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A Sequential Palladium-Catalyzed Alder-Ene-Reductive Amination Reaction†

Christoph J. Kressierer and Thomas J. J. Müller*

Organisch-Chemisches Institut der Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

j.mueller@urz.uni-heidelberg.de

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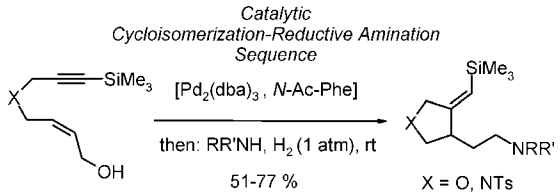
ABSTRACT



Alkyne allyl alcohols are readily transformed into β-amino ethyl alkylidene tetrahydrofurans or β-amino ethyl alkylidene pyrrolidines in a Pd-catalyzed cycloisomerization-reductive amination sequence with remarkable chemoselectivity leaving benzyl groups and trisubstituted double bonds intact.

Sequential transition metal catalysis is a conceptually challenging field of research and has recently aroused considerable interest.[1] Most remarkably, without further catalyst addition a particular metal complex readily shifts gears to catalyze further transformations either in a parallel or in a sequential fashion.[2] Additionally, one-pot transformations are economically and ecologically highly intriguing for developing efficient new synthetic processes. Transition-metal-catalyzed reactions can be directed in a domino fashion, generating a suitable reactive functionality en route.[3] Among numerous reorganization processes of π-electron systems the intramolecular Pd-catalyzed Alder-ene reaction,[4,5] i.e., the cycloisomerization of a 1,6-enyne to a 1,3-diene, represents an intriguing starting point for the development of novel sequential one-pot transformation.[5] Just recently, as part of our program directed to initiate new multicomponent reactions, one-pot sequences, and domino processes based upon transition-metal-catalyzed in situ activation of alkynes,[6] we have disclosed palladium-catalyzed cycloisomerizations of yne allyl alcohol substrates to γ,δ-enals and their subsequent stoichiometric Wittig reactions to carbo- and heterocyclic 2,6-diene carbonyl compounds,[7] as well as Leuckart-Wallach reactions to β-amino ethyl alkylidene tetrahydrofurans.[8] Here, we report first attempts to conduct sequential catalysis after palladium-catalyzed cycloisomerizations of yne allyl alcohols in a one-pot fashion.

In screening experiments[8] we found that the rate of palladium-catalyzed cycloisomerizations of yne allyl alcohol

† Dedicated to Prof. Dr. Günter Helmchen on the occasion of his 65th birthday.

(1) For recent reviews, see, e.g.: (a) Ajamian, A.; Gleason, J. L. *Angew. Chem.* **2004**, *116*, 3842. (b) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302.

(2) Braun, R. U.; Müller, T. J. J. *Mol. Diversity* **2003**, *6*, 251.

(3) For recent reviews on transition-metal-assisted sequential transformations and domino processes, see, e.g.: (a) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101. (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671. (c) Negishi, E.-I.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(4) For representative Pd-catalyzed Alder-ene reactions, see, e.g.: (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Trost, B. M. *Janssen Chim. Acta* **1991**, *9*, 3. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.

(5) For leading reviews on Pd-catalyzed cycloisomerizations, see, e.g.: (a) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, 215. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

(6) For representative examples, see, e.g.: (a) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem.* **2005**, *117*, 156; *Angew. Chem., Int. Ed.* **2005**, *44*, 153. (b) Kressierer, C. J.; Müller, T. J. J. *Angew. Chem.* **2004**, *116*, 6123; *Angew. Chem., Int. Ed.* **2004**, *43*, 5997. (c) Karpov, A. S.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2004**, 1502. (d) Braun, R. U.; Müller, T. J. J. *Synthesis* **2004**, 2391. (e) Karpov, A. S.; Müller, T. J. J. *Synthesis* **2003**, 2815. (f) Müller, T. J. J.; Ansorge, M.; Aktah, D. *Angew. Chem.* **2000**, *112*, 1323; *Angew. Chem., Int. Ed.* **2000**, *39*, 1253.

(7) Kressierer, C. J.; Müller, T. J. J. *Synlett* **2004**, 655.

(8) Kressierer, C. J.; Müller, T. J. J. *Tetrahedron Lett.* **2004**, *45*, 2155.

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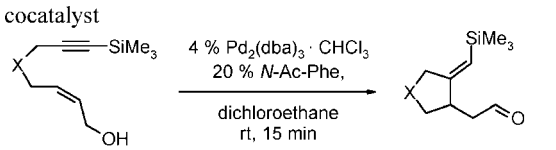
substrates to γ,δ-enals is largely dependent on the pK_a of the cocatalytic organic acid that can even be applied in substoichiometric amounts of formic acid such as 10 mol % with respect to alkynyl allyl alcohols. A survey of readily accessible acids brought our focus to α-heteroatom-substituted carboxylic acids.

Therefore, upon reacting the alkyne allyl alcohols **1a** and **1b**[9] in the presence of 4 mol % of $Pd_2(dba)_3$•$CHCl_3$ and 20 mol % of *rac*-*N*-acetyl phenylalanine in 1,2-dichloroethane at room temperature for 15 min, the expected cycloisomerized products **2a** and **2b** were obtained in good to excellent yields (Scheme 1).[10,11] Attempts to achieve the cycloisomerization of **1** with (*S*)-*N*-acetyl phenylalanine in an enantioselective fashion have remained unsuccessful so far.

Scheme 1. Pd-Catalyzed Cycloisomerization of Yne Allyl alcohols **1** with 20 % *N*-Acetyl Phenylalanine as Acid Cocatalyst



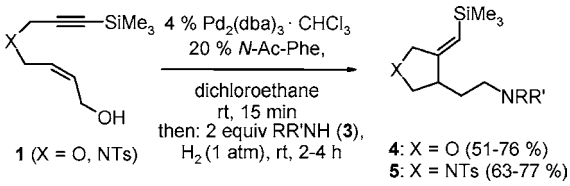
1a, X = O
1b, X = NTs

2a, X = O (85 %)
2b, X = NTs (96 %)

The structures of the tetrahydrofuran-3-yl-acetaldehyde **2a** and pyrrolidin-3-yl-acetaldehyde **2b** were unambiguously supported by spectroscopic analyses (^{1}H, ^{13}C and DEPT, COSY, NOESY, HETCOR, and HMBC NMR experiments, IR, UV−vis, mass spectrometry). 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 (^2J = 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 5.5. The *Z*-configuration can be unambiguously deduced from the appearance of significant cross-peaks (olefinic methine signals and the α-methylene proton resonances 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 between 1711 and 1725 cm^{-1} is most characteristic for aliphatic aldehydes.

These two showcases clearly demonstrate that the Pd-catalyzed cycloisomerization can be performed in the presence of catalytic amounts of a carboxylic acid with suitable acidity. Additionally and apparently, the catalyst system seems to be considerably more stable than under our previously applied conditions[8] using formic acid in excess. Neither precipitation nor a change in color of the catalyst−product solution can be detected. This observation encouraged us to test the possibility of performing sequential catalysis with the obviously intact Pd catalyst system. Therefore, upon reacting the alkyne allyl alcohols **1** in the presence of 4 mol % of $Pd_2(dba)_3$•$CHCl_3$ and 20 mol % of *rac*-*N*-acetyl phenylalanine in 1,2-dichloroethane at room temperature for 15 min and upon subsequently adding a secondary amine **3** to the reaction mixture and placing a hydrogen filled-balloon (1 atm) on the reaction vessel, the β-amino ethyl alkylidene tetrahydrofurans **4** and pyrrolidines **5** were obtained in moderate to good yields (Scheme 2, Table 1).[10,12]

Scheme 2. Sequential Pd-Catalyzed Cycloisomerization-Reductive Amination Reaction



1 (X = O, NTs)

4: X = O (51-76 %)
5: X = NTs (63-77 %)

The structures of the β-amino ethyl alkylidene tetrahydrofurans **4** and β-amino ethyl alkylidene pyrrolidines **5** were

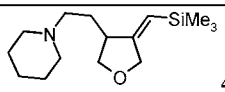
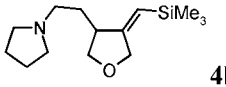
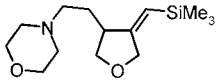
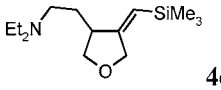
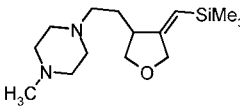
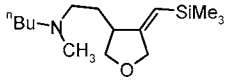
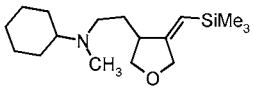
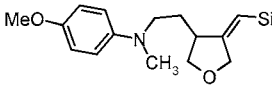
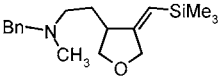
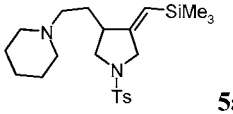
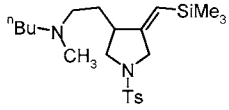
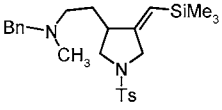
(9) The synthesis of alkynyl allyl alcohol substrates were performed according to Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981. The detailed protocols will be described elsewhere.

(10) All compounds have been fully characterized spectroscopically and by correct elemental analysis or HRMS, respectively.

(11) **Typical Procedure (Compound 2a).** To a solution of 42 mg (0.04 mmol) of $Pd_2(dba)_3$•$CHCl_3$ in 10 mL of dichloroethane in a screw-cap vessel were added 0.198 g (1.00 mmol) of **1a** and 42 mg (0.20 mmol) of *rac*-*N*-acetyl phenylalanine. The reaction mixture was stirred at room temperature for 15 min and then diluted with 150 mL of diethyl ether. After filtration the solvents were evaporated in vacuo, and the residue was immediately chromatographed on silica gel to give 0.169 g (85%) of **2a** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.09 (s, 9 H), 2.56 (ddd, J = 1.1, 7.7, 18.0 Hz, 1 H), 2.77 (ddd, J = 1.1, 4.6, 18.0 Hz, 1 H), 3.04−3.17 (m, 1 H), 3.46 (dd, J = 6.6, 8.9 Hz, 1 H), 4.13 (dd, J = 7.2, 8.7 Hz, 1 H), 4.25−4.39 (m, 2 H), 5.41−5.46 (m, 1 H), 9.82 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 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, 2897, 2837, 2722, 1725, 1633, 1406, 1248, 1064, 935, 839, 692. 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). 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.

(12) **Typical Procedure (Compound 4g).** To a solution of 41 mg (0.04 mmol) of $Pd_2(dba)_3$•$CHCl_3$ in 10 mL of dichloroethane in a ground necked vessel were added 0.198 g (1.00 mmol) of **1a** and 42 mg (0.20 mmol) of *rac*-*N*-acetyl phenylalanine. The reaction mixture was stirred at room temperature for 15 min. Then, 226 mg (2.00 mmol) of **3g** were added, and an H_2 atmosphere was introduced into the vessel. The reaction mixture was stirred at room temperature for another 2 h and then diluted with 150 mL of diethyl ether. After filtration the solvents were evaporated in vacuo, and the residue was immediately chromatographed on basic alumina (Brock Mann activity IV) (hexane/diethyl ether 3:1) to give 193 mg (65%) of **4g** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.06 (s, 9 H), 0.97−1.30 (m, 5 H), 1.36−1.52 (m, 1 H), 1.54−1.65 (m, 1 H), 1.67−1.86 (m, 5 H), 2.22 (s, 3 H), 2.27−2.52 (m, 3 H), 2.53−2.67 (m, 1 H), 3.43 (dd, J = 7.3, 8.3 Hz, 1 H), 4.01 (dd, J = 7.3, 8.4 Hz, 1 H), 4.20−4.36 (m, 2 H), 5.37−5.42 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = −0.6 (CH_3), 25.9 (CH_2), 26.0 (CH_2), 26.3 (CH_2), 28.3 (CH_2), 28.8 (CH_2), 30.8 (CH_2), 37.6 (CH_3), 44.6 (CH), 51.7 (CH_2), 62.7 (CH), 70.7 (CH_2), 73.2 (CH_2), 117.0 (CH), 160.5 (C_{quat}). IR (neat): $\tilde{\nu}$ [cm^{-1}] 2929, 2853, 2791, 1717, 1633, 1451, 1248, 1118, 1061, 936, 839, 691. EI MS (70 eV, *m*/*z* (%)): 295 (M^+, 16), 280 ($M^+ - CH_3$, 10), 252 (18), 222 (17), 162 (21), 126 ($[C_8H_{16}N]^+$, 100), 73 ($[Si(CH_3)_3]^+$, 45). HRMS calcd for $C_{17}H_{33}NOSi$: 295.2331. Found: 295.2321. Anal. Calcd. for $C_{17}H_{33}NOSi$ (295.5): C 69.09, H 11.25, N 4.74. Found: C 69.26, H 11.09, N 4.87.

Table 1. Cycloisomerization-Reductive Amination Sequence of Yne Allyl Alcohols **1a** and **1b** to β-Amino Ethyl Alkylidene Tetrahydrofurans **4** or β-Amino Ethyl Alkylidene Pyrrolidines **5**[a]

entry	yne allyl alcohol **1**	amine **3**	β-amino ethyl alkylidene tetrahydrofurans **4** or β-amino ethyl alkylidene pyrrolidines **5** (yield)[b]
1	**1a**	piperidine (**3**)	 **4a** (76 %)
2	**1a**	pyrrolidine (**3b**)	 **4b** (68 %)
3	**1a**	morpholine (**3c**)	 **4c** (65 %)
4	**1a**	diethylamine (**3d**)	 **4d** (51 %)
5	**1a**	*N*-methyl piperazine (**3e**)	 **4e** (61 %)
6	**1a**	*n*butyl methyl amine (**3f**)	 **4f** (53 %)
7	**1a**	cyclohexyl methyl amine (**3g**)	 **4g** (65 %)
8	**1a**	*N*-methyl-*p*-methoxy aniline (**3h**)	 **4h** (63 %)
9	**1a**	*N*-methyl benzylamine (**3i**)	 **4i** (72 %)
10	**1b**	**3a**	 **5a** (63 %)
11	**1b**	**3f**	 **5b** (63 %)
12	**1b**	**3i**	 **5c** (77 %)

[a] Reaction conditions: 1.0 equiv of yne allyl alcohols **1a** or **1b** (0.1 M in dichloroethane), 0.2 equiv of *N*-acetyl-phenylalanine, 0.04 equiv of $Pd_2(dba)_3 \cdot CHCl_3$; after 15 min addition of 2 equiv of secondary amine **3**, 1 atm H_2. [b] Yields refer to isolated yields of compounds **4** or **5** after flash chromatography on basic alumina to be ≥95% pure as determined by NMR spectroscopy and elemental analysis and/or HRMS.

unambiguously supported by ^1H, ^{13}C and DEPT, H−H- and H−C-COSY NMR experiments, IR, and mass spectrometry. As indicated before, the methylene protons are diastereotopic. The *Z*-configuration of the exocyclic double bonds is retained under the reaction conditions and can be deduced from the appearance of significant cross-peaks in the NOESY NMR spectra. Their signals are detected in the ^1H NMR spectra between δ 5.30 and 5.50. Additionally, the ^{13}C NMR and mass spectra support the structures of compounds **4** and **5** and their molecular composition is confirmed either by HRMS and/or elemental analysis. To the best of our knowledge this is the first cycloisomerization-reductive amination reaction sequentially catalyzed by palladium complexes. Furthermore, in homogeneous phase reductive aminations of carbonyl compounds with hydrogen[13] or formic acid[14] as reducing agents, only rhodium and iridium com-

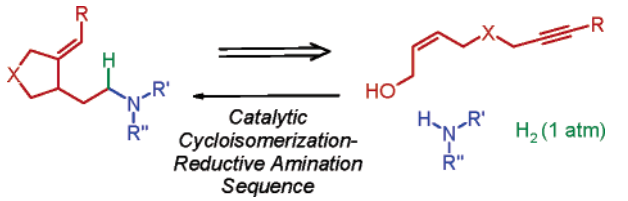
(13) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Fischer, C.; Börner, A. *Adv. Synth. Catal.* **2004**, *346*, 561.
(14) Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* **2002**, *67*, 8685.

plexes have proven to be effective so far, whereas in heterogeneous phase reductive aminations palladium on carbon is effective, but with low chemoselectivity.

In contrast to our previously published cycloisomerization-Leuckart-Wallach sequence,[8] this new sequential catalysis requires hydrogen as a reducing agent, as well as *rac*-*N*-acetyl phenylalanine and $Pd_2(dba)_3 \cdot CHCl_3$ as catalysts if the second step is performed independently and after isolation of the enals **2**. Therefore, no conversion to the tertiary amines **4** or **5** is detected if either of these components are left out. At this stage the Pd species that is responsible for the catalytic reductive amination step is still unknown. Mechanistic investigations elucidating this remarkable catalyst system are currently in progress.

Cyclic (Table 1, entries 1−3, 5, and 10), aliphatic (entries 2, 4, 6, 7, 9, 11, and 12), and *N*-alkyl anilines (entry 8) as secondary amines can be applied in the reductive amination step. Preliminary results in our lab suggest that also groups different from trimethylsilyl may give satisfactory results. Therefore, this consecutive, mild (room temperature), straightforward (1 atm of hydrogen), catalytic sequence (Scheme 3) encompasses a fairly broad methodological scope. Surprisingly, with respect to hydrogenolysis of sensitive functionalities, benzyl groups (entries 9 and 10) and trisubstituted double bonds (all examples) can be carried untouched through the sequence, rendering the Pd-catalyzed cycloisomerization-reductive amination sequence a remarkably chemoselective, valuable, and yet quite atom-economical access to β-amino ethyl alkylidene tetrahydrofurans and pyrrolidines.

Scheme 3. Sequential Catalytic Approach to β-Amino Ethyl Alkylidene Tetrahydrofurans and Pyrrolidines



In conclusion, we have developed a sequential Pd-catalyzed cycloisomerization-reductive amination reaction of yne allyl alcohols **1**, secondary amines **3**, and hydrogen giving rise to β-amino ethyl alkylidene tetrahydrofurans **4** or pyrrolidines **5** in good yields. Applying *rac*-*N*-acetyl phenylalanine as acid not only lowers the cocatalyst loading to catalytic quantities but also enhances the stability of the catalyst system. Additionally, the stage is set for sequential catalysis. Interestingly, the Pd-catalyzed reductive amination with hydrogen as a reducing agent in homogeneous phase proceeds smoothly and with remarkable chemoselectivity, e.g., leaving trisubstituted double bonds and benzyl groups untouched. Studies addressing this unusual catalyst system, its generality in reductive aminations, and the scope of this new sequential catalytic process to enhance molecular diversity in pharmaceutically interesting targets are currently under investigation.

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Supporting Information Available: Experimental procedures and characterization of compounds **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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