A Novel One-Pot Cycloisomerization-Wittig Sequence with Yne-Allyl Alcohols

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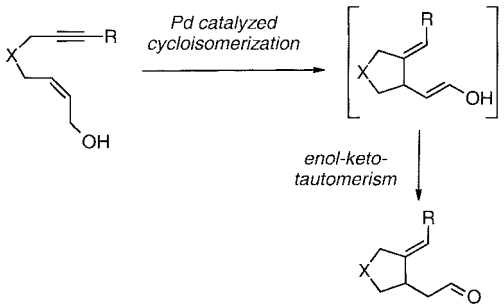
Abstract: Alkyne allyl alcohols **1** are cycloisomerized under Pd catalysis to give γ,δ-enals **2** in moderate to good yields. These mild reaction conditions are fully compatible with a subsequent Wittig olefination. Thus, the cycloisomerization-Wittig olefination sequence of yne allyl alcohols **1** and stabilized phosphorus ylides **3** furnishes 2,3,6,7-bisunsaturated carbonyl compounds **4** in moderate to good yields in a one-pot fashion.

Key words: alkynes, catalysis, domino reactions, ene reactions, Wittig reactions

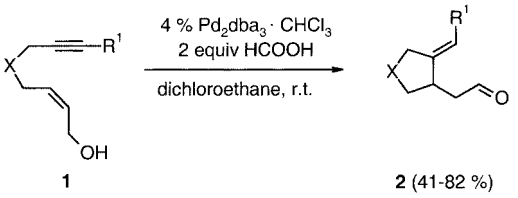
Sequential one-pot transformations are economically and ecologically highly intriguing for developing efficient new synthetic processes. Mastering unusual combinations of elementary organic reactions under similar conditions is the major conceptual challenge in engineering novel types of sequences. Transition metal catalyzed reactions with exceptionally mild reaction conditions are of a paramount benefit if they can be directed in a domino fashion generating a suitable reactive functionality en route.[1] In particular, among numerous catalytic carbon-carbon bond-forming processes the intramolecular transition metal catalyzed Alder–ene reaction,[2,3] 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. 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,[4] here we communicate first palladium catalyzed cycloisomerizations of yne allyl alcohol substrates to γ,δ-enals and their subsequent Wittig olefinations to give a rapid access to structurally complex carbo- and heterocyclic 2,6-diene carbonyl compounds.

Although the palladium-catalyzed cycloisomerization of enynes has been developed to a synthetically useful methodology with broad scope,[2a–c,5] the transformation of yne allyl alcohols furnishing γ,δ-enals as a consequence of the instantaneous enol-aldehyde tautomerism of the initially formed 1,3-dienol has remained unexplored to date (Scheme 1).

Therefore, we first investigated the Pd-catalyzed domino cycloisoerization-tautomerism of alkyne allyl alcohol substrates. The reaction of alkyne allyl alcohols **1**[6] in the presence of a catalytic amount of Pd_2dba_3 complex and 2 equivalents of formic acid in dichloroethane at room temperature gives rise to the formation of the cycloisomerized γ,δ-enals **2** in moderate to good yields (Scheme 2, Table 1).[7,8]



Scheme 1 Palladium catalyzed cycloisomerization as an entry to γ,δ-enals.



Scheme 2 Palladium catalyzed cycloisomerization of yne allyl alcohols **1** to γ,δ-enals **2**.

The structures of the cycloisomerization products **2** were unambiguously supported by ^{1}H, ^{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 and cyclopentane 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

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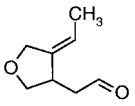
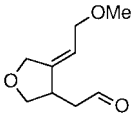
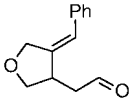
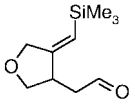
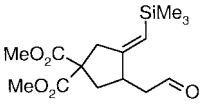
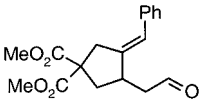
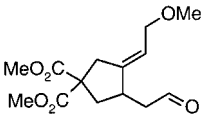
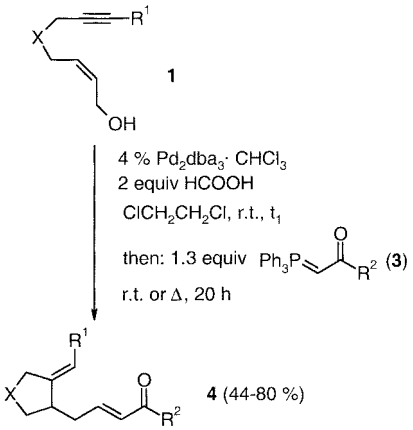
Table 1 Palladium Catalyzed Cycloisomerization of Yne Allyl Alcohols **1** to γ,δ-Enals **2**[a]

Entry	Yne allyl alcohol **1**	Time (h)	γ,δ-Enal **2** (yield,%)[b]
1	**1a**: X = O, R^1 = CH_3	18	 **2a** (41)
2	**1b**: X = O, R^1 = CH_2OCH_3	0.5	 **2b** (65)
3	**1c**: X = O, R^1 = Ph	1.25	 **2c** (65)
4	**1d**: X = O, R^1 = $SiMe_3$	0.5	 **2d** (82)
5	**1e**: X = $C(CO_2Me)_2$, R^1 = $SiMe_3$	2	 **2e** (79)
6	**1f**: X = $C(CO_2Me)_2$, R^1 = Ph	1.6	 **2f** (76)
7	**1g**: X = $C(CO_2Me)_2$, R^1 = CH_2OCH_3	6	 **2g** (60)

[a] Reaction conditions: 1.0 equiv of the yne allyl alcohol **1**, 2 equiv of HCOOH, 0.04 equiv of $Pd_2(dba)_3{\cdot}CHCl_3$, (0.1 M in dichloroethane).
[b] Yields refer to isolated yields of compounds **2** after flash chromatography on silica gel to be ≥ 95% pure as determined by NMR spectroscopy and elemental analysis and/or HRMS.

elemental analysis. In the IR spectra the dominant carbonyl valence vibration at 1720 cm^{-1} is most characteristic for aliphatic aldehydes.

With this facile cycloisomerization of alkyne allyl alcohols to γ,δ-enals in hand the stage is set for sequential one-pot transformations that are compatible with the mild reaction conditions of the initial Pd-catalyzed process. The newly formed aldehyde functionality is perfectly suited for a subsequent Wittig olefination 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 equivalents of formic acid in dichloroethane at room temperature and, after subsequent addition, with stabilized phosphorus ylides **3** at room temperature or in boiling dichloroethane furnishes the 2,3,6,7-bisunsaturated carbonyl compounds **4** in moderate to good yields (Scheme 3, Table 2).[8,9]



Scheme 3 A cycloisomerization-Wittig sequence of yne allyl alcohols **1** to 2,3,6,7-bisunsaturated carbonyl compounds **4**.

The structures of the cycloisomerization-Wittig olefination products **4** 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 newly formed double bond the *E*-configuration can be readily assigned in the ^1H spectra by the appearance of olefinic methine resonances with dominant vicinal coupling constants (J = 18 Hz). 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 before, all methylene protons are diastereotopic and appear in the ^1H spectra 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 cycloisomerization of yne allyl alcohols **1** to γ,δ-enals **2** we have developed a novel one-pot cycloisomerization-Wittig olefination sequence to carbo- and heterocyclic 2,3,6,7-bisunsaturated carbonyl compounds **4**. Studies addressing the scope of this novel sequence and related sequential transformations to enhance molecular diversity in pharmaceutically interesting targets are currently underway and will be reported in due course.

Acknowledgment

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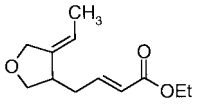
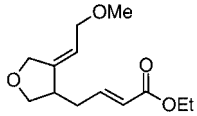
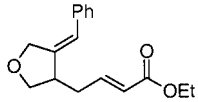
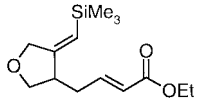
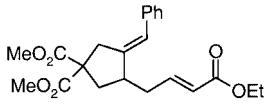
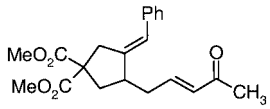
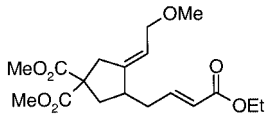
Table 2 Cycloisomerization–Wittig Sequence of Yne Allyl Alcohols **1** and Phosphorus Ylides **3** to 2,3,6,7-Bisunsaturated Carbonyl Compounds **4**[a]

Entry	Yne allyl alcohol **1**	Ylide **3**	Time (h)	2,3,6,7-Bisunsaturated carbonyl compound **4** (yield,%)[b]
1	**1a**	**3a**: R^2 = OEt	18	 **4a** (41)
2	**1b**	**3a**	0.5	 **4b** (51)
3	**1c**	**3a**	1.25	 **4c** (44)
4	**1d**	**3a**	0.5	 **4d** (69)
5	**1f**	**3a**	2	 **4e** (80)
6	**1f**	**3b**: R^2 = Me	1.6	 **4f** (67)
7	**1g**	**3a**	6	 **4g** (71)

[a] Reaction conditions: 1.0 equiv of the yne allyl alcohol **1**, 2 equiv of HCOOH, 0.04 equiv of $Pd_2(dba)_3{\cdot}CHCl_3$, 1.3–1.8 equiv of ylide **3** (0.1 M in dichloroethane).

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

References

(1) For recent excellent 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.

(2) For representative transition metal catalyzed Alder-ene reactions, see e.g.: (a) Pd: Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Pd: Trost, B. M. *Janssen Chim. Acta* **1991**, *9*, 3. (c) Pd: Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (d) Ru: Trost, B. M. *Chem. Ber.* **1996**, *129*, 1313. (e) Ru: Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739. (f) Rh: Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490. (g) Rh: Cao, P.; Zhang, X. *Angew. Chem. Int. Ed.* **2000**, *22*, 4104. (h) Rh: Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198. (i) Ir: Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433. (j) Ti: Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976.

(3) 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.

(4) (a) Karpov, A. S.; Rominger, F.; Müller, T. J. J. *J. Org. Chem.* **2003**, *68*, 1503. (b) Yehia, N. A. M.; Polborn, K.; Müller, T. J. J. *Tetrahedron Lett.* **2002**, *43*, 6907. (c) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297. (d) Müller, T. J. J.; Robert, J. P.; Schmälzlin, E.; Bräuchle, C.; Meerholz, K. *Org. Lett.* **2000**, *2*, 2419. (e) Müller, T. J. J.; Ansorge, M.; Aktah, D. *Angew. Chem. Int. Ed.* **2000**, *39*, 1253.

(5) (a) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625. (b) Yamada, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 3027.

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

(7) Typical Procedure (**2e**, entry 5): To a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (31 mg, 0.03 mmol) in dichloroethane (10 mL) were added **1e** (0.312 g, 1.00 mmol) and HCOOH (92 mg, 2.0 mmol). The reaction mixture was stirred at r.t. for 2 h and then diluted with of Et_2O (150 mL). After filtration the solvents were evaporated in vacuo and the residue was chromatographed on silica gel to give 0.246 g (79%) of **2e** as a yellow oil. IR (neat): 2954 (s), 2897 (w), 2844 (w), 2724 (w), 1736 (s), 1626 (m), 1436 (s), 1251 (s), 1201 (s), 1165 (s), 1122 (m), 1077 (m), 1026 (w), 961 (w), 866 (s), 841 (s), 748 (w), 693 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.11 (s, 9 H), 1.85 (dd, *J* = 10.5, 13.0 Hz, 1 H), 2.48 (ddd, *J* = 2.0, 8.2, 17.3 Hz, 1 H), 2.62–2.82 (m, 2 H), 2.91 (dt, *J* = 3.2, 17.0 Hz, 1 H), 2.96–3.05 (m, 1 H), 3.10 (d, *J* = 17.0 Hz, 1 H), 3.73 (s, 3 H), 3.75 (s, 3 H), 5.30 (q, *J* = 2.3 Hz, 1 H), 9.79 (t, *J* = 1.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = –0.6 (CH_3), 38.9 (CH), 39.0 (CH_2), 40.2 (CH_2), 48.2 (CH_2), 52.7 (CH_3), 52.8 (CH_3), 58.6 ($C_{quat.}$), 120.6 (CH), 158.7 ($C_{quat.}$), 171.7 ($C_{quat.}$), 171.8 ($C_{quat.}$), 201.2 (CH). EI–MS (70 eV): *m*/*z* (%) = 312 (6) [M^+], 297 (9) [$M^+ - CH_3$], 281 (17), 270 (27), 252 (29), 237 (15), 225 (10), 209 (10), 193 (14), 163 (43), 149 (18), 137 (17), 120 (22), 89 (66), 73 (100) [$Si(CH_3)_3^+$], 59 (30). HRMS: *m*/*z* calcd for $C_{15}H_{24}O_5Si$: 312.1393; found: 312.1397.

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

(9) Typical Procedure (**4e**, entry 5): To a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (41 mg, 0.04 mmol) dichloroethane (10 mL) were added **1f** (0.316 g, 1.00 mmol) and HCOOH (92 mg, 2.0 mmol). The reaction mixture was stirred at r.t. for 2 h and then **3a** (0.627 g, 1.80 mmol) was added. Then, the reaction mixture was stirred at r.t. for 24 h before it was diluted with Et_2O (150 mL). After filtration the solvents were evaporated in vacuo and the residue was chromatographed on silica gel to give 0.308 g (80%) of **4e** as a yellow oil. IR (Film): 2955 (m), 1735 (s), 1653 (m), 1492 (w), 1435 (m), 1368 (w), 1265 (s), 1203 (s), 1171 (s), 1044 (m), 752 (m), 697 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.20 (t, *J* = 7.2 Hz, 3 H), 1.76 (dd, *J* = 10.6, 12.9 Hz, 1 H), 2.16–2.30 (m, 1 H), 2.46–2.66 (m, 2 H), 2.77–2.93 (m, 1 H), 3.07–3.18 (m, 1 H), 3.29 (d, *J* = 17.7 Hz, 1 H), 3.61 (s, 3 H), 3.64 (s, 3 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 5.83 (d, *J* = 15.4 Hz, 1 H), 6.19–6.25 (m, 1 H), 6.89 (dt, *J* = 7.1, 15.5 Hz, 1 H), 7.07–7.16 (m, 1 H), 7.16–7.30 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.4 (CH_3), 36.7 (CH_2), 38.6 (CH_2), 38.9 (CH_2), 42.8 (CH), 52.7 (CH_3), 52.8 (CH_3), 58.9 ($C_{quat.}$), 60.1 (CH_2), 122.8 (CH), 123.0 (CH), 126.4 (CH), 128.2 (CH), 128.3 (CH), 137.7 ($C_{quat.}$), 143.3 ($C_{quat.}$), 146.1 (CH), 166.1 ($C_{quat.}$), 171.7 ($C_{quat.}$). UV–Vis (CH_2Cl_2): $_{max}$ (ε) = 258 (18846), 286 (1135) nm. EI–MS (70 eV): *m*/*z* (%) = 386 (44) $[M]^+$, 355 (6) $[M - H - 2CH_3]^+$, 340 (17) $[M - H - 3CH_3]^+$, 280 (22), 273 (20), 241 (19), 213 (100), 181 (10), 153 (48), 91 (18). HRMS: *m*/*z* calcd for $C_{22}H_{26}O_6$: 386.1729; found: 386.1735.