OL Organic Letters

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Dehydrative Re_2O_7-Catalyzed Approach to Dihydropyran Synthesis

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03526 Read Online

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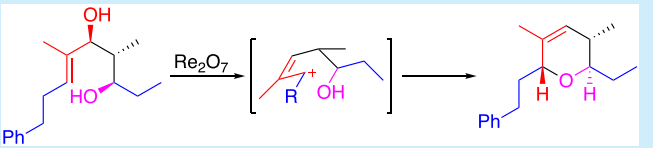
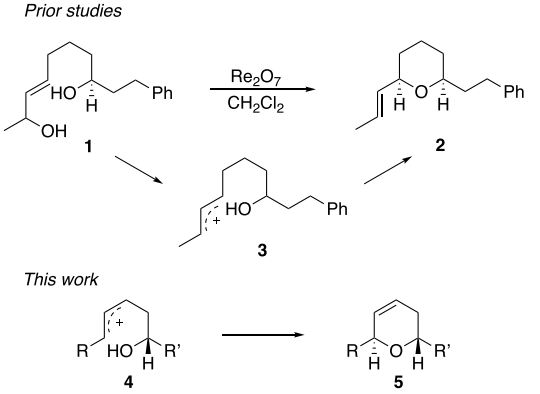
ABSTRACT: Monoallylic 1,3- and 1,5-diols undergo Re_2O_7-mediated ionization to form allylic cations that engage in cyclization reactions to form dihydropyran products. The reactions give the 2,6-*trans*-stereoisomer as the major products as a result of minimizing steric interactions in a boat-like transition state. The results of these studies are consistent with cationic intermediates, with an intriguing observation of stereochemical retention in one example.



Catalytic dehydrative routes to prepare heterocycles provide efficient access to important units from structurally simple starting materials with minimal waste generation. Numerous approaches have been developed to achieve this objective from allylic alcohol substrates, based on both soft[1] and hard[2] Lewis acids. As part of our exploration of the synthetic utility of oxorhenium catalysis,[3] we have developed catalytic, dehydrative routes to a number of heterocyclic structures from allylic alcohols in the presence of Re_2O_7 or $HOReO_3$.[4] These processes, as exemplified by the conversion of **1** to **2** in Scheme 1, proceed through ionization of the allylic alcohol followed by

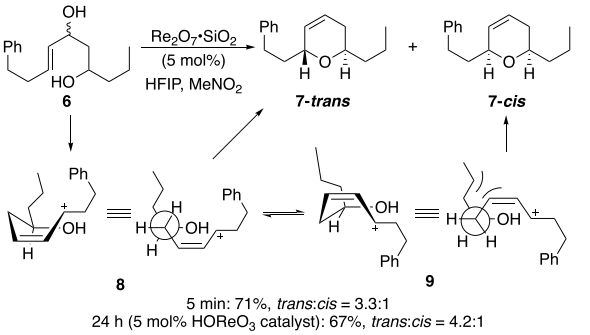
Scheme 1. Re_2O_7-Catalyzed Dehydrative Cyclizations



trapping by a tethered nucleophile at the proximal terminus of the resulting allylic cation (**3**), resulting in the formation of an alkenyl-substituted heterocycle. An alternative reaction pathway is illustrated by the conversion of **4** to **5**, in which the nucleophile reacts with the distal end of the allylic cation to form a heterocycle with an endocyclic alkene. The dihydropyrans that can be accessed through this transformation are subunits in several natural products[5] and have frequently been used as precursors to functionalized tetrahydropyrans.[6] This manuscript describes the development of dihydropyran syntheses from monoallylic 1,3- or 1,5-diols, the observation of 2,6-*trans* stereoisomers as the major products,[7] and the demonstration of a unique S_Ni cyclization pathway.

This process was initially demonstrated through the cyclization of monoallylic 1,3-diol **6**, prepared as a mixture of diastereomers, to dihydropyran **7** in the presence of 5 mol % $Re_2O_7{\cdot}SiO_2$ (Scheme 2). The reaction proved to be sensitive to

Scheme 2. Demonstration of Concept



solvent. Employing CH_2Cl_2, the solvent that was utilized for previous tetrahydropyran-forming reactions, provided a low yield of **7** with substantial diene formation through an E1 pathway being observed. Hexafluoroisopropyl alcohol (HFIP), which we have used for other dehydrative processes, led to a more efficient transformation though the yield was still moderate. Inspired by Hall's use of HFIP/$MeNO_2$ mixtures in dehydrative processes,[8] we ultimately found that the reaction proceeded in 71% yield as a 3.3:1 mixture of *trans*- and *cis*-

Received: October 22, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03526
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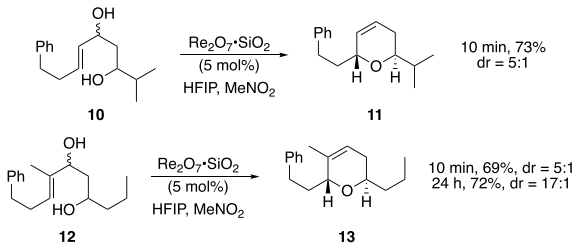
isomers in a 9:1 mixture of HFIP and $MeNO_2$ within 5 min at rt. An explanation for the reproducible improvement that results from the addition of a small amount of $MeNO_2$ remains elusive. Extending the reaction time to 24 h resulted in a moderate increase in the *trans* to *cis* ratio, indicating that the *trans*-isomer is preferred both kinetically and thermodynamically, providing a stereochemical complement to our previously reported tetrahydropyran-forming reactions. Perrhenic acid ($HOReO_3$) proved to be a competent catalyst for the prolonged exposure study, indicating that it is likely to be the true catalyst in these processes. This catalyst, being a liquid, is easier to handle than Re_2O_7 under humid conditions. The kinetic stereochemical outcome for this reaction arises from the requirement that it proceed through a boat-like transition state due to the need to generate the *cis*-alkene in the product. Intermediate **8**, leading to *trans*-**7**, is preferred over **9**, the precursor of *cis*-**7**, because of the lower degree of torsional strain. This can be seen in the Newman projections of the intermediates. The slight thermodynamic preference for the *trans*-isomer can be attributed to the moderate degree of $A^{1,2}$-strain[9] between a pseudoequatorial alkyl group and the alkenyl hydrogen of *cis*-**7**. This reaction can be conducted on >1 mmol scale with only a moderate decrease in yield (58%). Notably, the results of this reaction contrast the $BF_3{\cdot}OEt_2$-catalyzed *cis*-selective processes of similar substrates reported by Hanessian.[2c] We exposed **6** to $BF_3{\cdot}OEt_2$ and observed only a low yield of **7** with the *trans*-isomer again being favored. Additionally we exposed *trans*-**7** to $BF_3{\cdot}OEt_2$ and did not observe isomerization.[10] A closer examination of the substrates in the Hanessian work revealed the presence of a benzyloxy group adjacent to the nucleophilic hydroxy group that we propose can engage in an electrostatic attraction, rather than a steric repulsion, with the allylic cation in *cis*-selective transition states related to **9**.

The hypotheses regarding the kinetic and thermodynamic preferences for the formation of the *trans*-isomer were examined as shown in Scheme 3. The assumption that torsional strain

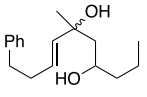
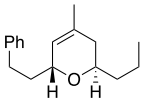
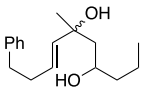
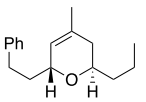
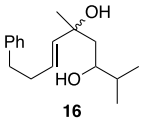
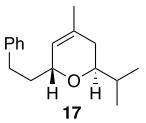
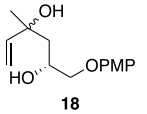
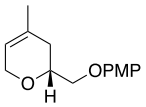
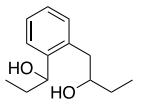
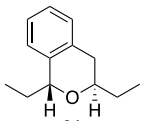
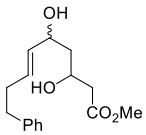
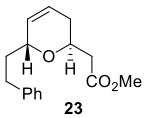
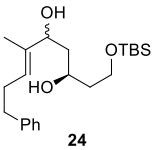
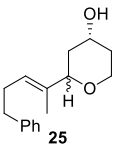
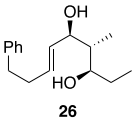
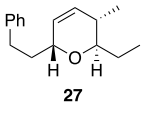
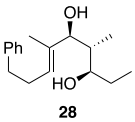
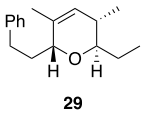
Scheme 3. Tests of Kinetic and Thermodynamic Control



mitigation is the source of the difference in transition state energies was tested by increasing the bulk of the side chain on the nucleophilic alcohol group. Isopropyl-containing substrate **10** reacted with $Re_2O_7{\cdot}SiO_2$ to form **11** in 73% yield as a 5:1 mixture favoring the *trans*-isomer after 10 min. This is consistent with an enhanced *gauche* interaction between the branched chain and the incipient ring. The thermodynamic preference was explored by increasing the $A^{1,2}$-strain that would be encountered in the *cis*-isomer. This was achieved by exposing trisubstituted alkene substrate **12** to $Re_2O_7{\cdot}SiO_2$ to produce **13**. The *trans*-isomer was favored in a 5:1 ratio at a reaction time of 10 min, and in a 17:1 ratio after 24 h.

These results provided the basis for an examination of the scope of the reaction (Table 1). Tertiary alcohols are suitable substrates for the process, as shown by the conversion of **14** to

Table 1. Scope Studies[a]

entry[b]	substrate	product	yield (%)[c]	dr[d]
1[e]	 **14**	 **15**	68	1.5:1
2[e,f]	 **14**	 **15**	79	2:1
3	 **16**	 **17**	79	1.7:1
4	 **18**	 **19**	62	*g*
5	 **20**	 **21**	74	5:1
6	 **22**	 **23**	55	1:1
7	 **24**	 **25**	59	1.5:1
8	 **26**	 **27**	47	*h*
10	 **28**	 **29**	77	*h*

[a]The reactions were conducted with the substrate in HFIP and $MeNO_2$ (9:1, 0.1 M) and $Re_2O_7{\cdot}SiO_2$ (5 mol %) at rt for 10 min, unless otherwise noted. [b]Schemes for the syntheses of starting materials and spectral data are available in the Supporting Information. [c]Combined yield of both stereoisomers. [d]Determined by integrating the ratios of peaks in crude ^1H NMR spectra. Stereoisomers were assigned based on analogy to observed chemical shifts and coupling constants in **7** or through NOESY analyses. [e]Reaction was run with $HOReO_3$. [f]Reaction was run for 24 h. [g]No loss of enantiomeric purity was observed. [h]A single stereoisomer was isolated.

15 (entry 1), though the diastereoselectivity is somewhat lower in comparison to the cyclization of the corresponding secondary alcohol. Prolonging the reaction time to 24 h, as before, led to moderately higher diastereocontrol (entry 2). The substituent at

https://dx.doi.org/10.1021/acs.orglett.0c03526
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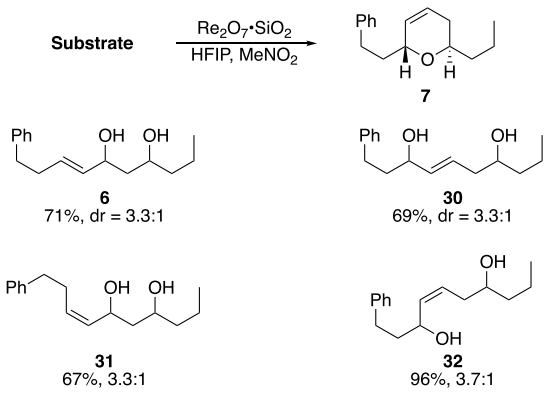
the 4-position appears to inhibit stereochemical equilibration by utilizing steric interactions to induce a conformation that promotes rapid reclosure from cationic intermediates. Interestingly, this trisubstituted alkene substitution pattern did not show an increase in kinetic diastereocontrol when the propyl group was replaced by an isopropyl group, though the yield was improved (entry 3). We postulate that the cation can form so readily from this substrate due to its enhanced stability that the cisoid allylic cation can be formed competitively, leading to an alternate pathway 2,6-*cis*-stereoisomer formation. This additional cation stabilization allows for the synthesis of monosubstituted tetrahydropyrans, as seen in the conversion of **18** to **19** (entry 4). Exposing enantiomerically enriched **18** to the reaction conditions did not result in a loss of stereochemical integrity in **19**. Benzylic alcohols are suitable substrates for the process as seen in the conversion of diol **20** to isochroman **21** (entry 5). Functionalized side chains can be incorporated into the substrates, as seen in the cyclization of **22** to **23** (entry 6), though the reactions proceed somewhat less efficiently due to inductive mitigation of the alcohol's nucleophilicity and allow E1 to become a competitive pathway. The conversion of **24** to **25** (entry 7) shows that *exo*-cyclizations of the allylic cation intermediate are faster than *endo*-cyclizations, even when the nucleophile for the *exo*-cyclization is protected as a silyl ether. Multiple stereocenters can be incorporated into cyclization substrates. These stereocenters, when matched to form a diequatorial relationship in the product, can deliver products with exceptional diastereoselectivity, as seen in the conversions of **26** and **28** to **27** and **29**, respectively, in entries 8 and 9.

The allylic cation intermediates in this study could, in principle, be formed from four different precursors that arise from two alcohol regioisomers and two alkene geometries. We sought to determine if the efficiency of the cyclization reactions was influenced by the starting material isomer. Therefore, we prepared compounds **30**−**32** as diastereomeric mixtures and subjected them to the standard cyclization conditions to yield **7**. The results were compared to those from the cyclization of **6** (Scheme 4). These studies showed that the cyclization yields from **6**, **30**, and **31** were very similar and that the diastereoselectivity was identical, though the cyclization of **32** was significantly more efficient and moderately more stereoselective. Therefore, accessing the requisite *cis*-geometry for the allylic cation is equally facile from either alkene isomer for 1,3-diol substrates and for the *trans*-1,5-diol. The superior efficacy of *cis*-1,5-diol **32** in the process, however, suggests that the mechanism for this substrate might be unique, and proceed through either an S_N2 pathway or, more likely, an S_N1 pathway via a tight ion pair[11] due to its preorganization for cyclization.

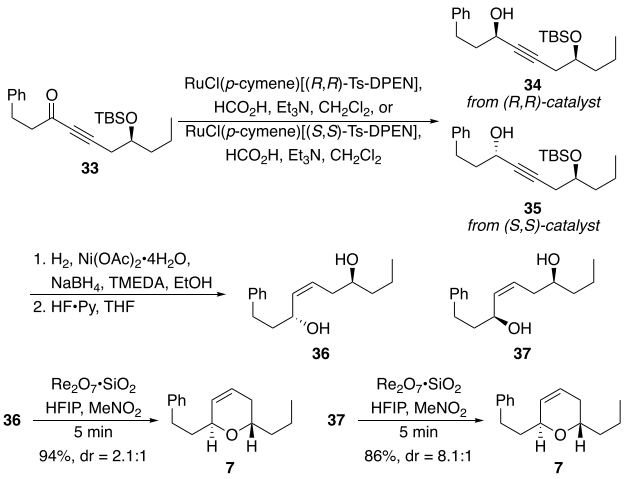
Scheme 4. Consequences of Allylic Cation Precursor Structure[a]



[a]All reactions were run for 5 min with 5 mol % catalyst.

We tested the ion pairing hypothesis by preparing individual diastereomers of **32**. This was achieved by conducting stereocomplementary Noyori reductions[12] on ketone **33**, prepared from enantiomerically pure epichlorohydrin, followed by alkyne reduction[13] and deprotection to form substrates **36** and **37** (Scheme 5). The absolute stereochemical orientation of

Scheme 5. Cyclization Reactions of 1,5-Diol Diastereomers



all stereocenters was confirmed by Mosher ester analysis,[14] showing that the reaction outcomes were consistent with literature precedents. We observed that the cyclization reactions of both isomers proceeded very efficiently but gave different stereochemical outcomes, with **37** being much more selective than **36**.

The hypothesis of the reaction efficiency being dictated by a tight ion pair intermediate[15] would predict that **36** would proceed smoothly to generate the *trans*-stereoisomer through a backside approach via intermediate **38**, while intermediate **39** from **37** would cyclize more slowly and lead to the solvent-separated allylic cation that forms from **6**, **30**, and **31** (Scheme 6). We observed the opposite result, with **37** reacting efficiently through a pathway to stereochemical *retention*, rather than inversion, and **36** reacting in high yield but with only a moderate preference for stereochemical inversion. The reactions were conducted for identical 5-min intervals. Our previous equilibration studies showed that negligible epimerization proceeds at short reaction times, indicating that these outcomes reflect kinetic control. These results can be reconciled through invoking an S_Ni pathway, as proposed in the conversion of alcohols to alkyl chlorides by $SOCl_2$.[16] We postulate that the mechanism proceeds through cyclic perrhenate diester formation, seen in the conversion of **37** to **40**. Cyclic Re(VII) diesters have previously been proposed as intermediates in oxidative cyclization reactions of bis-homoallylic alcohols.[17] Ionization to generate **41** followed by a nucleophilic attack and concomitant $HOReO_3$ loss that is faster than bond rotation will result in the formation of **7**-*trans*, as a result of stereochemical retention at the allylic center. HPLC analysis confirmed that no loss of enantiomeric purity occurred in this reaction. The lower stereocontrol for the cyclization of **36** does not invalidate the ion pairing mechanism but most likely arises from competition from

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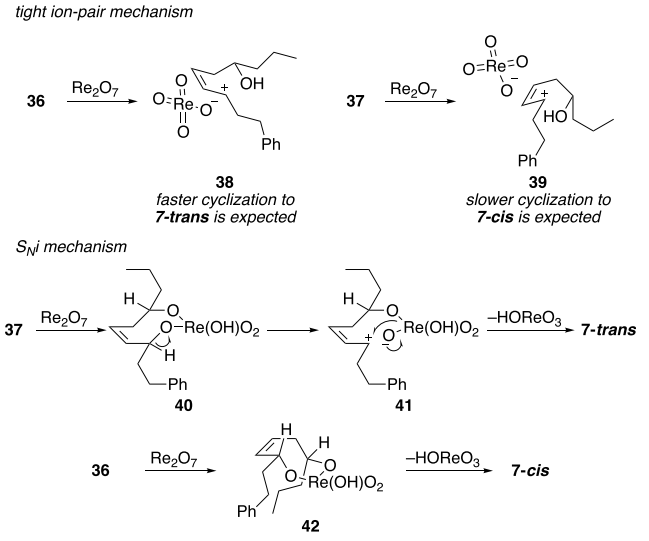
Scheme 6. Mechanistic Options for 1,5-Diols



the S_Ni pathway through perrhenate diester intermediate **42**, which decomposes to form 7-*cis*. The high yield indicates that the competing and stereochemically complementary ion pairing and S_Ni pathways are both very efficient. The formation of cyclic perrhenate diesters are also likely intermediates for reactions of 1,3-diol substrates, but the stereochemical information will be lost as the intermediate cation assumes the proper conformation for cyclization.

We have demonstrated that dihydropyrans can be prepared through a Re_2O_7-catalyzed dehydrative route from monoallylic 1,3- or 1,5-diols, whereby a hydroxy group reacts with the distal terminus of an appended allyl cation. The reactions proceed quickly to give the 2,6-*trans*-isomer with moderate to good levels of stereocontrol. The *trans*-isomer is the kinetic product, resulting from a boat-like transition state, and equilibration studies show that is also the thermodynamic product due to $A^{1,2}$-strain minimization. This stereochemical outcome is complementary to prior dehydrative cyclizations that proceed through hydroxy groups reacting at the proximal terminus of appended allylic cations. Primary allylic alcohols can serve as substrates, allowing for the formation of enantiomerically enriched monosubstituted dihydropyrans. Structural variations of cyclization substrates show that (*E*)- and (*Z*)-1,3- and (*E*)-1,5-monoallylic diols form the same cation upon ionization as determined by reaction yields and stereochemical outcomes. (*Z*)-1,5-Monoallylic diols, however, react more efficiently and with stereochemical retention being observed to an unexpectedly high degree, suggesting an intriguing S_Ni mechanism that is unique to this substitution pattern.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03526.

Schemes for substrate syntheses, cyclization protocols, stereochemical determinations, and ^1H and ^{13}C NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **6**, **7**, **10**−**37**, **S1**, **S2**, and **S5** (ZIP)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Institutes of Health (R01-GM103886) for generous funding of this project.

■ REFERENCES

(1) (a) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776. (b) Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett.* **2000**, *2*, 2427. (c) Makabe, H.; Kong, L. K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27. (d) Uenishi, J.; Ohmi, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2756. (e) Kawai, N.; Lagrange, J.-M.; Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006**, *71*, 4530. (f) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669. (g) Hande, S. M.; Kawai, N.; Uenishi, J. *J. Org. Chem.* **2009**, *74*, 244. (h) Tanaka, S.; Seki, T.; Kitamura, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8948. (i) Hanessian, S.; Focken, T.; Oza, R. *Org. Lett.* **2010**, *12*, 3172. (j) Aponick, A.; Biannic, B. *Org. Lett.* **2011**, *13*, 1330. (k) Mukherjee, P.; Widenhoefer, R. A. *Org. Lett.* **2011**, *13*, 1334. (l) Miyata, K.; Kutsuna, H.; Kawakami, S.; Kitamura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4649. (m) Unsworth, W. P.; Stevens, K.; Lamont, S. G.; Robertson, J. *Chem. Commun.* **2011**, *47*, 7659. (n) Mukherjee, P.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 1405. (o) Ghebreghiorgis, T.; Biannic, B.; Kirk, B. H.; Ess, D. H.; Aponick, A. *J. Am. Chem. Soc.* **2012**, *134*, 16307.

(2) (a) Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808. (b) Guérinot, A.; Serra-Muns, A.; Bensoussan, C.; Reymond, S.; Cossy, J. *Tetrahedron* **2011**, *67*, 5024. (c) Hanessian, S.; Focken, T.; Oza, R. *Tetrahedron* **2011**, *67*, 9870. (d) Zheng, H.; Ghanbari, S.; Nakamura, S.; Hall, D. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 6187. (e) Zhang, F.-Z.; Tian, Y.; Li, G.-X.; Qu, J. *J. Org. Chem.* **2015**, *80*, 1107. (f) Hoshiya, N.; Noda, K.; Mihara, Y.; Kawai, N.; Uenishi, J. *J. Org. Chem.* **2015**, *80*, 7790.

(3) For reviews on Re_2O_7-mediated transformations, see: (a) Volchkov, I.; Lee, D. *Chem. Soc. Rev.* **2014**, *43*, 4381. (b) Bellemin-Laponnaz, S. *ChemCatChem* **2009**, *1*, 357. For more specific examples: (c) Hu, J.; Xu, D.; Zhang, Q.; Shang, Y.; Shi, M.; Huangfu, Y.; Liu, L.; Liang, R.; Lai, Y.; He, Y.; Gao, J.-m.; Xie, W. *RSC Adv.* **2016**, *6*, 52583. (d) Yun, S. Y.; Hansen, E. C.; Volchkov, I.; Lo, W. Y.; Lee, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4261. (e) Herrmann, A. T.; Saito, T.; Stivala, C. E.; Tom, J.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 5962. (f) Bellemin-Laponnaz, S.; Gisie, H.; Le Ny, J. P.; Osborn, J. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 976. (g) Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059.

(4) (a) Asari, A. H.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2020**, *59*, 6622. (b) Qin, Q.; Xie, Y.; Floreancig, P. E. *Chem. Sci.* **2018**, *9*, 8528. (c) Rohrs, T. M.; Qin, Q.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2017**, *56*, 10900. (d) Xie, Y.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2014**, *53*, 4926. (e) Xie, Y.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 625.

https://dx.doi.org/10.1021/acs.orglett.0c03526
Org. Lett. XXXX, XXX, XXX−XXX

(f) Xie, Y.; Floreancig, P. E. *Chem. Sci.* **2011**, *2*, 2423. (g) Jung, H. H.; Seiders, J. R.; Floreancig, P. E.; II. *Angew. Chem., Int. Ed.* **2007**, *46*, 8464.
(5) For representative examples, see: (a) Kito, K.; Ookura, R.; Namikoshi, M.; Ooi, T.; Kusami, T. *Org. Lett.* **2008**, *10*, 225−225. (b) Williams, D. E.; Roberge, M.; Van Soest, R.; Andersen, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 5296−5297. (c) Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159−162. (d) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469−2471.
(6) Jacques, R.; Pal, R.; Parker, N. A.; Sear, C. E.; Smith, P. W.; Ribaucourt, A.; Hodgson, D. M. *Org. Biomol. Chem.* **2016**, *14*, 5875.
(7) For a conceptually related approaches, see: (a) Venegas, E. R.; Willis, C. L. *Org. Lett.* **2020**, *22*, 2548. (b) Flamme, E. M.; Roush, W. R. *Beilstein J. Org. Chem.* **2005**, *1*, 7.
(8) Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, J. A.; Hall, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 9694.
(9) Johnson, F. *Chem. Rev.* **1968**, *68* (4), 375.
(10) Please see the Supporting Information for details.
(11) Winstein, S.; Klinedinst, P. E., Jr.; Robinson, G. C. *J. Am. Chem. Soc.* **1961**, *83*, 885.
(12) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.
(13) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226.
(14) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451.
(15) Rodriguez del Rey, F.; Floreancig, P. E. Submitted for publication.
(16) (a) Sharkey, B. E.; Jentoft, F. C. *ACS Catal.* **2019**, *9*, 11317. (b) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792. (c) Morimoto, Y.; Iwai, T. *J. Am. Chem. Soc.* **1998**, *120*, 1633. (d) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 7823.
(17) Lewis, E. S.; Boozer, C. E. *J. Am. Chem. Soc.* **1952**, *74*, 308.

https://dx.doi.org/10.1021/acs.orglett.0c03526
Org. Lett. XXXX, XXX, XXX−XXX