

Palladium-Catalyzed [1,3]-O-to-C Rearrangement of Pyrans toward Functionalized Cyclohexanones

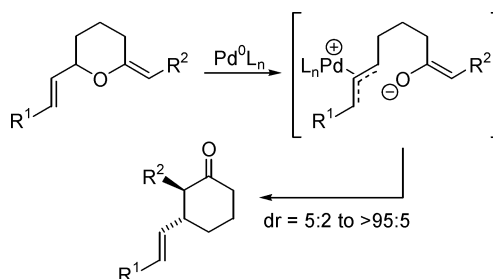
Julien C. R. Brioché,[†] Thomas A. Barker,[†] David J. Whatrup,[‡] Michael D. Barker,[§]
and Joseph P. A. Harrity^{*,§}

Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, S3 7HF,
United Kingdom, GlaxoSmithKline, Tonbridge, Kent, TN11 9AN, United Kingdom, and
GlaxoSmithKline Research and Development, Gunnels Wood Road, Stevenage,
Hertfordshire, SG1 2NY, United Kingdom

j.harrity@sheffield.ac.uk

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ABSTRACT



Functionalized cyclohexanones are prepared from cyclic enol ethers via a Pd-catalyzed [1,3]-O-to-C rearrangement reaction. α -Arylketones are generated with excellent diastereocontrol when basic phosphine ligands are used. In contrast, a Lewis acid is required to promote the rearrangement of the alkyl-substituted enol ether systems.

[1,3]-Oxygen-to-carbon rearrangement processes represent a potentially powerful strategy for synthesis, and have been widely employed since the pioneering studies of Ferrier.¹ The significant majority of these approaches have involved the use of acetal functionality as a prelude to an oxocarbenium ion intermediate. Accordingly, O-based heterocycles are commonly generated by this technique. In an effort to uncover alternative carbocation stabilizing motifs that promote O-to-C rearrangements, we have been exploring the potential of transition metal complexes and have demonstrated that the hexacarbonyldicobalt alkyne cluster can perform effectively in this manner, allowing access to a broad

range of functionalized carbocycles.^{2–4} A significant drawback to this methodology, however, is the requirement of stoichiometric Lewis acid and cobalt carbonyl complex. Therefore, we have turned our attention to exploring the potential of an analogous *but catalytic* [1,3]-O-to-C rear-

[†] University of Sheffield.

[‡] GlaxoSmithKline, Tonbridge.

[§] GlaxoSmithKline, Stevenage.

(1) (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455. (b) For an overview of [1,3]-O-to-C rearrangement reactions see: Meek, S. J.; Harrity, J. P. A. *Tetrahedron* **2007**, *63*, 3081.

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(4) For examples of thermal rearrangements via non-stabilized enolates see: (a) Letsinger, R. L.; Lansbury, P. T. *J. Am. Chem. Soc.* **1959**, *81*, 935. (b) Morrow, G. W.; Wang, S.; Swenton, J. S. *Tetrahedron Lett.* **1988**, *29*, 3441. (c) Swenton, J. S.; Bradin, D.; Gates, B. D. *J. Org. Chem.* **1991**, *56*, 6156.

rearrangement to access cyclic ketones, and report our initial observations herein.

Surprisingly little precedent for such a catalytic transformation can be found in the literature. Nonetheless, Trost and Tsuji independently demonstrated that furan-based enol ethers can be transformed to cyclopentanones in good yield, in the presence of a low-valent palladium source.⁵ This concept was later used by Langer in an intramolecular variant in order to access bicyclo[3.2.1]octan-8-ones.⁶ Notably, all of these examples exploited the intermediacy of a stabilized enolate by appending electron-withdrawing substituents on the enol ether moiety.

We wanted to investigate the rearrangement of nonstabilized pyran enol ethers such as **2** ($R_{E/Z}$ = aryl, alkyl) into 2,3-substituted cyclohexanones **3** using substoichiometric quantities of a transition metal catalyst (Figure 1). A key

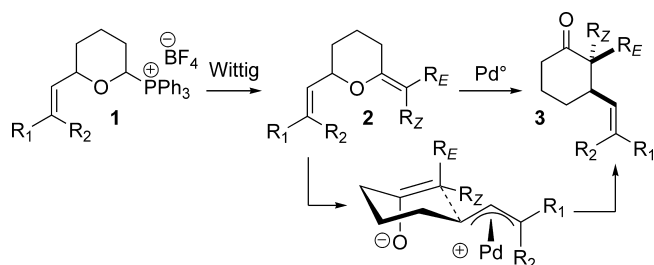


Figure 1. Pd-catalyzed O-to-C rearrangement.

step in this process is the intramolecular Pd-catalyzed allylic alkylation (AA) of a ketone enolate, which is generated in situ. The regio- and diastereoselective Pd-catalyzed AA of ketone enolates remains a challenging transformation, and is often restricted to stabilized ketone enolates or substrates bearing a single point of enolization.⁷ An alternative approach employs functional groups that act as a masked enolate.⁸ In our approach, we wished to exploit a cyclic enol ether as a masked ketone enolate that would be generated after Pd-promoted ionization of an allyl ether. As highlighted in Figure 1, one would expect the stereochemistry of the enol ether alkene moieties to play a role in determining the diastereoselectivity of cyclohexanone product formation, as

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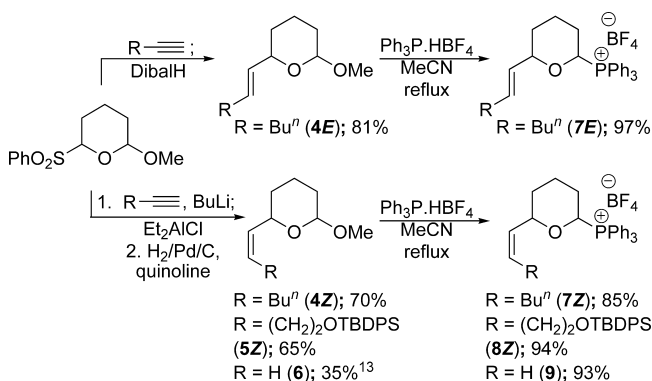
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Trost has shown that Pd-enolates do not isomerize on the time scale of allylic alkylation.⁹ Moreover, we opted to prepare *E*- and *Z*-allyl ethers to establish whether these stereoisomers would converge to a single *E*-olefin substituted cyclohexanone via rapid *syn*-*anti*-isomerization of the Pd- π -allyl complex.¹⁰

The required phosphonium salts were prepared by using a protocol originally developed by Ley, and by analogy to the method reported in our Co-mediated rearrangement study (Scheme 1).^{2,11} Specifically, addition of a vinyl aluminum

Scheme 1. Synthesis of Enol Ether Precursors



species generated from DibalH and terminal alkyne¹² allowed us to access *E*-pyranyl ether substrates. Alternatively, alkylation with preformed alkynylaluminum species, followed by hydrogenation provided *Z*-pyranyl ether substrates. Finally, a terminal alkene substrate was prepared in three steps following a literature procedure.¹³ The Wittig salts **7–9** could be prepared on multigram scale and in high yield by treatment of the respective pyranyl ethers with triphenylphosphonium tetrafluoroborate.

The subsequent Wittig reaction was next investigated by using a range of aromatic and aliphatic aldehydes (Table 1).

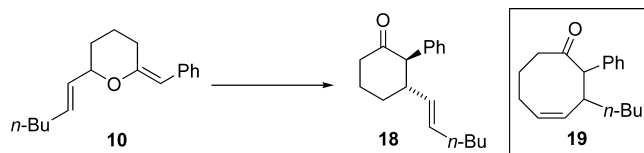
Table 1. Scope of the Wittig Reaction

Reaction scheme showing the synthesis of compounds **10-17** from enol ether **7-9** and aldehyde **R³CHO** using KHMDS.

entry	R ¹	R ²	R ³	yield ^a (<i>E</i> : <i>Z</i>) ^b
1	Bu ⁿ	H	Ph	10 ; 70% (5:1)
2	Bu ⁿ	H	4-MeOC ₆ H ₄	11 ; 80% (4:1)
3	Bu ⁿ	H	4-O ₂ NC ₆ H ₄	12 ; 78% (1:1)
4	Bu ⁿ	H		13 ; 76% (9:1)

5	H	Bu ⁿ	Ph	14 ; 76% (9:1)
6	H	(CH ₂) ₂ OTBDPS	Ph	15 ; 55% (9:1)
7	H	H	Ph	16 ; 70% (9:1)
8	H	H	(CH ₂) ₂ OBn	17 ; 78% (9:1)

^a Yield of isolated product. ^b Refers to enol ether stereochemistry.

Table 2. Optimization of the Rearrangement with Aryl Enol Ether Substrates

entry	catalyst (mol %)	additive (mol %)	conditions	yield ^a (trans:cis) ^b
1	Pd(PPh ₃) ₄ (15)		toluene, 55 °C, 20 h	0% (–)
2	Pd(PPh ₃) ₄ (15)	Zn(OTf) ₂ (50)	toluene, 110 °C, 20 h	27% (>95:5)
3	Pd(PPh ₃) ₄ (15)	Et ₂ AlCl (50)	toluene, 55 °C, 5 h	40% (>95:5)
4 ^c		Et ₂ AlCl (100)	toluene, 55 °C, 20 h	0% (–)
5	Pd(PPh ₃) ₄ (10)	Et ₂ AlCl (50)	MeCN, 55 °C, 20 h	60% (4:1)
6	Pd(PPh ₃) ₄ (10)		MeCN, 55 °C, 20 h	55% (70%) ^d (2:1)
7	Pd(OAc) ₂ (10) PBu ⁿ ₃ (60)		MeCN, 55 °C, 20 h	82% (>95:5)

^a Yield of isolated product. ^b Refers to stereochemistry of the cyclohexanone 2,3-substituents. ^c Compound **19** isolated in 47% yield. ^d Reaction performed over 48 h.

In all cases, the pyran enol ethers were obtained in moderate to good yield with generally high *E*:*Z* ratios.

With the required pyran-based enol ethers in hand, we turned our attention to the rearrangement transformation; our results are outlined in Table 2. We first tried Pd(PPh₃)₄, which has been reported by Trost to catalyze similar transformations,⁵ but only trace amounts (<5%) of **18** were observed (entry 1). We next decided to employ Lewis acids in an attempt to promote the ionization step. A preliminary screening study highlighted Zn(OTf)₂ and Et₂AlCl as potentially useful promoters, providing **18** in 27% and 40% yields, respectively (entries 2 and 3). At this stage, we decided to confirm that the Lewis acid did not itself mediate the O-to-C rearrangement in a similar manner to that reported by Rovis;¹⁴ only Claisen product **19** was isolated in this case in 47% yield (entry 4). We envisaged that the ionization step could be further facilitated by the use of a polar solvent. Indeed, when the reaction was carried out in MeCN we were delighted to isolate **18** in improved yield (entry 5). This observation was surprising given that the Lewis basic solvent would be expected to attenuate the effects of the Lewis acid. Accordingly, we conducted the rearrangement in the absence of Lewis acid and were pleased to find that cyclohexanone **18** was isolated in good yield as a 1:2 cis:trans mixture, within the same reaction time (entry 6). Finally, we explored the use of more electron-rich phosphines and identified PBuⁿ₃

as an efficient ligand system, providing *trans*-cyclohexanone **18** in high yield with good diastereocontrol.

The optimized conditions were applied to freshly prepared aryl enol ether substrates (Table 3). Electron-rich (entry 1)

Table 3. Pd-Catalyzed O-to-C Rearrangement of Aryl Enol Ethers

The reaction scheme shows the O-to-C rearrangement of an aryl enol ether with substituents R¹ and R² to a cyclohexanone with substituents R¹ and R². The reaction conditions are Pd(OAc)₂ (10 mol %), P(Buⁿ)₃ (60 mol %), MeCN, 55 °C, 24 h. The products are labeled 18, 20-24.

entry	R ¹	R ²	yield ^a (trans:cis) ^b
1	(<i>E</i>)-Bu ⁿ	4-MeOC ₆ H ₄	20 ; 66%; >95:5
2	(<i>E</i>)-Bu ⁿ	4-O ₂ NC ₆ H ₄	21 ; 73%; >95:5
3 ^c	(<i>E</i>)-Bu ⁿ		22 ; 73%; >95:5
4	(<i>Z</i>)-Bu ⁿ	Ph	18 ; 84%; >95:5
5	(<i>Z</i>)-TBDPSO(CH ₂) ₂	Ph	23 ; 87%; >95:5
6	H	Ph	24 ; 84%; >95:5

^a Yield of isolated product. ^b Refers to stereochemistry of the cyclohexanone 2,3-substituents. ^c 100% PBuⁿ₃ employed in this case.

and electron-deficient (entry 2) aryl enol ethers were found to rearrange into their corresponding cyclohexanones in moderate to good yield with excellent *trans*-diastereoselectivity. The chemistry could also be extended to provide α -3-pyridyl-substituted cyclohexanones (entry 3). As we expected, pyran enol ether **14** and **15** gave the corresponding cyclohexanones having *E*-stereochemistry at the alkene moiety in good yield and excellent *trans*-diastereoselectivity (entries 4 and 5). Finally, terminal alkene-substituted enol ether **16** was also found to rearrange to *trans*-cyclohexanone **24** selectively and in very good yield (entry 6).

Surprisingly, attempts to perform the [1,3]-rearrangement of alkyl-substituted enol ether **17** failed to furnish any of

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(10) (a) Ogasawara, M.; Takizawa, K.-I.; Hayashi, T. *Organometallics* **2002**, *21*, 4853. (b) Solin, N.; Szabó, K. *J. Organometallics* **2001**, *20*, 5464, and references cited therein.

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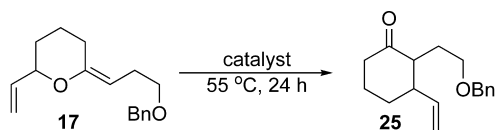
(12) Elzner, S.; Maas, S.; Engel, S.; Kunz, H. *Synthesis* **2004**, 2153, and references cited therein.

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the desired cyclohexanone product **25**, but gave complex mixtures that appeared to consist of acyclic polyolefinic material (Scheme 2). The formation of such material could

Scheme 2. Rearrangement of Aliphatic Enol Ethers^a



10% Pd(OAc)₂, 60% PBuⁿ₃, MeCN; 0%

10% Pd(OAc)₂, 40% DavePhos, 50% Et₂AlCl, toluene; 64% 5:2

^a DavePhos = 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl.

be explained by the higher basicity of the in situ generated enolate ($pK_a \approx 25$),¹⁵ which could enhance an elimination of the Pd- π -allyl complex intermediate.¹⁶ We therefore performed a further optimization study for these substrates and found that the combination of arylphosphine ligands and Lewis acid promoter allowed the cyclohexanone to be isolated in high yield, albeit with disappointing levels of diastereocontrol.¹⁷ The requirement of a Lewis acid in this case is intriguing and it may be that this serves to both activate the pyran ring as well as decrease the basicity of the in situ generated enolate. The difference in stereochemical

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(16) For studies on the mechanism of elimination reactions of Pd π -allyl complexes towards 1,3-dienes see: Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956.

(17) The diastereomers of **25** could not be separated thereby preventing a clear assignment of the identity of the major stereoisomer in this mixture.

outcome of the [1,3] rearrangement reactions of aryl-substituted enol ethers **10–16** and substrate **25** is also noteworthy. Indeed, we had anticipated from our reaction design in Figure 1 that enol ether stereochemistry would be transmitted through to the cyclohexanone product whereby the *E*-enol ethers would provide *cis*-2,3-disubstituted-cyclohexanones, rather than the *trans* products obtained. While we are not at present able to provide a detailed stereochemical rationale for these reactions, it appears that product epimerization is at least partially responsible for the diastereocontrol observed in the reactions highlighted in Table 3.¹⁸

In summary, we have developed a Pd-catalyzed O-to-C rearrangement to access cyclohexanones from pyran enol ethers under mild conditions. The transformation was found to proceed in the presence of electron-rich phosphine ligands. The rearrangement of aromatic pyran enol ethers with Pd(OAc)₂/PBuⁿ₃ as catalyst in MeCN seems to be a general method and usually gives the cyclohexanone products in high yield with excellent levels of *trans*-selectivity. Alternative ligand systems are necessary when employing aliphatic enol ether substrates, and studies are underway to improve the diastereoselectivity of these particular processes.

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Supporting Information Available: Full experimental details for the syntheses reported. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) Subjection of a 1.2:1 diastereomeric mixture of *trans*- and *cis*-**18** to the rearrangement conditions (10% Pd(OAc)₂, 60% PBuⁿ₃, MeCN, 55 °C, 18 h) resulted in epimerization to a 5:1 mixture of *trans*:*cis* **18**.