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Regiochemical Control in the Pd(II)-Catalyzed Claisen Rearrangement via *In Situ* Enol Ether Exchange

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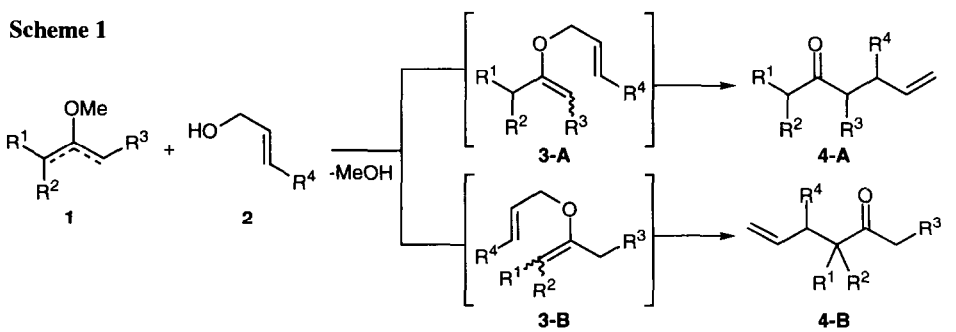
Abstract: *The titled reactions of unsymmetrical enol methyl ethers with allylic alcohols are shown to exhibit the opposite regioselectivities to those of the conventional thermal counterparts to result in the selective formation of the ketones arising from the less substituted enol allylic ethers.* Copyright © 1996 Elsevier Science Ltd

The Claisen rearrangement currently enjoys widespread application as a powerful tool for stereocontrolled C-C bond formations.[1] While the rearrangement is usually conducted in a thermolytic manner, much effort has recently been devoted to the development of transition metal-catalyzed Claisen versions.[2,3] Recently we have developed the Pd(II)-catalyzed Claisen modification via *in situ* enol ether exchange between an enol methyl ether and an allylic alcohol, which provide different stereoselectivities from those of the conventional thermal counterparts.[3] Disclosed herein are the unique regiochemical features of the Pd(II)-catalyzed Claisen modification.

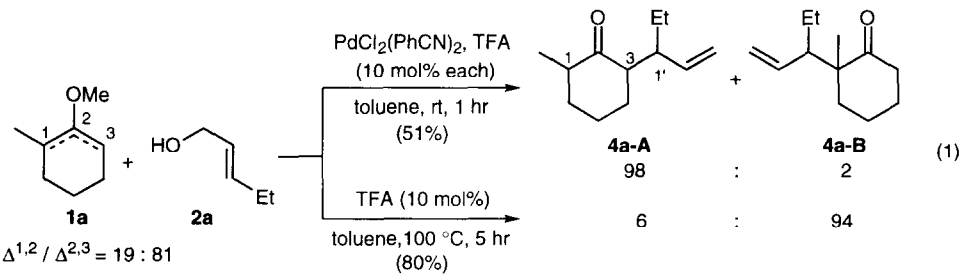
As depicted in Scheme 1, the *in situ* Claisen rearrangement between an *unsymmetrical* enol ether (**1**) and an allylic alcohol (**2**) should give rise to the two regioisomeric products, **4-A** from the less substituted enol ether **3-A** and **4-B** from the more substituted enol ether **3-B**. The conventional thermal rearrangements (R^1=alkyl, R^2,R^3=H) have been reported to provide ketone **4-B** as the main product,[4] while the triisobutylaluminum-promoted rearrangement (R^1=Ph, R^2,R^3=H) has been shown to proceed via the selective formation of the less substituted enol ether **3-A**.[5] As far as the Pd(II)-catalyzed process is concerned, we hypothesized that, based on the previously-proposed transition state model,[3c,d] **3-A** could coordinate more effectively with the Pd(II) complex than **3-B**, thus leading to the selective formation of ketone **4-A**.

Scheme 1



At first, we examined the regioselectivity in both the Pd(II)-catalyzed and trifluoroacetic acid (TFA)-catalyzed thermal rearrangements of a regioisomeric mixture of the enol ether **1a**[6] and (*E*)-allylic alcohol **2a** under the previously-reported conditions[3c] (eq 1). The Pd(II)-catalyzed process was found to provide the

opposite regiochemistry to that of the thermal counterpart to afford ketone **4a-A** as an essentially single regioisomer, albeit a mixture of the four stereoisomers.[7] Thus, an obvious question arises whether or not the high and opposite regioselectivity originates from the selective formation of the less substituted enol ether **3a-A** in the Pd-catalyzed enol ether exchange.[8]



To answer this question, we examined the regioselectivity in the enol ether exchange between the same regioisomeric mixture of **1a** and ethanol under similar Pd-catalyzed conditions. As shown in eq 2, the regioselectivity thus observed is significantly lower than the regioselectivity observed for the rearrangement, while the less substituted enol ether slightly predominates. This observation suggests that the overall regiochemistry of the Pd-catalyzed rearrangement is not governed by the regiochemistry of the enol ether exchange step. Instead, the regioselectivity might be determined mainly by the diffemce in rearrangement rate between the regioisomeric enol allylic ethers **3a-A** and **3a-B** which are interconvertible under the Pd-catalyzed conditions.[8,9] Thus, the almost exclusive formation of ketone **4a-A** is explained as a result that the boat-like[3] transition state $\mathbf{T_A}$ would be sterically favored over $\mathbf{T_B}$ which would suffer the steric repulsion as depicted.

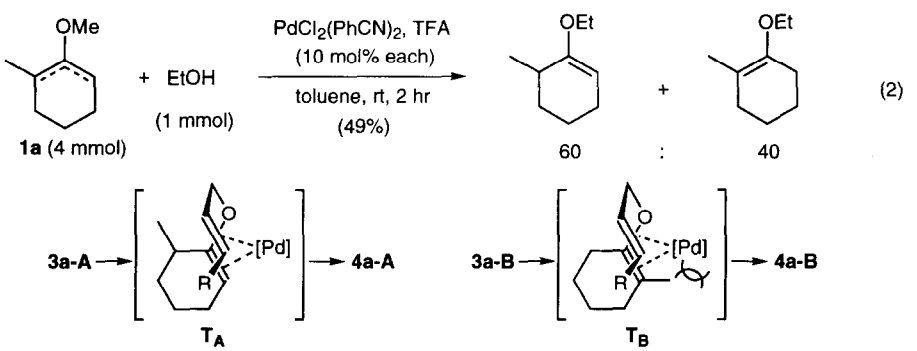
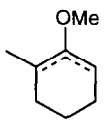
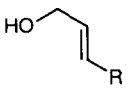
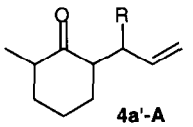
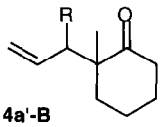
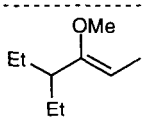
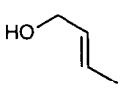
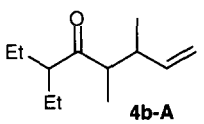
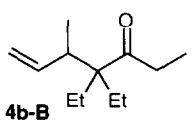
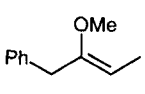
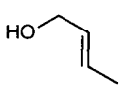
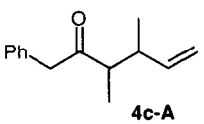
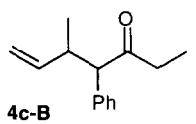


Table 1 summarizes the regiochemical outcomes of the Pd(II)-catalyzed Claisen rearrangements of different pairs of unsymmetrical enol methyl ethers and allylic alcohols, together with those of the thermal counterparts for comparison.[10] The results reveal significant regiochemical trends of the Pd-catalyzed rearrangement. First, the regioselectivity depends markedly on the substitution pattern of allylic alcohols used. While the rearrangements of **1a** (entry 1) and **1b** (entry 5) with (*E*)-crotyl alcohol provide essentially the same regiochemistry as described in eq 1, whereas the use of allyl alcohol results in a considerable decrease in regioselectivity (entry 3).[11] This means that the presence of a γ-substituent on the allylic alcohol is essential for the high regioselectivity and the regiochemical changeover as well. Second, the regioselectivity is, of course, dependent on the structure of enol methyl ethers used. As seen in entry 7, the rearrangement of **1c** provides a

Table 1. The Claisen Rearrangements between Various Enol Methyl Ethers and Allylic Alcohols.

Entry	1	2	Method[a]	% Yield[b]	Product[c]	
					 **4a'-A**	 **4a'-B**
1	**1a**	R = Me (**2b**)	**A**	54	96[d]	: 4
2			**B**	77	7	: 93[e]
3		R = H (**2c**)	**A**	30[f]	39[g]	: 61
4			**B**	39	11	: 89
					 **4b-A**	 **4b-B**
5	**1b**	**2b**	**A**	60	>99[h]	: <1
6			**B**	42	66[i]	: 34
					 **4c-A**	 **4c-B**
7	**1c**	**2b**	**A**	22	40[j]	: 60[k]
8			**B**	73	5	: 95[l]

[a] **Method A**: $PdCl_2(PhCN)_2$, TFA (10 mol% each), toluene, rt; **Method B**: TFA (10 mol%), toluene, 100 °C. [b] Isolated yield. [c] The isomeric retios were determined by GLC analyses and/or ^1H NMR analyses. [d] 1,3-*trans*-3,1'-*anti* / *trans-syn* / *cis-anti* / *cis-syn* = 64: 3: 32: 1 (ref 7). [e] 94% *syn* (ref 7). [f] The ketal intermediate (ca. 15%) was obtained as a by-product. [g] 64% *trans*. [h] Obtained as a single diastereomer (presumably *anti*). [i] 61% *anti*. [j] 94% *anti*. [k] 94% *anti*. [l] 82% *anti*.

very low regioselectivity, apparently due to the small steric difference between the two substituents (Ph and CH_3), whereas the thermal counterpart affords ketone **4c-B** in a high selectivity.

In summary, this work has revealed the interesting regiochemical features of the Pd(II)-catalyzed Claisen rearrangement via *in situ* enol ether exchange, which are different in nature from those of the conventional thermal Claisen counterparts. Further works are in progress on the improvement of this methodology and its synthetic applications.

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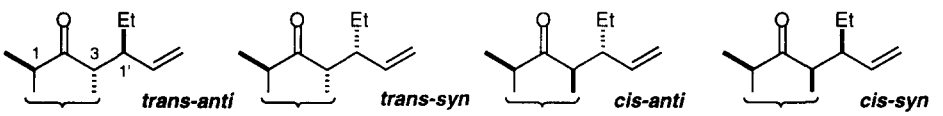
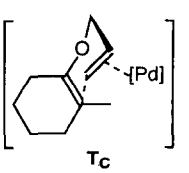
5. Rychnovsky, S. D.; Lee, J. L. *J. Org. Chem.* **1995**, *60*, 4318-4319.

6. The regioisomeric mixture of **1a** was prepared from 2-methylcyclohexanone according to the reported procedure: Wohl, R. A. *Synthesis* **1974**, 38-40.
7. The regioisomeric ratios of the products were determined by GLC analyses and their structures were unequivocally assigned by ^{1}H NMR analyses. The diastereomeric ratio of **4a-A** was determined by GLC analysis to be 1,3-*trans*-3,1'-*anti* / *trans-syn* / *cis-anti* / *cis-syn* = 67 : 4 : 27 : 2. Their configurations were tentatively assigned on the basis of the following facts and experimentations. (a) This type of Pd-catalyzed rearrangement shows a high 3,1'-*anti*; (b) this type of 1,3-*cis* isomer is thermodynamically more stable than the *trans* isomer in general; (c) the hydrogenated compounds, 2-methyl-6-(3-pentyl)cyclohexanone, of the 1st and 2nd major product separated by column chromatography were diastereomeric each other and the former saturated ketone was epimerized to the latter with MeONa in MeOH: *trans-anti*-**4a-A**, ^{1}H NMR 0.82 (t, *J*=7.4 Hz, 3H), 1.02 (d, *J*=6.6 Hz, 3H), 1.05-1.27 (m, 2H), 1.28-1.48 (m, 2H), 1.48-1.86 (m, 2H), 1.90-2.10 (m, 2H), 2.16-2.28 (m, 1H), 2.28-2.43 (m, 1H) 2.51 (ddq, *J*=12.3, 9.1, 3.9 Hz, 1H), 5.06 (dd, *J*=17.1, 2.1 Hz, 1H), 5.12 (dd, *J*=10.2, 2.1 Hz, 1H), 5.34 (ddd, *J*=17.1, 10.2, 9.1 Hz, 1H). ^{13}C NMR 11.8, 14.9, 20.4, 25.3, 30.2, 36.6, 42.6, 46.1, 54.4, 117.2, 139.8, 216.5.; *cis-anti*-**4a-A**, ^{1}H NMR 0.84 (t, *J*=7.4 Hz, 3H), 1.00 (d, *J*=6.3 Hz, 3H), 1.08-1.55 (m, 4H), 1.63-1.77 (m, 1H), 1.78-1.88 (m, 1H), 2.0-2.14 (m, 2H), 2.20-2.32 (m, 1H), 2.30-2.48 (m, 2H), 4.99 (dd, *J*=16.8, 2.1 Hz, 1H), 5.03 (dd, *J*=10.2, 2.1 Hz, 1H), 5.51 (ddd, *J*=16.8, 10.2, 9.3 Hz, 1H). ^{13}C NMR 12.1, 14.6, 25.7, 25.8, 32.9, 37.8, 44.6, 46.3, 54.6, 116.0, 140.2, 213.9.



Interestingly, the regioisomeric ketone **4a-B** obtained by the thermal rearrangement was found to consist of a single diastereomer (by ^{1}H NMR analysis), probably with *syn*-configuration, as judged from the previous studies[3]; **4a-B**, ^{1}H NMR 0.84 (t, *J*=7.2 Hz, 3H), 0.94 (s, 3H), 0.96-1.18 (m, 1H), 1.30-1.55 (m, 2H), 1.54-1.94 (m, 4H), 1.94-2.06 (m, 1H), 2.20-2.48 (m, 3H), 4.94 (dd, *J*=16.8, 2.1 Hz, 1H), 4.99 (dd, *J*=10.2, 2.1 Hz, 1H), 5.42 (ddd, *J*=16.8, 10.2, 9.6 Hz, 1H). ^{13}C NMR 12.6, 20.0, 20.7, 21.1, 27.1, 35.5, 39.4, 49.8, 52.1, 117.0, 137.5, 215.3.

8. Of particular note here is that the Pd-catalyzed rearrangement of each of $\Delta^{1,2}$- and $\Delta^{2,3}$-**1a** once separated gave essentially the same regiochemical outcome.
9. The enol allylic ethers concerned are likely to form *reversibly* via an alcohol addition to **1a** followed by an alcohol elimination from the acetal thus formed.
10. The enol methyl ethers **1b** and **1c** were prepared following the literature procedure: Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410-4412.
11. This dramatic decrease in regioselectivity by the *absence* of γ-substituent might be interpreted as a result of the significant contribution of the *chair-like* transition state $\mathbf{T_C}$, as previously suggested,[3c,d] which is sterically *less* congested than the boat-like counterpart.



T_C

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