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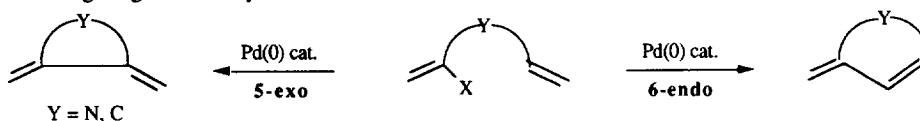
Intramolecular Heck-type Reactions in Aqueous Medium. Dramatic Change in Regioselectivity

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Abstract : Efficient intramolecular Heck-type cyclizations were carried out in aqueous medium using water-soluble Pd/TPPTS catalysts. Under these conditions, the generally observed *exo* process was reversed in favor of the regioselective formation of *endo* cyclized compounds.

In the course of our study on palladium promoted reactions, we recently developed a versatile water-soluble catalytic system generated *in situ* from a mixture of Pd(OAc)₂ and TPPTS¹ resulting in the formation of an active palladium zerovalent intermediate². Efficient removal of allyloxycarbonyl protecting groups³ as well as cross-coupling reactions⁴, especially high-yielding arylations of alkenes, were achieved in homogeneous and biphasic aqueous-organic media in the presence of this catalyst. Some seminal examples of Heck-type reactions involving arenediazonium salts in MeOH/H₂O as solvent⁵, and some arylations of olefins in neat water⁶ were also reported using various Pd(0) sources. The intramolecular version of Heck-type couplings was largely developed as an elegant access to polycyclic molecules^{7,8}, and when substrates are likely to cyclize via *exo* or *endo* processes, the ring closure is generally described to occur with high regioselectivity in favor of the *exo* mode⁹.

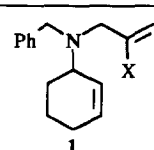
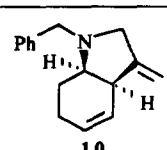
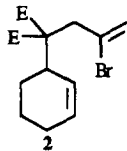
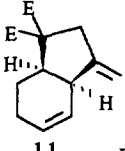
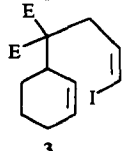
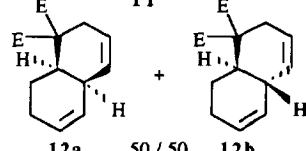


Nevertheless, the change from 5-*exo* to 6-*endo* preference was recently reported for the intramolecular carbopalladation of 1,6-enynes by modifying the catalyst¹⁰; another example was also noted for the cyclization of highly functionalized enamides where the unexpected *endo* process was observed under the Jeffery conditions¹¹. These findings prompted us to present our first results on intramolecular Heck-type cyclizations promoted by Pd(OAc)₂/TPPTS and PdCl₂/TPPTS catalytic systems, in CH₃CN/H₂O medium. In contrast with the preference for the *exo*-mode process usually described in the literature, these conditions afforded the unanticipated *endo* selectivity.

We first investigated the cyclization of substrates which do not compete for the regioselectivity of the ring closure (Table 1). Both iodide and bromide precursors derived from cyclohex-2-ene underwent smooth cyclization in the presence of 5 to 10% of Pd(0) catalysts¹² and diisopropylethylamine (1.2 eq) in CH₃CN/H₂O (6/1) medium, giving the corresponding fused bicyclic products in good yields¹³. At moderate temperatures, ranging from 60 to 80°C, reactions were completed within 12 to 18 hours. It is noteworthy that when the halogen is branched on the internal position of the double bond, the cyclization exclusively led to the *cis* isomers **10**¹⁴ and **11** (entries 1, 2), whereas substrate **3** holding the iodine atom on the terminal carbon of the double bond gave an equimolar mixture of *cis* and *trans* diastereomers **12a** and **12b**.

In fact, in the first case, insertion of the halogenopalladate intermediate in the olefin can only occur on the upper side of the cyclohexene ring due to steric constraints, while the iodopalladate adduct stemming from substrate **3** is more flexible so that the two faces of the cyclohexene ring become accessible, affording two diastereomers.

Table 1 : Intramolecular Heck-type reactions of cyclohexene derivatives using water-soluble Pd(0) catalyst^{a)}

Entry	Substrate	Cat (mol%)	Temp (°C) Time	Products	Yield (%) ^{b)}
1	 1	(a) PdCl ₂ / TPPTS mol.10%	70°C 12h	 10	(a) 77
		(b) PdCl ₂ / TPPTS mol.10%	80°C 12h		(b) 68
(a) X = Br; (b) X = I					
2	 2	PdCl ₂ / TPPTS mol.5%	80°C 18h	 11	50
3	 3	Pd(OAc) ₂ / TPPTS mol.5%	60°C 18h	 12a 50 / 50 12b	80

a) conditions : (iPr)₂NEt 1.2 eq.; solvent : CH₃CN / H₂O (6/1); b) isolated yield

We next investigated the reaction of substrates that are likely to undergo both 5-exo-trig and 6-endo-trig cyclization pathways (Table 2). When treated with 10% of water-soluble PdCl₂ / TPPTS species, N-benzylated iododiene **4** cyclized to the endo heterocycle **13a** with high regioselectivity since only trace amounts of the 5-exo product (4%) were isolated (entry 1). The bromide analog **5**, treated under the same conditions, underwent the predominant endo process to produce a 93/7 mixture of six and five membered heterocycles in 65% yield (entry 2(a)). These results suggest that under aqueous conditions, it is possible to reverse the usual 5-exo preference observed in standard anhydrous Heck conditions, to obtain the 6-endo mode with a large predominance. In order to confirm this change in the regioselectivity of the ring closure, some comparative assays were carried out. For instance, when performed in anhydrous CH₃CN, using 5% of Pd(OAc)₂, 15% of PPh₃, 1 eq. of Ag₂CO₃ and 1.2 eq. of diisopropylethylamine at 80°C, the reaction led to the predominant 5-exo-product (entry 2(b)) with the opposite regioselectivity as in aqueous medium. We also tested the phase transfer system introduced by Jeffery¹⁵ which resulted in a 47/53 mixture of **13a** and **13b**¹⁴ (entry 2(c)) indicating a tendency to reverse the usual exo preference, but with lower selectivity than with our water soluble catalyst. Moreover, in the presence of 10% PdCl₂/TPPTS, sulfonamides **6a** and **6b** resulted in the exclusive formation of the 6-membered rings **14a** and **14b**, with partial migration of the double bond (entry 3). Under the same catalytic conditions, the diallylamine derivative **7** smoothly reacted at 70°C to give a 65/35 mixture of 6-endo and 5-exo heterocycles in 91% yield (entry 4(a)), and the same transformation on the iodide analog **8** produced a 80/20 ratio of the cyclized isomers **15a** and **15b**, at 50°C (entry 5(a)).

Remarkably, when the reaction was performed under anhydrous conditions, only the 5-membered heterocycle was obtained in 77% yield (entry 4(b)), which is believed to be the kinetically controlled product of the intramolecular process^{9b,c}. Moreover, the fact that under our aqueous conditions, the 5-exo process decreases from 20 to 10% when the temperature is increased from 50 to 80°C (entries 5(a) and 5(b)) is in accordance with the assumption that **15b** is the kinetic product and **15a** the thermodynamic product of the cyclization. Moreover the 6-endo regioselectivity observed in aqueous medium is not limited to nitrogen containing substrates, since the dimethylmalonate derivative **9** (E = CO₂Me) cyclized to the six membered ring **16a** with non optimized 30% yield (entry 6). To our knowledge, this inversion in the regioselectivity of the ring closure by simply changing the reaction medium has never been observed on such substrates.

Table 2

Entry	Substrate	Cat (mol%)	Temp. (°C) Time	Products	Yield (%)
1		PdCl ₂ /TPPTS mol.10%	65°C 14h	 13a + 13b	96 / 4 61
2		(a) PdCl ₂ /TPPTS mol.10% (b) Pd(OAc) ₂ /PPh ₃ ¹ mol.5% (c) Pd(OAc) ₂ /PPh ₃ ² nBu ₄ NCl 1,1 eq	70°C 24h 90°C 20h 40°C 12h		93 / 7 14 / 86 47 / 53 65 60 70
3	 (a) X = Br (b) X = I	PdCl ₂ /TPPTS mol.10%	reflux 24h	 14a + 14b	31 / 69 25 / 75 70 59
4		(a) PdCl ₂ /TPPTS mol.10% (b) Pd(OAc) ₂ /PPh ₃ ¹ mol.5%	70°C 14h 80°C 20h	 15a + 15b	65 / 35 0 / 100 91 77
5		(a) Pd(OAc) ₂ /TPPTS mol.10% (b) Pd(OAc) ₂ /TPPTS mol.10%	50°C 10h 80°C 10h		80 / 20 90 / 10 82 79
6		(a) PdCl ₂ /TPPTS mol.10%	90°C 24h	 16a + 16b	100 / 0 30

1) conditions : (iPr)₂NEt 1.2 eq.; Ag₂CO₃ 1 eq.; CH₃CN; 2) phase transfert conditions : K₂CO₃ 2,8 eq; DMF / εH₂O

In summary, an efficient methodology was developed for the synthesis of carbo and heterocyclic compounds through intramolecular cyclization promoted by water-soluble Pd(0) catalysts. Moreover, these aqueous conditions offer the opportunity to reverse the usual exo-process, affording access to the endo-products. By proper choice of the reaction medium, it is thus possible to obtain either the endo or the exo-ring closure starting from the same substrate. Further applications of this change in regioselectivity are under investigation in our laboratory for the synthesis of more elaborated polycyclic molecules.

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References and notes

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- 11 Rigby, J.H.; Hughes, R.C.; Heeg, M.J. *J. Am. Chem. Soc.* **1995**, *117*, 7834-7835.
- 12 In this study, two water-soluble catalytic systems were used : the first one is generated *in situ* from Pd(OAc)₂ and TPPTS in a 1/3 ratio; the second one is preformed in water at 80°C from a (1/3) mixture of PdCl₂ and TPPTS until a dark red solution is obtained (15 to 30 minutes).
- 13 Typical procedure for the intramolecular cyclization in aqueous-organic medium : CH₃CN and H₂O were degazed during 15 minutes before the reaction. The substrate (1 mmol) was dissolved in CH₃CN (3 ml) , under an argon atmosphere. Diisopropylethylamine (1.2eq) was added to the stirred solution, followed by rapid introduction of the catalyst (mol. 5-10% of Pd(OAc)₂ and mol.15-30% of TPPTS dissolved in 0,5 ml of H₂O or a solution (0.5 ml) of the preformed PdCl₂ / TPPTS (1/3) catalyst). The reaction mixture was heated at temperatures ranging from 50 to 90°C and the evolution was monitored by TLC and gas chromatography. After completion, the solution was cooled to room temperature, then treated by 5 ml of H₂O and extracted by 3x8ml of AcOEt. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.
- 14 Data for compound 10 : ¹H NMR (CDCl₃; 200MHz; δ) : 7.35 and 7.28 (5H, 2m, H_{arom}), 5.78 (1H, dm, ³J = 10.3Hz, HC=), 5.58 (1H, d, ³J = 10.3Hz, HC=), 4.90 (2H, m, H₂C=); 4.08 and 3.26 (2H, 2d, ²J = 13.2 Hz, CH₂Ph), 3.52 and 2.94 (2H, 2dd, ²J = 13.2 Hz and ⁴J = 1.5Hz, NCH₂), 3.17 (1H, m, HC), 2.91 (1H, m, HC), 2.27 (1H, m, CH₂), 1.94 (2H, m, CH₂), 1.66 (1H, m, CH₂); ¹³C NMR (CDCl₃; 50MHz; δ) : 150.82, 139.17, 128.68, 128.11, 126.72, 125.97, 105.21, 61.63, 58.19, 57.40, 43.43, 22.20, 20.14; IR (film) : 3059, 3020, 2927, 1658, 1600, 1490, 1448, 1330; GC/MS (m/z) : 225 (M⁺), 210, 171, 134, 91. Compounds 13a : ¹H NMR : 7.37 and 7.28 (5H, 2m, H_{arom}), 6.25 (1H, d, ³J = 9.8Hz, HC=), 5.83 (1H, dt, ³J = 9.8Hz and ³J = 2.5Hz, HC=), 4.88 and 4.78 (2H, 2s, H₂C=), 3.63 (2H, s, CH₂Ph), 3.22 and 3.10 (4H, 2m, CH₂); ¹³C NMR : 140.37, 137.86, 129.13, 128.17, 127.87, 127.53 (2C=), 127.05, 110.71, 61.87, 55.85, 52.15; GC/MS (m/z) : 185 (M⁺), 108, 91, 65, 41; 13b : ¹H NMR: 7.35 and 7.29 (5H, 2m, H_{arom}), 5.39 (2H, t, ⁴J = 2.1 Hz, H₂C=), 4.92 (2H, s, H₂C=), 3.66 (2H, s, CH₂Ph), 3.32 (4H, m, CH₂); ¹³C NMR : 144.52, 128.77, 128.19, 127.02, 103.25, 60.48, 59.80 (2CH₂); GC/MS (m/z) : 185 (M⁺), 108, 91, 65.
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