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Cyclopentene-regioselective palladium-catalyzed cycloisomerization under neutral and bis-cationic reaction conditions

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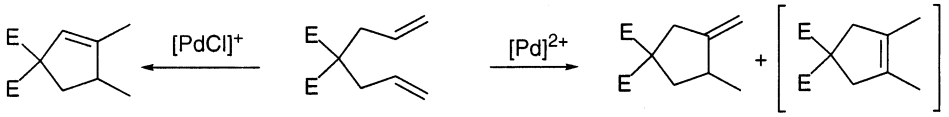
Abstract—A series of 1,6-dienes is cyclized to cyclopentene derivatives under neutral conditions with palladium chloride in ethanol or with in situ generated LPd^{2+} in acetonitrile.

The palladium-catalyzed transformation of unsaturated compounds has become an important tool for the obtention of carbo- and heterocyclic compounds.[1] Wacker-type oxidative cyclization of conjugated[2] and non conjugated dienes[3] have been studied quite extensively in the last decade. The non-oxidative transformation of dienes in the presence of metal catalysts by simple cycloisomerization[4] also merits attention and the recent studies, with diallyl malonates as substrates[5–7] support the increasing interest in these reactions.

We have shown in a preliminary study that the regioselectivity and enantioselectivity of the cyclization of diethyl diallylmalonate **1a** could be modulated via the mode of activation of the neutral palladium chloride.[8] Indeed, it was possible to orient the reaction towards **2a** with a 1/1 Pd(II)/Ag(I) precatalyst mixture, whereas a 1/2 Pd(II)/Ag(I) ratio lead to a mixture containing **3a** as the major product (with **2a** and/or **4a**) (Eq. (1)). In the presence of chiral chelating bis-amine ligands **3a** was obtained with promising 60% enantiomeric excess; no chiral induction takes place in case of compound **2a** under the 'monocationic' reaction conditions.[9] Though the regioselectivity is higher, apparently the enantiocontrol is less efficient with the latter catalyst.

Actually, palladium is the only metal that can mediate, the formation of **2**,[6,8–10,12] **3**,[8] and **4**[11] quite selectively under the appropriate reaction conditions. Other transition metals such as Ru[5] simply mediate the formation of **3** selectively. We describe in this communication our results on unreported reaction conditions of the cyclization of **1**. Indeed, we found quite unexpectedly[12] that ordinary palladium chloride in a primary alcohol such as ethanol leads, selectively and nearly quantitatively, to **2** in less than 2 h at 78°C in an extremely clean reaction. The same result is obtained with $[LPd(MeCN)_2](BF_4)_2$ (L = chelating bisimine-type ligand) in refluxing acetonitrile. We also report the transformation of several malonate-type 1,6-hexadienes under these conditions.

Two very recent mechanistic studies revealed the importance of palladium hydride(s) for the cycloisomerization of dialkyl diallyl malonates **1**.[6,7] Thus, Widenhoefer and Goj[6] have reported the intermediacy of $[phenPd(CH_3CN)H]^+$ as active species for the isomerization of **1**. The oxidation of alcohols to ketones is catalyzed by palladium(II) salts in the presence of dioxygen.[13] It is conceivable, that the reaction starts with the coordination of the alcohol to the PdX_2



2 **1a** E = CO_2Et **1b** E = CO_2Me **3** **4** (1)

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Table 1. Cycloisomerization of **1b** in alcoholic medium in the presence of $PdCl_2$

Entry	Solvent, catalyst: $PdCl_2$[a]	Temp (°C)	Time (h)	Products[b]		
				2b	**3b**	Dienes
1	MeOH	65	4	90	8	
2	EtOH	78	2	>95	Traces	
3	*i*-PrOH	90	4	46	50% (**3** and dienes)	
4	CF_3CH_2OH	90	4	60	10	30
5	CF_3CH_2OH	25[c]	4	30	15	
6	(*S*)-Et–lactate[d]	90	4	>97		
7	(*S*)-EtCH(Me)–CH_2OH[d]	80–90	4	>97		
8	*i*-PrOH[e]	90	24	No reaction[f]	No reaction[f]	

[a] 5 mol%, 0.025 mmol $PdCl_2$ in 1 mL ROH (2.5×10^{-2} M).
[b] Ratios determined by ^1H NMR of the crude reaction mixture.
[c] 45% conversion.
[d] No chiral induction.
[e] Catalyst: $LPdCl_2$ (L = $PhSCH_2CH_2SPh$, bisimine **18**, bisoxazoline **19**) or $[\eta^3$-(*S*)-pinenyl-$PdCl]_2$.
[f] **1b** is recovered without visible changes.

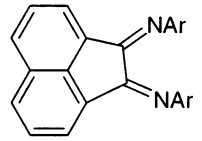
catalyst and the appearance of X–Pd^{II}–H species after β-hydride elimination. To probe the reactivity of such a system we decided to treat the bis allyl malonate with palladium dichloride in primary and secondary alcohols as solvents. Indeed, with the system $PdCl_2$–ROH **1b** is rapidly and efficiently cyclized to **2b**.[14] Under certain conditions (entries 6 and 7) the reaction is extremely selective and we could not see any signals of **3b** and **4b** in the proton NMR spectra. The transformation of **1** in ethanol was followed by proton NMR.[15] It is remarkable that the polymeric palladium chloride is so easily activated with a primary or *sec* alcohol in the presence of **1**. Some of the results are listed in Table 1.

The active catalyst is less reactive than $(RCN)_2PdCl_2$ in nitrile solvents;[9] however, the isomerization proceeds much more rapidly than under conditions described with cationic $[phenPd(CH_3CN)H]^+$ in dichloroethane (80% conversion after 18 h).[6]

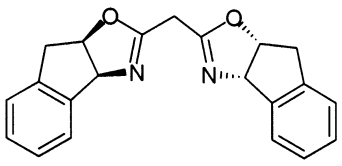
Ligands that are easily displaced with dienes are tolerated (COD, MeCN, dimethylcyclooctadiene). In the presence of better coordinating ligands, such as phosphines, bis-amines or dithioethers, the starting diene remains unaffected, even after prolonged reaction times (entry 8). However, when cationic complexes are generated in situ from $LPdCl_2$ (L = **18**–**20**)[16] with 2 equiv. of $AgBF_4$ in acetonitrile, once more, the cyclopentene derivative **2b** was obtained exclusively after a few hours at 82°C in the same solvent. Apparently the coordinating properties of MeCN are in favor of the formation of the trisubstituted double bond in **2b**. This selectivity is in sharp contrast to the reaction of **1** in dichloroethane[17] or in chloroform[8] with reaction mixtures composed of compound **3** as the main product. With these promising elements in hand we decided to extend the reaction to a number of geminal 4-substituted 1,6-dienes (**5**–**11**) (Table 2).

It should be noted that the conditions developed for the isomerization of dialkyl diallyl malonates can also be applied to more complex substrates. However, as expected, the transformation of compounds **5**–**11** is not always as selective as the reaction of **1**. The ketal **10** is cyclized and hydrolizes at the same time. If a carbonyl group is present at position-4, a high preference of trisubstituted cyclopentenes is still observed, and the yields are quite high (80% and higher: entries 1–3, 6, 8, 11–16). The stabilizing effect of a keto group for the cationic catalyst is well known in the palladium catalyzed copolymerization of ethylene/carbon monoxide.[18] Stable γ-ketopropyl–σ-Pd complexes are readily isolated from CO and ethylene.[19]

The cationic cyclopentane–palladium σ-complex **21** which was shown to be the major intermediate during the formation of cyclopentene **2b** was also recently isolated.[6,20] Thus, the preference for compound **2** may be understood as the result of combined stabilization of **21** with the chelating ligand and the acetonitrile solvent. However, the absence of a CO group in the diene only slightly alters the regioselectivity and the reactivity of the system (entries 9–14). Similarly, it is difficult to see how efficient stabilization of a σ-Pd–C species might be effective with the neutral $PdCl_2$–alcohol combination. An interesting hydroindene **17** is formed, highly regioselective, from allyl cyclohexenyl malonate **11**. There is no stereocontrol during the cyclization step and we obtain the *exo*- and *endo*-isomers of **17** in about 1:1 ratio. Although ester groups are present in the molecule the CO-stabilization of the final Pd-intermediate do not account for the formation of **17**. In this



18 Ar=2,6-$C_6H_3(i\text{-}Pr)_2$



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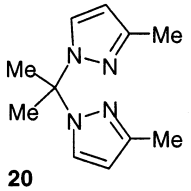

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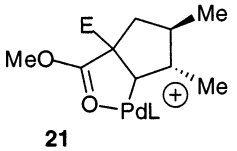

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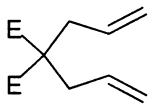
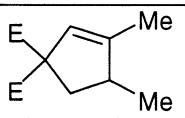
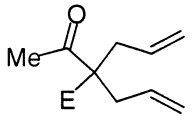
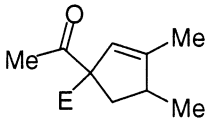
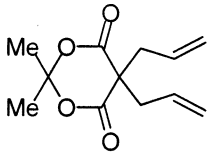
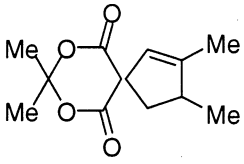
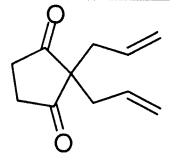
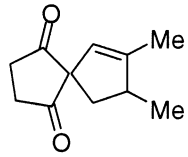
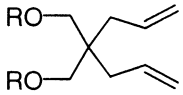
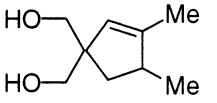
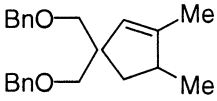
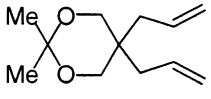
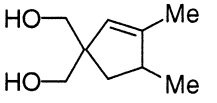
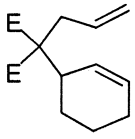
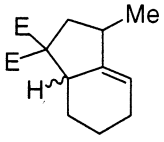
Table 2. Cycloisomerization of various 1,6-hexadienes mediated by $PdCl_2$ and $[LPd(CH_3CN)_2]^{2+}\cdot 2[BF_4]^-$

	Diene	Cyclic compound	Catalyst[a] Solvent/time	Temp. °C	Transformation[b] (yield)[c], [purity][b] %
1			**18**-Pd^{2+}, MeCN, 4h	82	Quant [>97]
2			**19**-Pd^{2+}, MeCN, 4h	82	quant [>97][d]
	1b (E=CO_2Me)	**2b** (E=CO_2Me)			
3			$PdCl_2$, EtOH, 4h	78	86, [94]
4			**20**-Pd^{2+}, MeCN, 4h	82	(77)
	5 (E=CO_2Me)	**12** (2 isomers)			
5			$PdCl_2$, MeCN, 5h	82	70 (66)
6			**20**-Pd^{2+}, MeCN, 4h	60	quant [80]
	6	**13**			
7			$PdCl_2$, EtOH, 4h	78	mixture
8			**18**-Pd^{2+}, MeCN, 4h	82	(92)
	7	**14**			
9			$PdCl_2$, EtOH, 4h	78	55 [85]
10			**20**-Pd^{2+}, MeCN, 4 h	60	65 (90)
	8 R=H	**15**			
11	**9** R=Bn		$PdCl_2$, MeCN, 4h	82	(80) [95]
12			**20**-Pd^{2+}, MeCN, 4h	82	(81) [88]
		16			
13			$PdCl_2$, MeCN, 6h	78	80 [95]
14			**20**-Pd^{2+}, MeCN, 3h	82	(46) [95]
	10	**15**			
15			$PdCl_2$, MeCN, 4h	82	80 [75]
16			**20**-Pd^{2+}, MeCN, 4h	60	quant [70]
	11 (E=CO_2Me)	**17** (2 isomers)			

(a)LPd^{2+}: $LPdCL_2$ (0.025 mmol), $AgBF_4$ (0.06 mmol) in MeCN, (1mL), 10 min, 25°C, centrifuge; (b) determined with ^{1}H NMR; (c) after flash chromatography; (d) no chiral induction.

compound the double bond is 'exomethylene' to the five-membered ring and, most probably, the migration of the palladium to a bridgehead position, necessary for the obtention of the tetrasubstituted 'regular' compound (double bond inside the cyclopentane ring) seems energetically less favored. This result is complementary to the cyclization with a cationic palladium of cyclohexenyl allyl sulfonamide leading to the substrate with a non-bridgehead double bond in the six-membered ring.[21]

The regiodefined cycloisomerization of **1** to the highly substituted cyclopentene **2** has been less studied than the reactions leading to compound **3** (exomethylene double bond). Different to the Widerhoefer system with a catalyst, composed of $[LPd(Me)MeCN]^+[BAr_4]^-$ we

have presented in this note new reaction conditions for the obtention of **2** with neutral palladium chloride in alcohols and cationic Pd–ligand combinations in acetonitrile (counterion BF_4^-).

Acknowledgements

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References

1. Poli, G.; Giabastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959.
2. Bäckvall, J.-E. In *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Ed.; Wiley: New York, 1997; Vol. 1, pp. 653–681.
3. Heumann, A. In *Stereochemistry of Organometallic and Inorganic Compounds Volume 5: Chains*, *Clusters*, *Inclusion Compounds*, *Paramagnetic Labels*, *and Organic Rings*; Zanello, P., Ed.; Elsevier: Amsterdam, 1994; Vol. 5, pp. 557–623.
4. Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.
5. For Ru catalysts, see: Yamamoto, Y.; Nakagai, Y.; Ohkoshi, N.; Itoh, K. *J. Am. Chem. Soc*. **2001**, *123*, 6372.
6. For Pd catalysts, see: Goj, L. A.; Widenhoefer, R. A. *J. Am. Chem. Soc*. **2001**, *123*, 11133.
7. For Pd catalysts, see: Bray, K. L.; Charmant, P. H.; Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Eur. J*. **2001**, *7*, 4205.
8. Heumann, A.; Moukhliss, M. *Synlett* **1998**, 1211.
9. When repeating the reaction with $[(MeCN)_3PdCl]^+$ and deuterated $^2H_2$-**1** as diene, Lloyd-Jones and co-workers observed scrambling of $^2H_2$ in **2** (both methyl groups as $CH_2D_{0.5}$) which has to account for a secondary isomerization. This phenomenon was not observed with neutral $(MeCN)_2PdCl_2$. See: Bray, K. L.; Fairlamb, I. J. S.; Lloyd-Jones, G. C. *J. Chem. Soc*., *Chem. Commun*. **2001**, 187.
10. Cyclopentene **2** was obtained as a main product in the reaction of **1** with Ru catalysts (ratio **2**/**3** = 50/50 after 4 days (*i*-PrOH, reflux). See: Heumann, A., unpublished; see also Ref. 5.
11. The selective formation of **4** with $(\eta^3\text{-}C_3H_5)Pd(Cl)PCy_3$/$NaB[3,5\text{-}C_6H_3(CF_3)_2]_4$ requires several equivalents of silane. See: Kisanga, P.; Widenhoefer, R. A. *J. Am. Chem. Soc*. **2000**, *122*, 10026.
12. Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R. M. *J. Chem. Soc*., *Perkin Trans. 1* **1984**, 1745.
13. (a) Blackburn, T. F.; Schwartz, J. *J. Chem. Soc*., *Chem. Commun*. **1977**, 157; (b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Lett*. **1998**, *39*, 6011; (c) Peterson, K. P.; Larock, R. C. *J. Org. Chem*. **1998**, *63*, 3185; (d) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc*. **2001**, *123*, 7475; (e) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc*. **2001**, *123*, 7725.
14. Compound **1a** reacts quite similarly.
15. Ratio of **1**/**2** (after time): 75/25 (10 min), 50/50 (25 min), 15/85 (70 min), 10/90 (105 min), 3/95 (120 min). In the final mixture: **3** (1–2%).
16. For **18**, see: Johnson, L. K.; Killian, C. M.; Brookhart, M. *J. Am. Chem. Soc*. **1995**, *117*, 6414; **19**: Aldrich; **20**: prepared from 2,2-dimethoxypropane and 3-methylpyrazole.
17. (a) For the formation of **3** (<85%) together with variable amounts of **2** and **4**, see: Heumann, A.; Moukhliss, M., unpublished; (b) See also: Oh, C. H.; Kim, J. D.; Han, J. W. *Chem. Lett*. **2001**, 1290.
18. For a review, see: Drent, E.; Budzelaar, P. H. M. *Chem. Rev*. **1996**, *96*, 663.
19. Reddy, K. R.; Tsai, W.-W.; Surekha, K.; Lee, G.-H.; Peng, S.-M.; Chen, J.-T.; Liu, S.-T. *J. Chem. Soc*., *Dalton Trans*. **2002**, 1776.
20. See also: Perch, N. S.; Widenhoefer, R. A. *Organometallics* **2001**, *20*, 5251.
21. Bothe, U.; Rudbeck, H. C.; Tanner, D.; Johannsen, M. *J. Chem. Soc*., *Perkin Trans. 1* **2001**, 3305.