9H), 2.56 (ddd, $J = 18.0$ Hz, $J = 7.7$ Hz, $J = 1.1$ Hz, 1H), 2.77 (ddd, $J = 18.0$ Hz, $J = 4.6$ Hz, $J = 1.1$ Hz, 1H), 3.04–3.17 (m, 1H), 3.46 (dd, $J = 8.9$ Hz, $J = 6.6$ Hz, 1H), 4.13 (dd, $J = 8.7$ Hz, $J = 7.2$ Hz, 1H), 4.25–4.39 (m, 2H), 5.41–5.46 (m, 1H), 9.82 (s, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 0.00 (CH_3), 40.4 (CH), 47.0 (CH_2), 70.5 (CH_2), 72.7 (CH_2), 118.4 (CH), 158.7 (C_{quat}), 200.8 (CH). IR (neat): $\tilde{\nu}$ [cm^{-1}] 2954 (m), 2897 (w), 2837 (w), 2722 (w), 1725 (s), 1633 (m), 1406 (w), 1248 (s), 1064 (m), 935 (m), 839 (s), 692 (w). EI MS (70 eV, m/z (%)): 198 (M^+, 4), 183 (M^+-CH_3, 6), 168 ($M^+-C_2H_6$, 21), 155 (M^+-H_3CCO, 14), 108 (18), 101 (30), 75 (68), 73 ($Si(CH_3)_3^+$, 100), 49 (33). HRMS calcd. for $C_{10}H_{18}O_2Si$: 198.1076. Found: 198.1066. Anal. calcd for $C_{10}H_{18}O_2Si$ (198.3): C, 60.56; H, 9.15. Found: C, 60.04; H, 9.02.
9. All compounds have been fully characterized spectroscopically and by correct elemental analysis or HRMS, respectively.
10. For reviews, see for example: (a) Moore, M. L. *Org. React.* **1949**, *5*, 301–330; (b) Lukasiewicz, A. *Tetrahedron* **1963**, *19*, 1789–1799.
11. Typical procedure (**4f**, entry 6): To a solution of 62 mg (0.06 mmol) of $Pd_2(dba)_3{\cdot}CHCl_3$ in 15 mL of dichloroethane were added 0.298 g (1.50 mmol) of **1a** and 138 mg (3.0 mmol) of formic acid. The reaction mixture was stirred at room temperature for 45 min and then 0.595 g (6.00 mmol) of **3f** and 552 mg (12.0 mmol) of formic acid were added. Then the reaction mixture was heated to 60 °C for 2.5 h when the evolution of carbon dioxide began. After cooling to room temperature the mixture was diluted with 150 mL of diethylether. After filtration the solvents were evaporated in vacuo and the residue was chromatographed on basic alumina (activity stage IV) (hexane/diethylether 1:2) to give 0.376 g (89%) of **4f** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.08 (s, 9H), 1.46–1.55 (m, 1H), 1.59–1.71 (m, 8H), 1.81–1.89 (m, 1H), 2.45–2.57 (m, 2H), 2.59–2.70 (m, 5H), 3.47–3.52 (m, 1H), 4.06–4.10 (m, 1H), 4.28–4.33 (m, 1H), 4.36–4.41 (m, 1H), 5.44–5.47 (m, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ −0.6 (CH_3), 26.9 (CH_2), 28.2 (CH_2), 30.5 (CH_2), 44.6 (CH), 55.5 (CH_2), 56.5 (CH_2), 70.7 (CH_2), 73.2 (CH_2), 116.8 (CH), 160.6 (C_{quat}). IR (film): $\tilde{\nu}$ [cm^{-1}] 2926 (s), 2852 (s), 1719 (w), 1632 (m), 1453 (m), 1248 (s), 1065 (m), 936 (m), 839 (s), 746 (w), 692 (w). EI MS (70 eV, m/z (%)): 281 ($[M]^+$, 8), 266 ($[M-CH_3]^+$, 7), 208 ($[M-Si(CH_3)_3]^+$, 12), 151 (13), 112 ($[C_7H_{14}N]^+$, 100). HRMS calcd. for $C_{16}H_{31}NOSi$: 281.2175. Found: 281.2165. Anal. calcd for $C_{16}H_{31}NOSi$ (281.5): C, 68.27; H, 11.10; N, 4.98. Found: C, 68.00; H, 10.97; N, 4.92.