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Allylic Alkylation and Ring-Closing Metathesis in Sequence: A Successful Cohabitation of Pd and Ru

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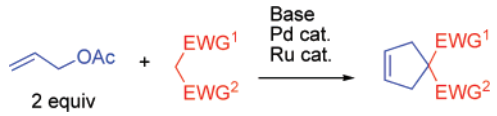
ABSTRACT



An allylic alkylation/ring-closing metathesis domino catalytic process, wherein a palladium and a ruthenium catalyst are concomitantly present in the reaction mixture from the outset of the reaction, is developed. Evidence for Grubbs' catalysts activity in allylic alkylation is also reported.

Sustainable chemistry processes appear to be a real challenge for 21st century chemists. In this respect, transition-metal catalysis and multistep one-pot processing are, among others, two powerful tools to reach such a goal. Indeed, transition-metal catalysis has proven to be of paramount importance, allowing more atom-economical transformations as compared to stoichiometric organometallic conditions.[1] On the other hand, domino reactions[2] allow the preparation of complex molecules in a single, step-economical, synthetic operation, thereby limiting the amount of solvent used as well as the time-consuming and costly workup and purification procedures. Therefore, combination of the two concepts would enable a big step toward a more sustainable chemistry. Despite this evidence, the domain of transition-metal catalyzed domino reactions is still in its infancy. We recently proposed a classification to distinguish the various conditions covering this concept.[3] While *pure-domino* sequences (TM−DOM) involve a single catalytic cycle, *pseudo-domino* ones (TM−PDOM) involve the succession of two or more catalytic cycles. In this latter case, a simple multitasking catalytic system may drive the cycles (TM−PDOM type I) or different and mutually compatible catalysts may be responsible for different cycles (TM−PDOM type II).

According to this classification most of the known transition-metal catalyzed domino processes are TM−DOM,[4] while TM−PDOM type I[5] have been scarcely studied. The conceptually intriguing and powerful potential of PDOM type II[6,7] has been explored thus far only by very few scientists.[8]

Among the transition-metal-catalyzed processes the Tsuji−Trost allylic alkylation[9] (AA) and the ring-closing metathesis (RCM)[10] have proven to be powerful tools for the construction of complex molecules. Accordingly, we decided to study the feasibility of an AA/RCM PDOM sequence.[11,12]

(1) (a) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley & Sons: Sussex, UK, 2000. (b) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Sausalito, CA, 1999.

(2) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Tietze, L. F.; Brasche, G.; Gericke K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(3) Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456−9459.

(4) For a review on Pd−DOM, see: Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959−5989.

(5) For examples of PDOM type I, see: (a) Poli, G.; Giambastiani, G.; Pacini, B. *Tetrahedron Lett.* **2001**, *42*, 5179−5182. (b) Lemaire, S.; Prestat, G.; Giambastiani, G.; Madec, D.; Pacini, B.; Poli, G. *J. Organomet. Chem.* **2003**, *687*, 291−300. (c) Maitro, G.; Vogel, S.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2006**, *8*, 5951−5954. (d) Tietze, L. F.; Nordmann, G. *Eur. J. Org. Chem.* **2001**, 3247−3253. (e) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609−4610. (f) Battistuzzi, G.; Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Adv. Synth. Catal.* **2007**, *349*, 297−302.

(6) For reviews, see: (a) Walsike, J.-C.; Obrey, J. O.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001−1020. (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379. (c) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302−312.

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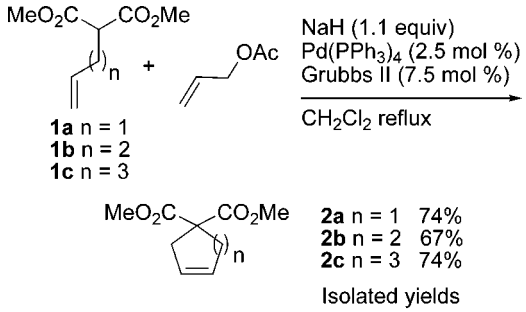
For a model reaction we chose to test the AA/RCM sequence using dimethyl allylmalonate **1a** and allyl acetate as substrates. After a number of optimization experiments, success was finally encountered when the sodium enolate of dimethyl allylmalonate was added to a mixture of $Pd(PPh_3)_4$ (2.5 mol %), allyl acetate (1.05 equiv), and Grubbs' catalyst second generation (**G2**, 7.5 mol %) in methylene chloride at reflux for 1 h. These conditions allowed the formation of the Pd/Ru PDOM cyclopentenyl product **2a** in 74% isolated yield (Scheme 1). It should be

Scheme 1. AA/RCM PDOM Sequence



pointed out that both catalysts are present in the reaction medium from the outset of the reaction. These conditions also allowed access to cyclohexenyl **2b** and cycloheptenyl **2c** PDOM products in, respectively, 67 and 74% isolated yields running the reaction with malonates **1b** and **1c**, respectively.

Representative optimization experiments are reported in Table 1 using dimethyl allylmalonate **1a**. First, replacement of $Pd(PPh_3)_4$ with $Pd(OAc)_2$ in the presence of a phosphine such as dppe (2.5 mol %) or PPh_3 (5 mol %) did not affect the conversion of the reaction (entries 1−3). Conversely, the use of PCy_3 with $Pd(OAc)_2$ afforded, after complete consumption of the starting malonate **1a**, a mixture of the allylic alkylation product **3** and the domino product **2a** in a 43:57 ratio, as observed in ^1H NMR (entry 4). Suppressing the phosphine or raising its concentration decreased the yield of the domino product **2a** (entries 5−6 vs entry 2). Decreasing the amount of **G2** to 5 or 2.5 mol % still afforded a reasonable amount of domino product (95 and 79% convn, entries 7−8). As opposed to **G2**, Grubbs' catalyst first generation (**G1**), bearing two PCy_3 and no *N*-heterocyclic carbene ligand, did not allow the domino process (entry 9), while the AA step was quantitative. Dimeric allylpalladium chloride and Pd_2dba_3 without phosphine added were found less efficient than $Pd(OAc)_2$ with or without phosphine (entries 11−12 vs entries 2 and 6).

The *N*-heterocyclic carbene-liganded Pd catalyst $[Pd(C_3H_5)(IPr)Cl]$[13] showed a good activity (entry 13). Changing solvent from CH_2Cl_2 to toluene induced a minor decrease in the domino yield (entry 14), while THF almost completely inhibited the RCM step (entry 15). Influence of the nature of the base was also studied. DBU, K_2CO_3, Cs_2CO_3, and BSA/AcOK induced a dramatic decrease of the domino product yield (entries 16−19).

Control experiments were next performed. As expected, when a Grubbs' catalyst was not added to the reaction mixture, no RCM product was observed (entry 20). Furthermore, when both Ru and Pd catalysts were omitted, neither **3** nor **2a** was observed. Surprisingly, when the reaction was run in the absence of a Pd source, but in the presence of **G2**, the partial formation of **3** was still observed (entry 21). These two experiments clearly indicate that **G2** was able to promote the allylic alkylation step. Although numerous nonmetathetic reactions have been reported using ruthenium metathesis catalysts,[14] to the best of our knowledge, this is the first example showing the activity of one of them in allylic alkylation.[15]

The influence of a more polar solvent was next tested. When **1a** and allyl acetate were treated with **G2** (7.5 mol %) in THF at reflux for 24 h, a 55% conversion to **3** was observed (entry 22). Similarly, replacing the latter catalyst with **G1** still allowed a 39% conversion to **3** (entry 23). The ruthenium-catalyzed allylic alkylation of the sodium enolate of the unsubstituted dimethyl malonate **4** was next tested. In this case, use of **G1** allowed isolation of an 89:11 mixture of mono- and diallylated products **1a** and **3**a in 37% yield (Scheme 2).

It is noteworthy that throughout the experiments no RCM product **2a** was ever detected. We therefore suspected that in the reaction medium the Grubbs' catalyst gave rise to a

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(8) This process has also been alternatively described as *concurrent tandem catalysis* (ref 6a), *tandem orthogonal catalysis* (ref 6b), or *cooperative sequential multicatalysis* (ref 6c).

(9) (a) Tsuji, J. The Tsuji−Trost reaction and related carbon−carbon formation reaction. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley & Sons: NY, 2002; pp 1669−1844. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

(10) *Handbook of Metathesis*; Grubbs, R. H., Ed.; John Wiley & Sons: New York, 2003.

(11) The only related work has been reported by Braddock et al. who studied the in situ Pd-catalyzed isomerisation of allylic acetates and Ru-catalyzed RCM of dienic substrates. These authors demonstrate that the critical point was the slippage of ligands from one metal center to the other which inhibits the activity of the catalysts. Optimal conditions were found using 5 mol % $Pd_2(dba)_3$·dba, 20 mol % PPh_3, and 5 mol % of Grubbs' catalyst second generation or Hoveyda−Grubbs' catalyst. These conditions allow a limited (57%) conversion of the tandem isomerization/RCM. See: (a) Braddock, D. C.; Wildsmith, A. J. *Tetrahedron Lett.* **2001**, *42*, 3239−3242. (b) Braddock, D. C.; Matsuno, A. *Tetrahedron Lett.* **2002**, *43*, 3305−3308.

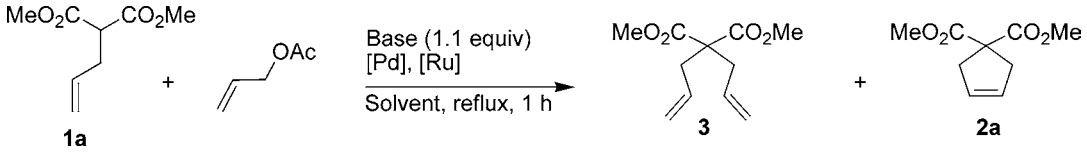
(12) A reverse one-pot sequence, Ru-catalyzed cross metathesis/Pd-catalyzed allylic carbonate reduction has been recently reported by Comins et al. In this sequence, the second catalytic system is added after completion of the first step, yielding a product in 65−85% yield. Comins, D. L.; Dinsmore, J. M.; Marks, L. R. *Chem. Commun.* **2007**, 4170−4171.

(13) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470−5472.

(14) (a) Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, *9*, 1259−1262. (b) Mukherjee, A. *Synlett* **2006**, 1128−1129.

(15) Ruthenium-catalyzed allylic alkylation is a well-known process see: Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096.

Table 1. AA/RCM PDOM Sequence



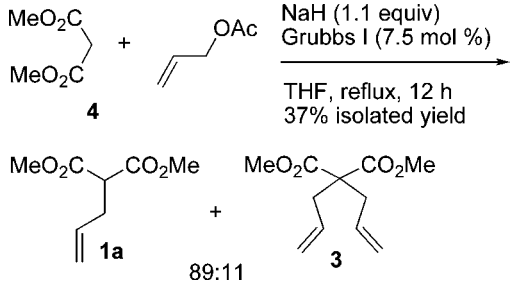
entry	[Pd]	ligand (mol %)		[Ru] (mol %)		base	solvent	convn (%)[a]	**3**:**2a**[a]
1	$Pd(PPh_3)_4$	–	–	G2[b]	7.5	NaH	CH_2Cl_2	100	0:100
2	$Pd(OAc)_2$	dppe	2.5	G2	7.5	NaH	CH_2Cl_2	100	0:100
3	$Pd(OAc)_2$	PPh_3	5	G2	7.5	NaH	CH_2Cl_2	100	0:100
4	$Pd(OAc)_2$	PCy_3	5	G2	7.5	NaH	CH_2Cl_2	100	43:57
5	$Pd(OAc)_2$	dppe	5	G2	7.5	NaH	CH_2Cl_2	83	12:88
6	$Pd(OAc)_2$	–	–	G2	7.5	NaH	CH_2Cl_2	100	44:56
7	$Pd(OAc)_2$	dppe	2.5	G2	5	NaH	CH_2Cl_2	100	5:95
8	$Pd(OAc)_2$	dppe	2.5	G2	2.5	NaH	CH_2Cl_2	100	21:79
9	$Pd(OAc)_2$	dppe	2.5	G1[c]	7.5	NaH	CH_2Cl_2	100	98:2
11	Pd_2dba_3	–	–	G2	7.5	NaH	CH_2Cl_2	100	80:20
12	$[Pd(C_3H_5)Cl]_2$	–	–	G2	7.5	NaH	CH_2Cl_2	70	57:43
13	$[Pd(C_3H_5)(IPr)Cl]$	–	–	G2	7.5	NaH	CH_2Cl_2	100	12:88
14	$Pd(OAc)_2$	PPh_3	5	G2	7.5	NaH	toluene	100	7:93
15	$Pd(OAc)_2$	PPh_3	5	G2	7.5	NaH	THF	92	91:9
16	$Pd(PPh_3)_4$	–	–	G2	7.5	DBU	CH_2Cl_2	62	100:0
17	$Pd(PPh_3)_4$	–	–	G2	7.5	K_2CO_3[d]	CH_2Cl_2	17	94:6
18	$Pd(PPh_3)_4$	–	–	G2	7.5	Cs_2CO_3[d]	CH_2Cl_2	76	96:4
19	$Pd(PPh_3)_4$	–	–	G2	7.5	BSA/AcOK[e]	CH_2Cl_2	67	48:52
20	$Pd(OAc)_2$	PPh_3	5	–	–	NaH	CH_2Cl_2	100	100:0
21	–	–	–	G2	7.5	NaH	CH_2Cl_2	35	100:0
22[f]	–	–	–	G2	7.5	NaH	THF	55	100:0
23[f]	–	–	–	G1	7.5	NaH	THF	39	100:0

[a] Consumption of **1a** and **3**:**2a** ratios as determined by ^{1}H NMR. [b] G2: Grubbs' catalyst second generation, $[(H_2IMes)RuCl_2(=CHPh)(PCy_3)]$. [c] G1: Grubbs' catalyst first generation, $[RuCl_2(=CHPh)(PCy_3)_2]$. [d] 2 equiv were used and Bu_4NBr (10 mol %) was added. [e] BSA (1.1 equiv), AcOK (10 mol %). [f] Reaction time: 24 h.

non-carbenic Ru species able to catalyze allylic alkylation. On the basis of this hypothesis, a ^{1}H NMR study was undertaken. The carbenic proton of **G1** appears as a singlet at 20.17 ppm in d_8-THF (NMR 1, Figure 1). Addition of sodium malonate (1 equiv) to the reaction mixture did not affect the carbenic region of the spectrum.

In an other experiment, allyl acetate was added to **G1** (10 mol %) in d_8-THF. After 30 min at room temperature the appearance of two new signals in the carbenic region was observed (NMR 2). The triplet (19.00 ppm, $J = 4$ Hz) was attributed to **5**, whereas the singlet (19.03 ppm) was attributed to **6**. These two compounds were evidently formed by olefin metathesis between allyl acetate and **G1**. Based on integration of the NMR spectra a 4:82:14 ratio of **G1**/**5**/**6** was obtained. Addition of sodium malonate (10 mol %) to this mixture induced, in 5 min, the complete disappearance of any

Scheme 2. Grubbs-Catalyzed Allylic Alkylation



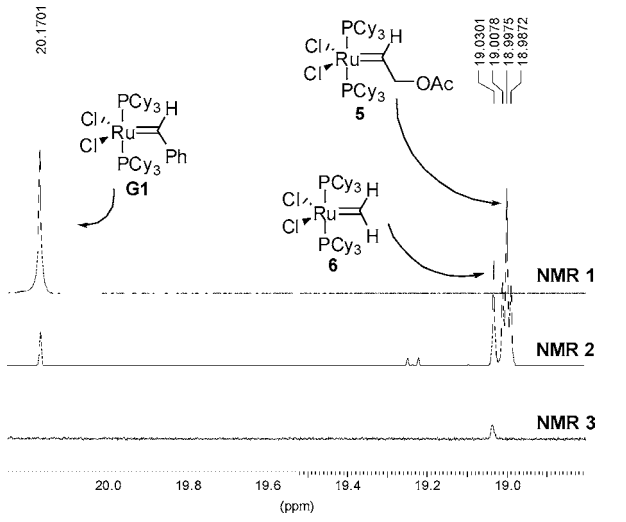
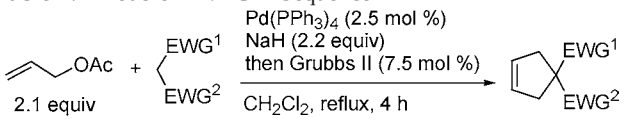
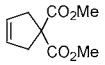
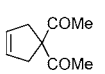
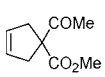
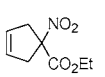
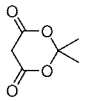
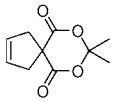
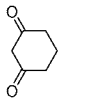
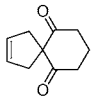
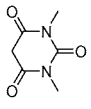
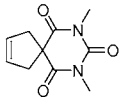


Figure 1. ^{1}H NMR spectra.

Table 2. Double AA/RCM Sequence[a]



entry			product		yield (%)[b]
1		**4**		**2a**	71
2		**7**		**13**	78
3		**8**		**14**	89
4		**9**		**15**	81
5		**10**		**16**	89
6		**11**		**17**	68
7		**12**		**18**	92

[a] All reactions were carried out on a 1 mmol scale. [b] Isolated yields.

carbenic signal (NMR 3). We thus assume that activation of Grubbs' catalyst requires both sodium malonate and allyl acetate. First, allyl acetate reacts with **G1** to generate the corresponding carbenic complex **5**. The latter then interacts with sodium malonate to generate a new allylic alkylation active non-carbenic ruthenium complex. While this pathway formally precludes the PDOM process, metathetic reactivity can still be observed since thermodynamic equilibration between **G1** and **5** is most likely slow compared to the Pd-catalyzed allylic alkylation step.

We finally tackled a more ambitious sequence wherein **2a** would be obtained directly from the unsubstituted dimethyl malonate **4** *via* a double allylic alkylation followed by a ring-closing metathesis step in a one-pot sequence. To our delight, when dimethyl malonate was submitted to the action of allyl acetate (2.1 equiv) using our optimized AA/RCM conditions, cyclopentene **2a** was isolated in 45% yield. This yield could be improved to 71% by simply adding the Grubbs' catalyst **G2** after complete conversion of dimethyl malonate to **3** (Table 2, entry 1). In this single synthetic step three new C−C bonds are formed. Similarly, acetylacetone **7**, methyl acetylacetate **8**, and ethyl nitroacetate **9** led to the desired products **13**, **14**, and **15** in 78%, 89%, and 81% yield, respectively (Table 2, entries 2−4). Cyclic precursors gave also quite satisfactory results. Indeed, Meldrum's acid **10**, cyclohexan-1,3-dione **11**, and 1,3-dimethyl barbituric acid **12** reacted smoothly affording the expected bicyclic products **16**, **17**, and **18** in 89%, 68%, and 92%, respectively (Table 2, entries 5−7).

In conclusion, we have developed the first allylic alkylation/ring-closing metathesis domino sequence concomitantly catalyzed by Pd and Ru. This study demonstrates the compatibility of the two catalytic systems. We also observed for the first time that Grubbs' catalysts can act as precatalysts for allylic alkylation.

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Supporting Information Available: General procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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