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A facile synthesis of bridged bicycloalkenones from enol silanes of medium and large rings by palladium(II) mediated cycloalkenylation reaction

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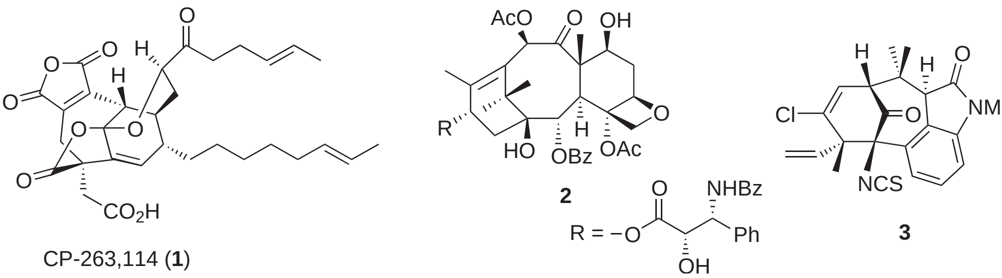
Abstract—Palladium mediated cycloalkenylation reaction of enol silanes of medium and large rings provides concise access to the corresponding bridged bicycloalkenones, a structural unit present in a large number of biologically active natural products. © 2001 Elsevier Science Ltd. All rights reserved.

The treatment of silyl enol ethers with a stoichiometric equivalent of $Pd(OAc)_2$ in CH_3CN provides a valuable route to α,β-unsaturated carbonyl compounds.[1] In 1978, Saegusa and Ito demonstrated the facile formation of simple cycloalkenones by cyclization of ω-vinyl silyl enol ethers that are structurally precluded from dehydrosilylation to conjugated enones.[2] The utility of the reaction methodology was further extended by Kende's group for the synthesis of bridged and spirocyclic bicycloalkenones from cyclohexyl silyl enol ethers.[3] Since the palladium(II) mediated cycloalkenylation reaction provides concise access to the bicycloalkenone framework, the reaction has been used as a key step in the syntheses of a number of complex natural products.[4] Recently, we have developed a catalytic version of the reaction and successfully adopted this strategy for the total synthesis of various polycyclic compounds.[5] However, surprisingly, the cycloalkenylation reaction has never been used for the construction of bicyclic systems from silyl enol ethers of medium and large rings. In continuation of our interest in palladium(II) promoted cyclization, we decided to probe the stoichiometric and catalytic variant of the reaction for the synthesis of bridged bicycloalkenones from medium and large ring compounds. This framework is an attractive target as it could be further elaborated into more functionalized systems such as those of the CP molecules **1**,[6] taxol **2**[7] and welwitindolinone **3** (Fig. 1).[8]

The precursor silyl enol ethers for the cycloalkenylation reaction were prepared by the following a sequence of reactions. The lithium enolates of cycloalkanones was treated with Mander's reagent[9] at −78°C in the presence of HMPA to give the corresponding β-keto esters which were subjected to deprotonation using NaH/DMF at 0°C, followed by alkylation with the corre-



CP-263,114 (**1**)

2

3

Figure 1.

Keywords: cyclization; silyl enol ethers; bridged bicycloalkenones; palladium and compounds.

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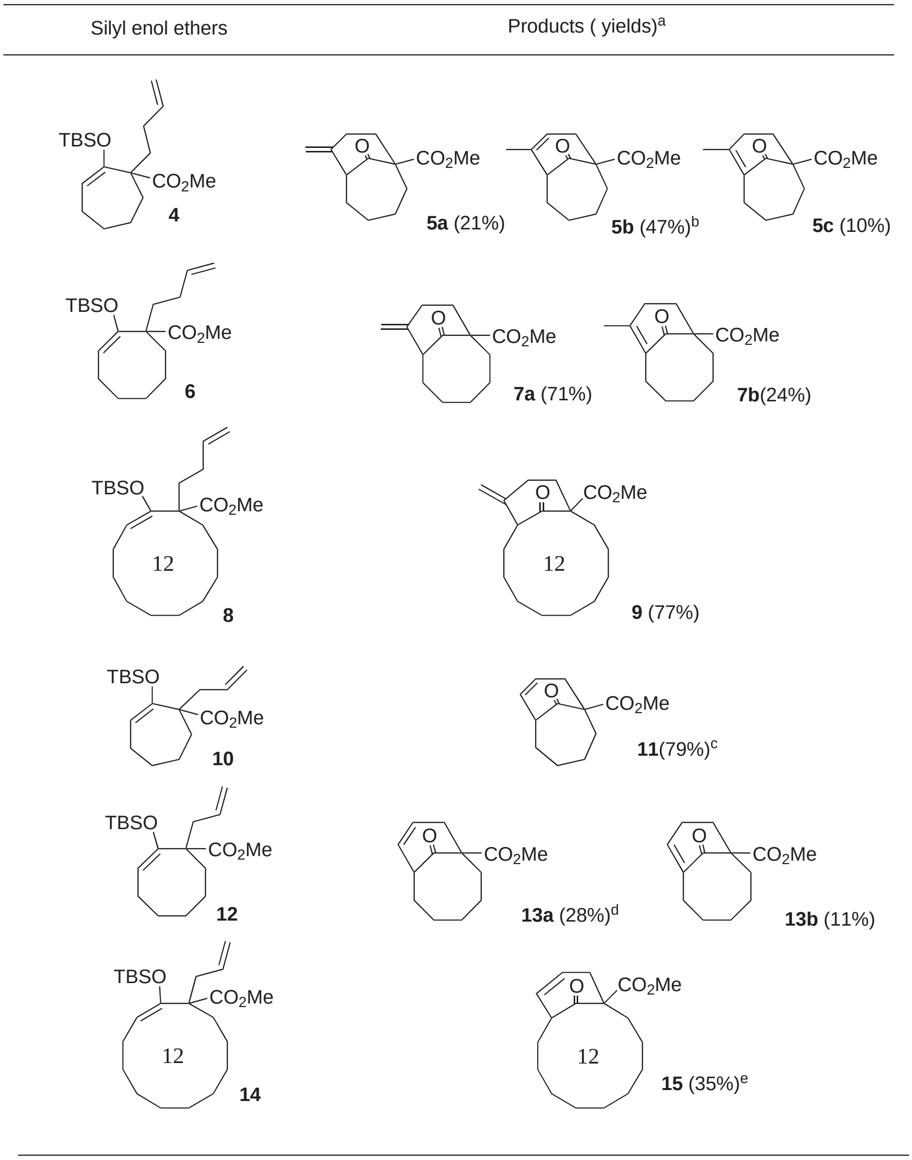
sponding alkyl bromides. The lithium enolate of these β-keto esters was then quenched with TBSCl in the presence of HMPA to furnish the corresponding silyl enol ethers.[10]

Initially, a cycloakenylation reaction of silyl enol ether **6** of cyclooctanone bearing a homoallyl side chain at the α-position was attempted using a stoichiometric amount of $Pd(OAc)_2$ in CH_3CN at room temperature. To our delight, the reaction furnished the desired bicycloalkenones **7a** and **7b** as a 3:1 regioisomeric mixture in an overall yield of 95%. The alternative reaction pathway to form the conjugated enone was strictly not observed in this case.[11]

In the case of cyclizations involving a homoallyl side chain, a strong preference for the formation of an exocyclic double bond was observed, especially in the case of 12- and 8-membered ring systems. However, in the case of 7-membered ring system, formation of the internal olefin was predominant. These results are summarized in Table 1.[12]

Table 1. Palladium(II) mediated cycloalkenylation reaction for the synthesis of bridged bicycloalkenones



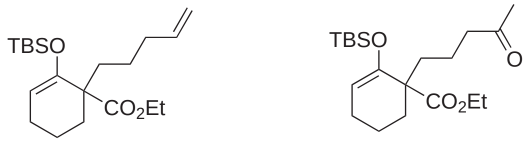
a: The yields refer to the isolated yields of the compounds after purification by chromatography, unless otherwise specified. The products were characterized by IR, HRMS, ^{1}H and ^{13}C NMR .

b: Compound **5a** and **5b** were obtained as an inseparable mixture. The yields were calculated based on the integration values in ^{1}H NMR spectrum.

c: 10% of uncyclized enone was also formed.

d: Compound **13a** was obtained as an inseparable mixture with 21% of uncyclized conjugated enone.

e: Compound **15** was obtained as an inseparable mixture along with 30% of uncyclized conjugated enone. However, by exposing a methanolic solution of the reaction mixture to a basic solution of aqueous H_2O_2 for 4 h, the enone could be selectively oxidized, furnishing pure **15** in 35% yield.



16 **17**

Figure 2.

However, when the cyclizations were attempted using an allylic side chain, at the α-position to the silyl enol ether, the reaction furnished internal olefins in considerable yield. In these cases, formation of the uncyclized conjugated enone competes with the formation of the bicyclic ketone, although to a lesser extent in the case of 7-membered ring. Thus, it was observed that the yield of formation of the bicyclic ketones is highly dependent on the size of the ring system. Also, as observed by Kende's group, a second directing functionality such as the ester group on the carbon bearing the alkenyl side chain was essential to bring about the desired transformation which may be explained on the basis of conformational preferences. In the absence of an ester group, exclusive formation of the α,β-unsaturated ketone was observed in high yield.

Interestingly, formation of the conjugated enone was not the alternative reaction pathway followed on default, by the silyl enol ether, when the formation of the bicyclic compound was not favourable. An example is the formation of Wacker oxidation product **17** in 35% yield from silyl enol ether **16** under standard reaction conditions using $Pd(OAc)_2$. It is intriguing that not even traces of enone could be observed in the reaction mixture.

Various efforts to run the reaction under the catalytic conditions developed by us for the cyclization of conjugated silyl enol ethers did not meet with success. However, taking into account the importance of the target molecules and widespread use of the Pd(II) mediated cycloalkenylation reaction in the total synthesis of complex natural products, this could be an attractive route for the syntheis of bridged bicycloalkenones from medium and large ring compounds (Fig. 2).

Typical experimental procedure

To a stirred solution of the silyl enol ether **8** (200 mg, 0.490 mmol) dissolved in 3 mL of CH_3CN was added $Pd(OAc)_2$ (110 mg, 0.490 mmol) at room temperature. The reaction mixture was stirred for 100 min and then concentrated under vacuum. The residue was dissolved in 2 mL of Et_2O and loaded over a column of silica gel. Elution with hexane–Et_2O (92:8) furnished bicyclic ketone **9** (110 mg, 0.376 mmol) in 77% yield.

Acknowledgements

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References

1. (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013; (b) For a more recent catalytic variant of the reaction, see: Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, 2423–2426.
2. (a) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494–496; (b) Ito, Y.; Aoyama, H.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 4519–4521.
3. Kende, A. S.; Roth, B.; Sanfilippo, P. J. *J. Am. Chem. Soc.* **1982**, *104*, 1784–1785.
4. (a) Kende, A. S.; Sanfilippo, P. J. *Synth. Commun.* **1983**, *13*, 715–719; (b) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808–5810; (c) Shibasaki, M.; Mase, T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090–2091; (d) Toyota, M.; Seishi, T.; Fukumoto, K. *Tetrahedron Lett.* **1993**, *34*, 5947–5950; (e) Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K. *Tetrahedron Lett.* **1993**, *34*, 6099–6102.
5. (a) Toyota, M.; Odashima, T.; Wada, T.; Ihara, M. *J. Am. Chem. Soc.* **2000**, *122*, 9036–9037; (b) Toyota, M.; Wada, T.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4565–4570; (c) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916–4925.
6. (a) Dabrah, T. T.; Harwood, H. L.; Huang, L. G.; Jankovich, N. D.; Kaneko, T.; Li, J.-C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1–7; (b) Dabrah, T. T.; Kaneko, T.; Massefski, Jr., W.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594–1598.
7. Wani, M. C.; Taylor, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327.
8. (a) Stratmann, K.; Burgoyne, D. L.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Org. Chem.* **1994**, *59*, 7219–7226; (b) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935–9942.
9. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, 5425–5428.
10. The silyl enol ethers were stable enough to be purified by column chromatography over silica gel using eluant containing 1% Et_3N.
11. (a) Paquette, L. A.; Sugimura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3841–3842; (b) Danishefsky, S.; Chackalamannil, S.; Harrison, P.; Silvestri, M.; Cole, P. *J. Am. Chem. Soc.* **1985**, *107*, 2474–2484.
12. Selected spectral data of the products: **Compound 7a**; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79–4.78 (m, 1H), 4.71–4.70 (m, 1H), 3.69 (s, 3H), 3.07 (t, 1H, $J=10.2$ Hz), 2.71–2.66 (m, 1H), 2.34–2.19 (m, 3H), 2.01–1.84 (m, 3H), 1.82–1.71 (m, 2H), 1.68–1.61 (m, 2H), 1.42–1.16 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.18, 173.91, 147.29, 111.07, 60.62, 59.37, 52.12, 33.90, 33.63, 32.30, 30.85, 25.75, 24.15, 24.06; IR (neat) 2925, 1738, 1699, 1253 cm^{-1}; HRMS calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1418. **Compound 9**; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (s, 1H),

4.64 (s, 1H), 3.69 (s, 3H), 3.45–3.40 (m, 1H), 2.60–2.53 (m, 1H), 2.46–2.39 (m, 1H), 2.30–2.20 (dt, 1H, J = 5.1, 12.9 Hz), 2.12–2.05 (m, 1H), 1.94–1.86 (m, 4H), 1.45–1.27 (m, 14H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 207.29, 173.15, 147.51, 108.41, 62.68, 51.86, 51.75, 35.98, 32.68, 31.68, 26.82, 25.91, 23.36, 23.20, 22.97, 22.35, 21.94, 21.08; IR (neat) 2935, 1742, 1718, 1255 cm^{-1}; HRMS calcd for $C_{18}H_{28}O_3$ 292.2039, found 292.2050. **Compound 11**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83–5.76 (m, 1H), 5.64–5.58 (m, 1H), 3.72 (s, 3H), 3.05–2.48 (m, 2H), 2.46–2.37 (m, 1H), 2.35–2.29 (m, 1H), 1.85–1.62 (m, 3H), 1.61–1.39 (m, 3H), 1.21–1.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.18, 174.10, 129.18, 125.90, 60.07, 52.15, 50.57, 36.83, 33.14, 31.32, 27.22, 25.96; IR (neat) 2933, 1746, 1712, 1440 cm^{-1}; HRMS calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1097. **Compound 15**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75–5.69 (m, 1H), 5.51–5.47 (m, 1H), 3.74 (s, 3H), 3.43–3.38 (m, 1H), 3.07–3.00 (m, 1H), 2.54–2.46 (m, 1H), 2.18–2.10 (m, 1H), 2.05–1.99 (m, 1H), 1.94–1.85 (m, 2H), 1.64–1.11 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.01, 173.22, 129.52, 125.95, 60.51, 51.97, 43.48, 39.65, 34.70, 26.96, 26.66, 25.64, 23.67, 23.16, 22.24, 22.16, 21.16; IR (neat) 2931, 1739, 1718, 1209 cm^{-1}; HRMS calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1869.