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

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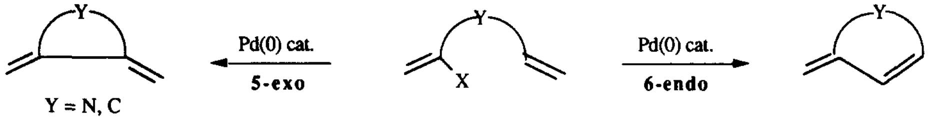
Abstract : Efficient intramolecular Heck-type cyclizations were carried out in aqueous medium using water-soluble Pd/TPPTS catalysts. Under these conditions, the generally observed exo process was reversed in favor of the regioselective formation of endo cyclized compounds.

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 TPPTS[1] resulting in the formation of an active palladium zerovalent intermediate[2]. Efficient removal of allyloxycarbonyl protecting groups[3] as well as cross-coupling reactions[4], 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 $MeOH/H_2O$ as solvent[5], and some arylations of olefins in neat water[6] 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 mode[9].

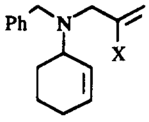
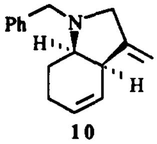
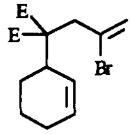
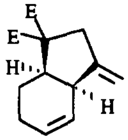
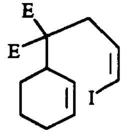
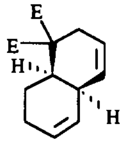
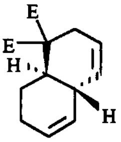


Nevertheless, the change from 5-exo to 6-endo preference was recently reported for the intramolecular carbopalladation of 1,6-enynes by modifying the catalyst[10]; another example was also noted for the cyclization of highly functionalized enamides where the unexpected endo process was observed under the Jeffery conditions[11]. These findings prompted us to present our first results on intramolecular Heck-type cyclizations promoted by $Pd(OAc)_2$/TPPTS and $PdCl_2$/TPPTS catalytic systems, in CH_3CN/H_2O 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) catalysts[12] and diisopropylethylamine (1.2 eq) in CH_3CN/H_2O (6/1) medium, giving the corresponding fused bicyclic products in good yields[13]. 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)]

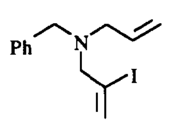
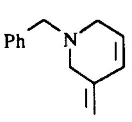
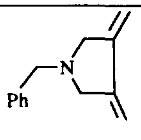
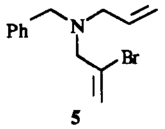
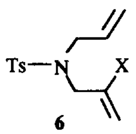
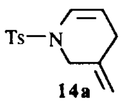
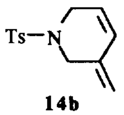
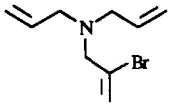
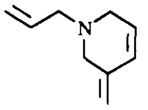
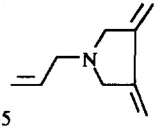
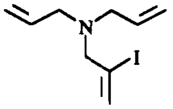
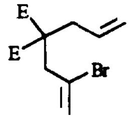
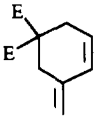
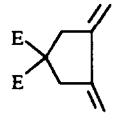
Entry	Substrate	Cat (mol%)	Temp (°C) Time	Products	Yield (%)[b)]
1	 **1** (a) X = Br; (b) X = I	(a) $PdCl_2$ /TPPTS mol.10% (b) $PdCl_2$ /TPPTS mol.10%	70°C 12h 80°C 12h	 **10**	(a) 77 (b) 68
2	 **2**	$PdCl_2$ /TPPTS mol.5%	80°C 18h	 **11**	50
3	 **3**	$Pd(OAc)_2$/TPPTS mol.5%	60°C 18h	 +  **12a** 50 / 50 **12b**	80

a) conditions : $(iPr)_2NEt$ 1.2 eq.; solvent : CH_3CN / H_2O (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 $PdCl_2$ / 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 CH_3CN, using 5% of $Pd(OAc)_2$, 15% of PPh_3, 1 eq. of Ag_2CO_3 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 Jeffery[15] which resulted in a 47/53 mixture of **13a** and **13b**[14] (entry 2(c)) indicating a tendancy to reverse the usual exo preference, but with lower selectivity than with our water soluble catalyst. Moreover, in the presence of 10% $PdCl_2$/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 limitated to nitrogen containing substrates, since the dimethylmalonate derivative **9** (E = CO_2Me) cyclized to the six membered ring **16a** with non optimized 30% yield (entry 6). To our knownledge, 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	 **4**	$PdCl_2$ /TPPTS mol.10%	65°C 14h	 **13a**	+ 96 / 4	 **13b**	61
2	 **5**	(a) $PdCl_2$ /TPPTS mol.10%	70°C 24h		93 / 7		65
		(b) $Pd(OAc)_2/PPh_3$[1] mol.5%	90°C 20h		14 / 86		60
		(c) $Pd(OAc)_2/PPh_3$[2] nBu_4NCl 1,1 eq	40°C 12h		47 / 53		70
3	 **6**	$PdCl_2$ /TPPTS mol.10%	reflux 24h	 **14a**	+	 **14b**	
	(a) X = Br				31 / 69		70
	(b) X = I				25 / 75		59
4	 **7**	(a) $PdCl_2$ /TPPTS mol.10%	70°C 14h	 **15a**	+ 65 / 35	 **15b**	91
		(b) $Pd(OAc)_2/PPh_3$[1] mol.5%	80°C 20h		0 / 100		77
5	 **8**	(a) $Pd(OAc)_2$/TPPTS mol.10%	50°C 10h		80 / 20		82
		(b) $Pd(OAc)_2$/TPPTS mol.10%	80°C 10h		90 / 10		79
6	 **9**	(a) $PdCl_2$ /TPPTS mol.10%	90°C 24h	 **16a**	+ 100 / 0	 **16b**	30

1) conditions : $(iPr)_2NEt$ 1.2 eq.; Ag_2CO_3 1 eq.; CH_3CN; 2) phase transfert conditions : K_2CO_3 2,8 eq; DMF / εH_2O

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

1 @TPPTS : (m.Sulfonated triphenylphosphine)

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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 $PdCl_2$ and TPPTS until a dark red solution is obtained (15 to 30 minutes).

13 Typical procedure for the intramolecular cyclization in aqueous-organic medium : CH_3CN and H_2O were degazed during 15 minutes before the reaction. The substrate (1 mmol) was dissolved in CH_3CN (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 H_2O or a solution (0.5 ml) of the preformed $PdCl_2$ / 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 H_2O and extracted by 3x8ml of AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel.

14 Data for compound **10** : ^1H NMR ($CDCl_3$; 200MHz; δ) : 7.35 and 7.28 (5H, 2m, H_{arom}), 5.78 (1H, dm, $^3J = 10.3$Hz, HC=), 5.58 (1H, d, $^3J = 10.3$Hz, HC=), 4.90 (2H, m, $H_2C=$); 4.08 and 3.26 (2H, 2d, $^2J = 13.2$ Hz, CH_2Ph), 3.52 and 2.94 (2H, 2dd, $^2J = 13.2$ Hz and $^4J = 1.5$Hz, NCH_2), 3.17 (1H, m, HC), 2,91 (1H, m, HC), 2.27 (1H, m, CH_2), 1.94 (2H, m, CH_2), 1.66 (1H, m, CH_2); ^{13}C NMR ($CDCl_3$; 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 ($M^{+\cdot}$), 210, 171, 134, 91. Compounds **13a** : ^1H NMR : 7.37 and 7.28 (5H, 2m, H_{arom}), 6.25 (1H, d, $^3J = 9.8$Hz, HC=), 5.83 (1H, dt, $^3J = 9.8$Hz and $^3J = 2.5$Hz, HC=), 4.88 and 4.78 (2H, 2s, $H_2C=$), 3.63 (2H, s, CH_2Ph), 3.22 and 3.10 (4H, 2m, CH_2); ^{13}C 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 ($M^{+\cdot}$), 108, 91, 65, 41; **13b** : ^1H NMR: 7.35 and 7.29 (5H, 2m, H_{arom}), 5.39 (2H, t, $^4J = 2.1$ Hz, $H_2C=$), 4.92 (2H, s, $H_2C=$), 3.66 (2H, s, CH_2Ph), 3.32 (4H, m, CH_2); ^{13}C NMR : 144.52, 128.77, 128.19, 127.02, 103.25, 60.48, 59.80 ($2CH_2$); GC/MS (m/z) : 185 ($M^{+\cdot}$), 108, 91, 65.

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