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Pd-Catalyzed kinetic resolution of cyclic enol ethers. An enantioselective route to functionalised pyrans†

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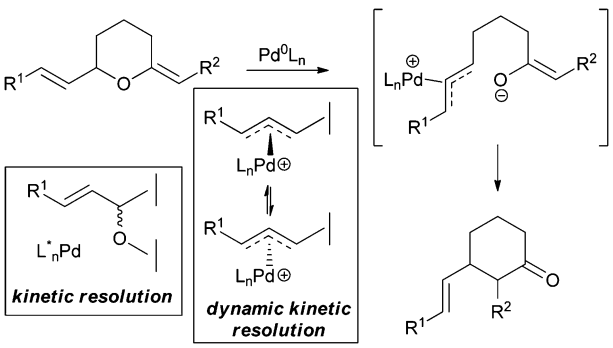
Functionalised cyclic enol ethers can be recovered with high levels of enantiocontrol after an asymmetric catalytic [1,3]-rearrangement reaction. These compounds can be further elaborated to a series of carbo- and heterocyclic products in good yield and with excellent levels of stereocontrol.

Oxygen-to-carbon rearrangement reactions constitute a powerful and attractive means for accessing a range of carbocyclic compounds. Although this field is dominated by [3,3]-sigmatropic rearrangement processes, [1,3]-variants have also proved to be popular, especially in the stereocontrolled synthesis of oxygen heterocycles.[1] To-date, [1,3]-rearrangements have largely relied upon oxocarbenium ion stabilisation to promote the reaction, however, recent studies in our labs have demonstrated that hexacarbonyldicobalt alkyne clusters can also stabilise the putative zwitterionic intermediate, providing access to a range of functionalised carbocycles.[2,3] More recently, we have reported a Pd-catalysed variant of this reaction.[4,5] As outlined in Scheme 1, the Pd-catalyst serves to ionise an allylic enol ether, thereby delivering an intermediate bearing an enolate and a Pd–π-allyl electrophile that undergoes ring closure to provide cyclohexanone products.

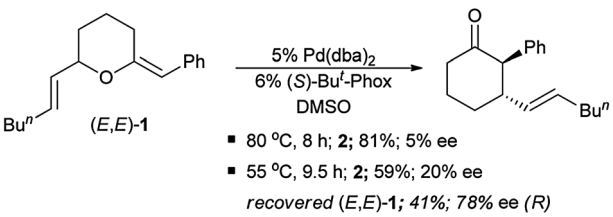
In considering an asymmetric variant of the rearrangement reaction depicted in Scheme 1, several interesting scenarios arise. Specifically, one can envisage that a chiral Pd-catalyst could promote a kinetic resolution (KR) of the racemic enol ether. This outcome would be of synthetic value given the opportunity to chemically differentiate the olefins in these compounds, together with their potential as substrates for [3,3]-rearrangement processes. Alternatively, stereochemical equilibration of the π-allyl complex would offer a dynamic kinetic resolution such that the product enantioselectivity would be determined at the enolate cyclisation step.



Scheme 1 Pd-catalysed [1,3] rearrangement.

We began our investigations into the asymmetric Pd-catalyzed [1,3]-rearrangement by screening several commercially available chiral ligands in the reaction of enol ether (*E*,*E*)-**1**. Amongst several catalyst systems screened, the use of Phox-ligands[6,7] in DMSO offered the most consistent conditions for the smooth rearrangement of enol ether into product ketone. As highlighted in Scheme 2, the rearrangement proceeded in high conversion when conducted at 80 °C over 9 h, but provided the product with low levels of enantiocontrol. When we performed the reaction at lower temperature and analysed the reaction at ~60% conversion, we noted a small increase in product enantioselectivity, however, the starting material was returned in an encouraging 78% ee, with the major enantiomer assigned with the (*R*)-configuration.[8]

The apparent compatibility of this reaction with a kinetic resolution prompted us to explore the scope of this strategy for



Scheme 2 Enantioselective [1,3] rearrangement reaction.

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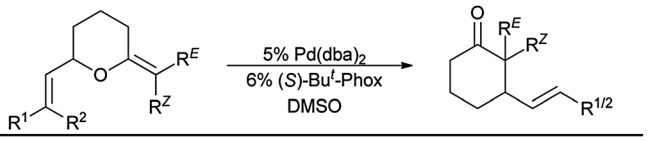
Table 1 Kinetic resolution of cyclic enol ethers

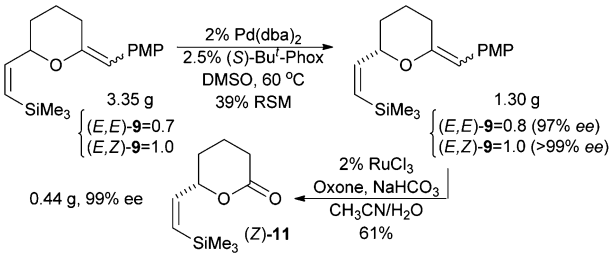


Entry[a]	R^1	R^2	R^E	R^Z	T (°C)	C (%)	RSM ee[b] (%)	k_{fast}/k_{slow}
1	Bu^n	H	H	Ph; **1**	40	63	>99 (*R*)	16.8
2	Bu^n	H	H	PMP; **3**	55	57	75 (*R*)	7.8
3	Bu^n	H	PMP	H; **3**	80	62	72 (*R*)	5.3
4	Bu^n	H	H	PNP; **4**	25	59	7	1.2
5	Bu^n	H	PNP	H; **4**	40	65	8	1.2
6	H	Bu^n	H	Ph; **5**	60	67	90 (*S*)	7.7
7	H	Bu^n	Ph	H; **5**	70	58	34 (*S*)	2.2
8	Bu^t	H	H	Ph; **6**	55	60	93	13.8
9	Bu^t	H	Ph	H; **6**	80	68	92	7.5
10	TMS	H	H	PMP; **7**	40	55	62 (*R*)	5.6
11	H	TMS	H	Ph; **8**	45	58	99 (*S*)	30.5
12	H	TMS	Ph	H; **8**	70	65	98 (*S*)	13.5
13	H	TMS	H	PMP; **9**	50	52	96 (*S*)	64.7
14	H	TMS	PMP	H; **9**	80	55	95 (*S*)	29.0
15	Bu^n	H	Pyr	H; **10**	40	65	98	13.5

[a] PMP: 4-$MeOC_6H_4$. PNP: 4-$O_2NC_6H_4$. 2-Pyr: 2-pyridyl. RSM: recovered starting material. *T*: temperature. *C*: conversion. [b] RSM configurations given in parentheses for selected substrates. See ESI for details.

the synthesis of enantiomerically enriched pyrans and our results are highlighted in Table 1. The kinetic resolution of isomeric enol ether (*E*,*Z*)-**1** proved to be more efficient than the substrate employed in our preliminary studies and furnished the recovered pyran in >99% ee at 63% conversion. We next explored the scope of the aromatic enol ether substituents; a *p*-anisyl group performed marginally less well than Ph, albeit at more elevated reaction temperatures (entries 2 and 3). In contrast, compound **3** bearing a *p*-nitrophenyl group underwent rapid rearrangement and provided almost no enantioselectivity (entries 4 and 5). Switching the allylic ether stereochemistry to the (*Z*)-configuration provided modest to reasonable levels of enantiocontrol whereas more sterically hindered allylic ethers offered generally effective kinetic resolution (entries 8–10). However, the (*Z*)-trimethylsilyl-substituted substrates **7**, **8** proved to be most effective, offering the most efficient kinetic resolutions (entries 11–14). Finally, we found the kinetic resolution to be compatible with heteroaromatic-substituted enol ethers. 2-Pyridyl substituted substrate **9** underwent highly enantioselective rearrangement to afford recovered starting material in 98% ee at 65% conversion (entry 15).

The studies outlined in Table 1 showed that the kinetic resolution of allylic ethers bearing a (*Z*)-silyl group were optimal, providing the corresponding products with excellent levels of enantiocontrol. However, from a practical viewpoint, the need to separate (*E*) and (*Z*)-enol ether isomers prior to KR meant that it was challenging to generate reasonable quantities of material by this route. In order to address this issue, we wanted to establish if the KR could be carried out directly on (*E*)/(*Z*)-enol ether mixtures. Moreover, we wanted to show that the two alkenes could be chemically differentiated. We opted to exemplify this in the context of (*Z*,*E*)/(*Z*,*Z*)-**9**, and our results are shown in Scheme 3. Subjection of an approximately equal mixture of enol



Scheme 3 KR of (*E*,*E*)/(*E*,*Z*)-enol ether isomer mixtures.

ether isomers of **9** to the asymmetric [1,3]-rearrangement allowed an enantiomerically enriched sample of product to be recovered at around 60% conversion on gram scale. The (*E*)/(*Z*)-ratio of enol ethers remained approximately the same suggesting that these isomers react at similar rates under these conditions. Finally, we were able to convert this mixture into enantiomerically pure lactone (*Z*)-**11** after oxidative cleavage of the enol ether, thereby converting the (*E*)/(*Z*)-enol ether mixture into a single compound. Enantiopure lactone (*Z*)-**11** offers the potential for further exploitation in synthesis towards enantioenriched products.

Elucidation of the absolute stereochemistry of recovered starting material from kinetic resolution of selected pyrans shown in Table 1 highlights that (*E*)-allylic ethers are matched with the (*S*)-enantiomer of substrate when (*S*)-But-Phox is employed, thereby allowing recovery of the (*R*)-enantiomer of starting material. In contrast, (*Z*)-allylic ethers appear to react preferentially though the (*R*)-enantiomer. Assuming an irreversible ionization step, we have formulated a working hypothesis to explain this trend, and this is shown in Fig. 1. Helmchen has documented that

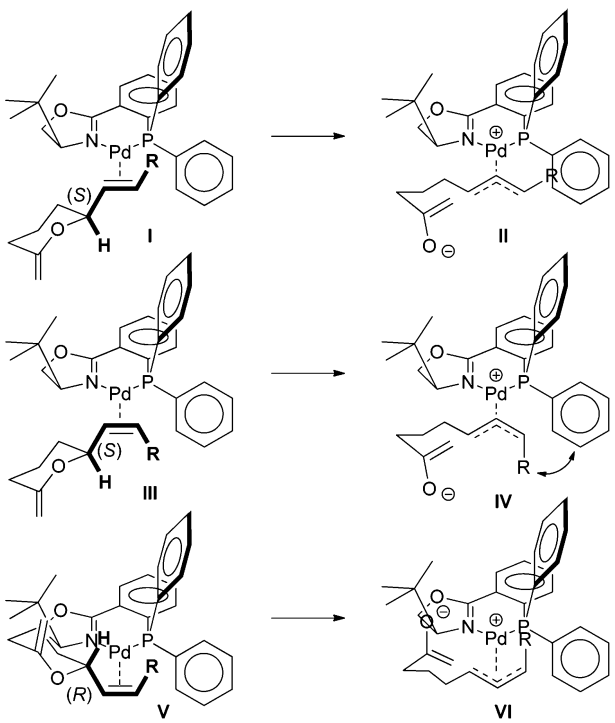
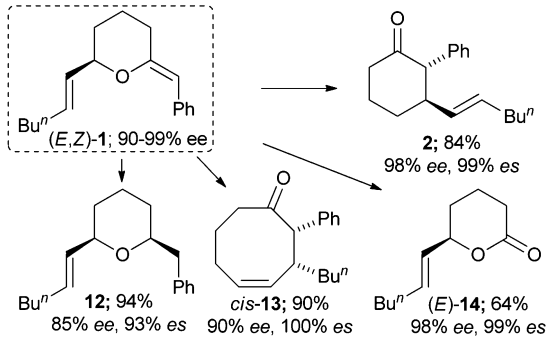


Fig. 1 Rationalising observed enantioselectivity.



Scheme 4 Stereoselective transformations of enantioenriched (*E,Z*)-**1**. Conditions for the synthesis of; **12**: (i) 10 eq. Et_3SiH; (ii) 3 eq. TFA, CH_2Cl_2, −78 °C, 45 min; **13**: μW, 300 W, DMF, 180 °C, 20 min; (*E*)-**14**: 1% $RuCl_3$, 1.5 eq. oxone, 4 eq. $NaHCO_3$ CH_3CN/H_2O (3/1); **2**: 5% $Pd(dba)_2$, 6% (±)-Bu^t-Phox, DMSO, 80 °C, 3 h.

nucleophilic addition to π-allyl palladium complexes bearing Phox-ligands proceeds at the carbon atom *trans*-to the phosphine moiety.[9] Based on the assumption that the oxidative insertion event follows a similar pathway (*i.e.* reverse reaction), we propose that, in the case of substrates bearing a *trans* allylic substituent, complexation and oxidative insertion at the (*S*)-enantiomer *via* **I** would proceed to generate the favoured *exo*-diastereomer **II**. An analogous insertion mode in substrates bearing a (*Z*)-allylic ether (**III**) would however form a π-allyl complex with the alkyl group in the *anti*-position, engendering a steric clash with the face-on presudoequatorial P–Ph moiety in **IV**.[10] This may be better accommodated by reaction through the (*R*)-substrate (**V** → **VI**). DFT studies aimed at providing a better understanding of the underpinning reasons for these selectivities are underway and will be reported in due course.

In order to demonstrate the synthetic potential of these enantioenriched allylic ethers in organic synthesis, we opted to perform a series of transformations on substrate (*E,Z*)-**1**. Specifically, Pd-catalyzed [1,3]-rearrangement of (*E,Z*)-**1** using racemic ligand delivered cyclohexanone **2** in high ee. Furthermore, chemoselective reduction of the enol ether provided *cis*-2,6-disubstituted pyran **12** in high yield.[11] Thermally promoted [3,3]-rearrangement delivered the corresponding cyclooctenone *cis*-**13** with excellent stereocontrol.[12] Finally, selective oxidative cleavage of the enol ether olefin provided lactone (*E*)-**14**. Therefore, the reactions shown in Scheme 4 highlight the potential of these enol ethers to undergo a versatile selection of transformations leading to a range of skeletally distinct products.

Chiral Pd-Phox catalysts offer an effective route to enantioenriched pyran derivatives *via* a kinetic resolution process. These compounds have versatile functionality that can be easily manipulated towards a range of new compounds with high enantiocontrol.

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