

A Novel Prins Cyclization through
Benzylic/Allylic C–H ActivationBinxun Yu,[†] Tuo Jiang,[†] Junpeng Li,[†] Yingpeng Su,[†] Xinfu Pan,[†] and
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ABSTRACT



A step-economic method to construct the tetrahydropyran ring, involving sequential benzylic/allylic C–H bond activation via DDQ oxidation and nucleophilic attack of an unactivated olefin, is described. The equatorial-trisubstituted Prins products are obtained from benzylic and allylic homoallylic ethers with high yield and stereochemical fidelity.

The Prins cyclization¹ has been widely recognized as a powerful tool to generate multisubstituted tetrahydropyrans,² an important section contained in a large number of natural

products and medicinally useful agents. Variation and modification toward this transformation have been highlighted in investigations.³ Among these methods, the segment-coupling Prins cyclization developed by Rychnovsky⁴ is considered as an elegant supplement in that it could avoid the side-chain exchange and the partial racemization observed in some of the direct alcohol–aldehyde cyclization protocols.^{3m} This method requires the key cyclization precursor to be an α -acetoxy ether, which is prepared by reductive acetylation of a homoallylic ester.⁵ However, aryl ester and α,β -unsaturated ester failed to undergo reduction and in situ acetylation of esters and further to complete the Prins cyclization (eq 1). Clearly, there is an urgent need to overcome this limitation and to extend the utility of the segment-coupling Prins cyclization. Herein, we report a novel segment-coupling Prins cyclization based on a process that C–H bond activation and intramolecular nucleophilic attack

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(1) For reviews on the Prins cyclization, see: (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *52*, 505. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. (c) Snider, B. B. In *The Prins Reaction and Carbonyl Ene Reactions*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527–561. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143.

(2) For a recent review on the synthesis of tetrahydropyran rings, see: Santos, S.; Clarke, P. A. *Eur. J. Org. Chem.* **2006**, 2045.

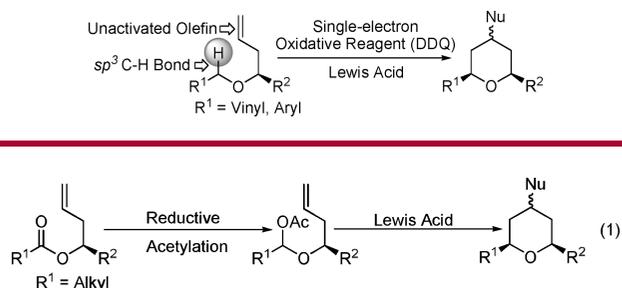
(3) For recent work on Prins cyclization methodology, see: (a) Miranda, P. O.; Ramirez, M. A.; Martin, V. S.; Padron, J. I. *Org. Lett.* **2006**, *8*, 1633. (b) Lee, C.-H. A.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 1641. (c) Overman, L. E.; Velthuisen, E. J. *J. Org. Chem.* **2006**, *71*, 1581. (d) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, *40*, 5097. (e) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939. (f) Bolla, M. L.; Patterson, B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 16044. (g) Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc.* **2004**, *126*, 8652. (h) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216. (i) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662. (j) Hart, M. L.; Bennet, C. E. *Org. Lett.* **2003**, *5*, 1499. (k) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429. (l) Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Bernejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979. (m) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577.

(4) (a) Rychnovsky, S. D.; Hu, Y. Q.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271. (b) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (c) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. (d) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (e) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904.

(5) (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191.

of olefin can occur in tandem to construct the tetrahydropyran unit (Scheme 1).

Scheme 1. Strategy for Prins Cyclization through Benzylic/Allylic C–H Activation



The discovery and development of methods to functionalize selectively sp^3 C–H bonds represent a long-standing goal in organic synthesis.⁶ The single-electron oxidative process has been a player in this field, and recently, several reports have highlighted the utility of DDQ to promote chemo- and regioselective C–H bond functionalization.⁷ Recently, DDQ-mediated oxidative annulation reaction, in which the enol acetate serves as nucleophile, has been reported by Floreancig's group.^{7h,i} Inspired by these studies, we postulated that benzylic or allylic sp^3 C–H bonds could be directly activated via a relay-activated procedure and that both single-electron oxidative reagent (DDQ) and Lewis acid generate highly activity oxonium ion precursor, followed by π -nucleophilic attack of an unactivated olefin, which leads to the tetrahydropyran structure via a Prins cyclization procedure.

Following this designed strategy, we chose the *p*-methoxybenzyl (PMB)-protected homoallylic alcohol **1a** as the standard substrate in our efforts to find an effective relay-activated condition for this type of Prins cyclization. As shown in Table 1, several Lewis acids were screened in the

Table 1. Optimization of the Prins Cyclization of Homoallylic Ether **1a** through C–H Activation^a

entry	Lewis acid	Nu ⁻	equiv	T (°C)	time (h)	yield ^b (%)
1	SnBr ₄	Br	1.1	–20 to rt	1	70
2	SnBr ₄	Br	1.1	rt	0.5	89
3	TiBr ₄	Br	1.1	–20 to rt	0.5	dec
4	TiCl ₄	Cl	1.1	–20 to rt	0.5	dec
5 ^c	InCl ₃	Cl	1.1	rt	6	55
6	AlBr ₃	Br	1.1	rt	0.5	trace
7	no acid			rt	6	0

^a All of the reactions were performed on a 1 mmol scale in DCM (0.1 M). ^b Yield of isolated product. ^c Accompanied by 32% of *p*-methoxybenzaldehyde byproduct. DCM = dichloromethane.

presence of DDQ as C–H bond activation reagent, and it was discovered that the SnBr₄/DDQ/CH₂Cl₂ system provided the desired tetrahydropyran product **2a** at ambient temperature with an excellent yield and without detectable epimerization at the C4-position. Addition of 4 Å molecular sieves was believed to be of necessity since it could effectively prevent the hydrolysis of oxonium ion.⁸ Meanwhile, we found that InCl₃ also induced the cyclization of homoallyl ether to afford the corresponding 4-chlorotetrahydropyran, but the reaction was much slower and a certain amount of decomposed product (*p*-methoxybenzaldehyde) was obtained even in the presence of 4 Å MS. Other Lewis acids (e.g., TiCl₄, TiBr₄, and AlBr₃) resulted in only trace conversion or decomposition of the starting material. Finally, no desired product was observed with a lack of any Lewis acid.

Efforts toward investigating the scope of the electron-rich benzyl substrate are outlined in Table 2. Under the optimized conditions, a wide range of aromatic substrates underwent reactions with high isolated yields and specified diastereoselectivities (Table 2, entries 1–11). When the unsubstituted benzyl ether **1b** was subjected to DDQ/SnBr₄/4 Å MS, the cyclized product **2b** was formed in moderate yield, although with a relatively slower rate (Table 2, entry 2). As revealed in entries 3–7, a variety of methyl- or methoxyl-substituted benzyl ethers (**1c**, **1d**, **1e**, **1f**, and **1g**) could be successfully utilized in this transformation. These results clearly indicated that the reaction activities were consistent with the electronic effect of the benzyl ring: the lower oxidation potential and the greater capacity for stabilizing the intermediate cation. In the cases of the moderate electron-rich benzyl ether **1h** and the 1-naphthyl methyl ether **1i**, the reactions provided products **2h** and **2i** in satisfactory yields. Entry 10 demonstrated a silyl ether **1j** could be tolerated even when strong Lewis acid was added to the reaction. Toward regiochemistry of this transformation, **1k** proved to be a suitable substrate for the cyclization in that only alkoxybenzyl hydrogen prefer to be activated and offer a similar skeleton precursor of (±)-centrolobine.⁹

Next, we turned our attention to allylic ethers to expand the scope of potential substrates (Table 3). As anticipated, although allylic hydrogen is relatively inert toward single-electron oxidative condition than benzylic hydrogen, successful cyclization examples were observed with uniformly exclusive diastereoselectivity. Trisubstituted alkene **1l** and phenylalkene **1p** were found to result in an increase in both

(6) For recent reviews and commentary, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422. (c) Murai, S. *Adv. Synth. Catal.* **2003**, *345*, 1033.

(7) (a) Xu, Y.-C.; Kohlman, D. T.; Liang, S. X.; Eriksson, C. *Org. Lett.* **1999**, *1*, 1599. (b) Ying, B.-P.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y.-C. *Org. Lett.* **2004**, *6*, 1523. (c) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949. (d) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. (e) Wang, L.; Seiders, J. R., II; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596. (f) Seiders, J. R., II; Wang, L.; Floreancig, P. E. *J. Am. Chem. Soc.* **2003**, *125*, 2406. (g) Jung, H. H.; Seiders, J. R., II; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8464. (h) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184. (i) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567.

(8) When 4 Å MS was not used to remove water that might be present in the reaction mixture, an amount of *p*-methoxybenzaldehyde was observed by TLC.

(9) For a recent synthesis of centrolobine via the Prins cyclization, see: Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 4491, and ref 4d.

Table 2. Cyclization of Benzyl Homoallylic Ethers^a

entry	substrate	product ^b	t (h)	yield (%)
1			0.5	89
2			5	70
3			2	85
4			3	80
5 ^c			0.25	90
6			0.5	87
7			0.25	92
8			0.5	95
9			4	84
10			1	68
11			1	75

^a All reactions were carried out under the optimal conditions reported in the text except entry 5. ^b A single diastereomer was observed by NMR analysis of the crude material. ^c The reaction was conducted at 0 °C. TBS = *tert*-butyldimethylsilyl; Cy = cyclohexyl.

the yield and the reaction rate than other substrates. Disubstituted allylic ethers **1m** and **1o** reacted smoothly to form desired products **2m** and **2o** in satisfactory yields, while the terminal alkene product **2n** was obtained via elevated temperature and prolonged reaction time.

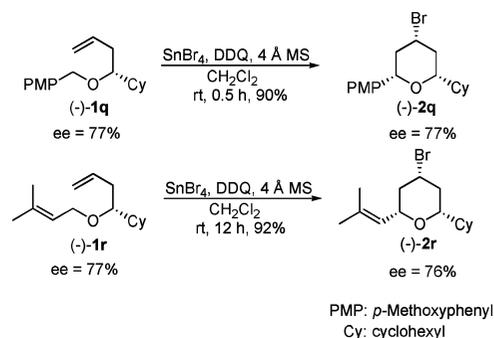
To determine whether racemization occurs in this procedure, the optically active homoallylic ethers **1q** and **1r** were prepared and underwent standard cyclization conditions to give the expected products **2q** and **2r** with high stereochemical fidelity (Scheme 2). It was obvious that this transforma-

Table 3. Cyclization of Allyl Homoallylic Ethers^a

entry	substrate	product ^b	t (h)	yield (%)
1			12	91
2			20	83
3 ^c			40	70
4			30	80
5			12	88

^a All reactions were carried out under the optimal conditions reported in the text except entry 3. ^b A single diastereoisomer was observed by NMR analysis of the crude material. ^c The reaction was conducted at 40 °C.

tion offered similar advantages for the segment-Prins cyclization of Rychnovsky's group that avoided the racemization

Scheme 2. Chirality Transfer in the Prins Cyclization through C–H Activation

mediated by oxonia-Cope rearrangement and allyl transfer.^{10,11}

On the basis of these results, a possible mechanism for this new transformation is proposed in Figure 1. The first step involves a single electron transfer from the arene or alkene to DDQ to generate a radical cation and DDQ radical anion, followed by hydride abstraction from the benzylic or allylic position of the substrate, to afford a charge-transfer complex **A**, in which the positive charge can serve as an oxonium ion. However, the oxonium ion is likely too weak in electrophilicity to be captured by the terminal olefin. Upon treatment with strong Lewis acid SnBr₄, the resulting

(10) (a) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939. (b) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640.

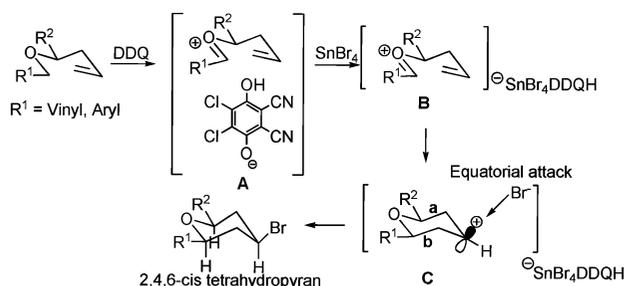
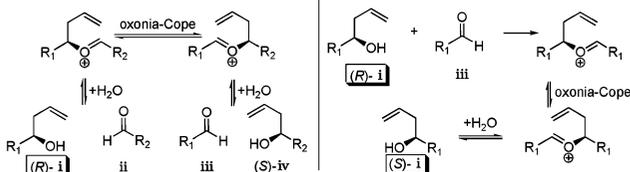


Figure 1. Proposed reaction pathway (see text for details).

tin-“ate” oxonium ion **B**, with better activity than the charge-transfer complex **A**, undergoes rapid C–C bond formation and generates cyclic intermediate **C** through a chairlike transition state. Subsequently, when the carbocation was trapped by bromide ion, the desired 4-bromotetrahydropyran is afforded.

(11) Allyl transfer processes can lead to a loss in optical activity for Prins cyclization reactions (see the mechanism below). Racemization relies on the presence of water. Direct Prins cyclizations utilizing homoallylic alcohols and aldehydes generate water upon condensation. Segment-coupling Prins cyclizations developed by Rychnovsky's group, however, do not generate water in situ and therefore can be used to avoid racemization.

Allyl Transfer Mechanism:



In all aforementioned examples, only the 2,4,6-*cis* configuration products were observed, as confirmed by NOE experiments. This result that the all three substituents on the tetrahydropyran ring occupy *equatorial* positions is consistent with Alder's computational calculation.¹² Tetrahydropyran cation **C** has increased stability due to delocalization in that bonds **a** and **b** and the lone pair on oxygen are in alignment with the empty *p* orbital. The optimal geometry for delocalization places the hydrogen at C4 in pseudoaxial geometry, thereby favoring nucleophilic trapping from an equatorial trajectory.

In summary, this paper describes a novel Prins cyclization with good substrate scope for both benzyl and allyl homoallylic ethers. This transformation proceeds via one single-electronic oxidation C–H bond activation step, followed by the attack of intramolecular unactivated olefin to form 2,4,6-*cis*-substituted tetrahydropyran. From the idea of step economy, our strategy is focus on endeavors to avoid unnecessary steps in the skeleton-forming process and attain a rapid increase in complexity of target structures. Further investigations toward the related reactions are currently underway.

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Supporting Information Available: Experimental details and ¹H and ¹³C NMR spectra of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960.