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Highly Enantiospecific Platinum-Catalyzed Cycloisomerizations: Synthesis of Enantioenriched Oxabicycloheptene Derivatives

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ABSTRACT

Enantiospecific cycloisomerizations of 1,6-enynes to form oxabicyclo[4.1.0]heptene derivatives are described. Enantiospecificity is consistently high regardless of alkene or alkyne substitution, providing a general approach to greatly enantioenriched cyclopropanes. Additionally, a model for stereochemical transfer is proposed.

Enyne cycloisomerizations based on alkyne π-activation represent a powerful class of transformations in their ability to provide an array of structurally diverse molecules.[1] Enantioselective variants based on asymmetric catalysis remain challenging, in part owing to the difficulty of establishing an appropriate chiral environment via single-point alkyne binding for general and uniform stereoinduction.[2] Because chiral induction in alkyne π-activation can be so demanding, alternative approaches toward enantioenrichment in cycloisomerization may prove equally if not more appealing. Enantiospecific cycloisomerizations from pregenerated chirality would represent one such opportunity if the following criteria were met: (1) the origin of chirality was easily obtained, and (2) the approach allowed for reaction versatility unseen in asymmetric catalysis.

Spurred by our interest in the area of alkyne π-activation,[3] a specific transformation that drew our attention was the cycloisomerization of heteroatom-tethered 1,6-enynes to form bicyclo[4.1.0]heptene derivatives.[4] There have been several notable achievements in enantioselectivity based on chiral catalysts (Scheme 1, **1** → **2**),[5] yet

(1) For select reviews on catalytic cycloisomerization initiated by alkyne activation, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (c) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296.

(2) For select recent reviews featuring asymmetric catalysis based on alkyne activation, see: (a) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899–2919. (b) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884–4908. (c) Pradal, A.; Toullec, P. Y.; Michelet, V. *Synthesis* **2011**, 1501–1514.

(3) (a) Rooke, D. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11926–11928. (b) Allegretti, P. A.; Ferreira, E. M. *Org. Lett.* **2011**, *13*, 5924–5927. (c) Allegretti, P. A.; Ferreira, E. M. *Chem. Sci.* **2013**, *4*, 1053–1058.

(4) For select examples, see: (a) Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567–5569. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869. (c) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511–10520. (d) Ota, K.; Lee, S. I.; Tang, J.-M.; Takachi, M.; Nakai, H.; Morimoto, T.; Sakurai, H.; Kataoka, K.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 15203–15211.

(5) For key representative examples of chiral catalysis approaches, see: (a) Shibata, T.; Kobayashi, Y.; Maekawa, S.; Toshida, N.; Takagi, K. *Tetrahedron* **2005**, *61*, 9018–9024. (b) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988–6990. (c) Brissy, D.; Skander, M.; Jullien, H.; Retailleau, P.; Marinetti, A. *Org. Lett.* **2009**, *11*, 2137–2139. (d) Nishimura, T.; Kawamoto, T.; Nagaosa, M.; Kumamoto, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1638–1641. (e) Nishimura, T.; Maeda, Y.; Hayashi, T. *Org. Lett.* **2011**, *13*, 3674–3677. (f) Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331–15342. (g) Barbazanges, M.; Augé, M.; Moussa, J.; Amouri, H.; Aubert, C.; Desmarets, C.; Fensterbank, L.; Gandon, V.; Malacria, M.; Ollivier, C. *Chem.—Eur. J.* **2011**, *17*, 13789–13794. (h) See the Supporting Information (SI) for related works.

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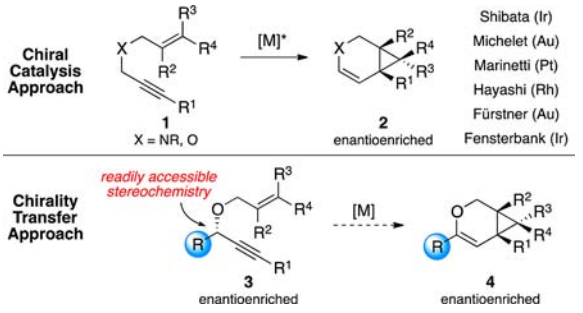
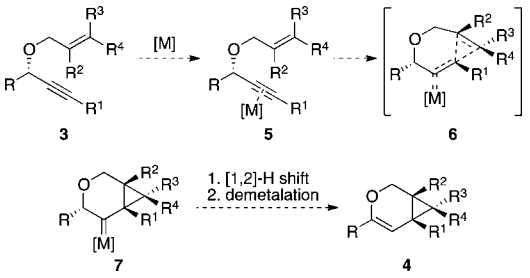
there remain limitations. In particular, most catalyst systems appear to be highly sensitive to the substrate substitution pattern; alkene and/or alkyne substituents specifically can have dramatic effects on the enantioselectivity. Ethereal substrates have also been decidedly more difficult compared to their N-tethered counterparts, being prone to oligomerization and decomposition promoted by the Lewis acidic metal. We hypothesized that an alternative approach, based on chirality transfer, could produce enantioenriched bicycles in this cycloisomerization. We anticipated that ether **3**, featuring a stereocenter in the propargylic position, would produce enantioenriched enol ether **4** under select cycloisomerization conditions. Herein, we disclose the realization of this goal, demonstrating that ethereal 1,6-enyne substrates can be isomerized to highly substituted bicyclo[4.1.0]heptene derivatives with excellent levels of enantiospecificity.

Scheme 1. Approaches to Developing Stereochemistry in Ether Cycloisomerization



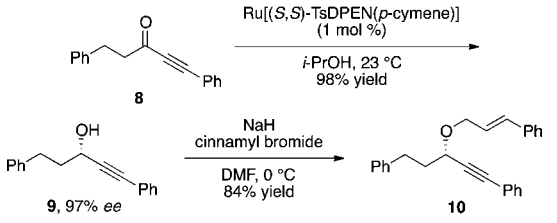
Our reaction design is depicted in Scheme 2. Although other catalytic reaction pathways have been proposed,[4a,5a,6] it is generally believed, in part based on previous calculations,[5f,7] that cyclopropanation occurs prior to the [1,2]-hydride shift. We hypothesized from this mechanism that the cyclopropane bond formation could be influenced by a stereocenter at the propargylic site. There have been reports of diastereoselective cyclopropane bond formation based on the allylic carbon; this stereocenter is maintained in the cycloisomerization product.[8] In contrast, the propargylic stereocenter is not conserved in our proposed transformation (**7** → **8**); this process would therefore represent a *traceless* generation of stereochemistry. If enantiospecificity were observed, it would constitute both an experimental validation of the proposed mechanistic pathway[9] and a differential approach to access these enantioenriched products. Notably, reports of different enantiospecifc processes in alkyne π-activation with propargylic esters[10,11] offered promise for our proposal.

Scheme 2. Mechanistic Potential for Enantiospecific Cycloisomerization



We expected this approach would be highly attractive owing to the general ease of synthesizing chiral propargylic alcohols.[12,13] To initiate our studies, we employed the transfer hydrogenation chemistry of Noyori[13a] to generate the target substrates. Ynone **8** was reduced to form propargylic alcohol **9** in excellent yield and *ee* (Scheme 3). Alkylation with cinnamyl bromide proceeded uneventfully to afford enyne **10**.

Scheme 3. Chiral Propargylic Ether Synthesis



With the target enantioenriched enyne in hand, we evaluated several reaction conditions (Table 1). Of the catalysts investigated, $PtCl_2$ in toluene provided the most promising lead with respect to both yield and enantiospecificity (*es*),[14] with enol ether **11** produced in 78% yield and 89% *es* (entry 4). Changing the solvent to THF

(6) He, R.-X.; Li, M.; Li, X.-Y. *THEOCHEM* **2005**, *717*, 21–32.

(7) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *J. Org. Chem.* **2004**, *69*, 8018–8023.

(8) (a) Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 3191–3194. (b) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306–6316. (c) Chen, Z.; Zhang, Y.-X.; Wang, Y.-H.; Zhu, L.-L.; Liu, H.; Li, X.-X.; Guo, L. *Org. Lett.* **2010**, *12*, 3468–3471. (d) Xia, J.-B.; Liu, W.-B.; Wang, T.-M.; You, S.-L. *Chem.—Eur. J.* **2010**, *22*, 6442–6446.

(9) Most alternative mechanistic pathways would involve destruction of the stereocenter prior to cyclopropyl bond formation.

(10) (a) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901–2904. (b) Fürstner, A.; Hannen, P. *Chem.—Eur. J.* **2006**, *12*, 3006–3019. (c) Fehr, C.; Winter, B.; Magpantay, I. *Chem.—Eur. J.* **2009**, *15*, 9773–9784. (d) Fürstner, A.; Schlecker, A. *Chem.—Eur. J.* **2008**, *14*, 9181–9191. (e) Soriano, E.; Marco-Contelles, J. *J. Org. Chem.* **2007**, *72*, 2651–2654.

(11) Gandon, Fensterbank, Malacria and coworkers have described an example of chirality transfer with propargylic ester substrates that first converts to a chiral allene intermediate. See: Gandon, V.; Lemière, G.; Hours, A.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7534–7538.

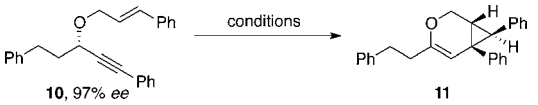
(12) (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824. (b) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963–983.

(13) (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102.

(14) Enantiospecificity ($es = ee_{product}/ee_{reactant} \times 100\%$) is a straightforward method for determining the conservation of stereochemistry in the transformation. See: (a) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233. (b) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293–4296.

provided a noticeable boost in yield, while modestly increasing *es*. Adding CO resulted in minimal effect.[15] While other Pt(II) catalytic conditions were comparable, ultimately 7 mol % $PtCl_2$ in THF at 70 °C gave the optimal reactivity,[16] with **11** formed in 90% yield and 90% *ee* (93% *es*).

Table 1. Catalyst Evaluation for Stereospecific Cycloisomerization



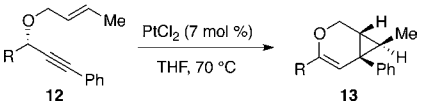
entry	catalyst (mol %)	solvent, temp (°C)	t (h)	yield	*ee* (%)	*es* (%)[a]
1	$(Ph_3P)AuNTf_2$ (5)	CH_2Cl_2, 23	0.5	52	84	87
2	$[Ir(dbcot)Cl]_2$ (2.5)[b,c]	$PhCH_3$, 100	3	68	84	87
3	$PtCl_4$ (5)	$PhCH_3$, 23	1	27	90	93
A	$PtCl_2$ (5)	$PhCH_3$, 60	22	78	86	89
5	$PtCl_2$ (5)	THF, 60	18	87	88	91
6	$PtCl_2$ (5)[b]	THF, 60	14	86	86	89
7	$[(C_2H_4)PtCl_2]_2$ (2.5)	THF, 23	28	84	86	89
8	$Pt(PhCN)_2Cl_2$ (7)	THF, 60	48	64	87	90
9	$PtCl_2$ (7)	THF, 70	18	90	87	90

[a] Enantiospecificity (es) = $[(ee_{product})/(ee_{substrate})] \times 100\%$. [b] Under 1 atm of CO. [c] dbcot: dibenzo[*a*,*e*]cyclooctatetraene.

We anticipated that the steric properties of the propargylic substituent would have a significant effect on the net chirality transfer. As shown in Table 2, there is indeed a trend correlating substituent size to the degree of chirality transfer. Methyl and isobutyl groups were the least effective substituents in inducing stereospecificity. The ether with a hydrocinnamyl group in the propargylic position provided a marked improvement. Optimally, larger groups such as cyclohexyl and isopropyl were incredibly effective, providing near-perfect chiral transfer (97% *es* and 99% *es*, respectively). A larger aliphatic substituent (*tert*-butyl) required higher temperatures for reactivity and consequently yielded a complex mixture.

With an effective method and conditions for chirality transfer, this enantiospecific transformation is efficient across a broad range of enyne substrates (Figure 1).[17] Both (*E*)- and (*Z*)-1,2-disubstituted alkenes afforded the corresponding bicycles (**13e**, **15a**–**c**), with the olefin geometry directly transferred to the cyclopropane stereochemistry. 1,1-Disubstituted alkenes were also efficient reactants in producing enol ethers (e.g., **15d**). Enynes based on trisubstituted alkenes were successful, although the prenyl-derived

Table 2. Effect of Propargylic Substituent on Chirality Transfer



entry	R	*ee* **12** (%)	product	yield[a] (%)	*ee* (%)	*es* (%)
1	Me (**12a**)	97	**13a**	90	80	82
2	*i*-Bu (**12b**)	97	**13b**	84	78	80
3	CH_2CH_2Ph (**12c**)	96	**13c**	93	90	94
4	Cy (**12d**)	99	**13d**	84	96	97
5	*i*-Pr (**12e**)	98	**13e**	80	97	99
6	*t*-Bu (**12f**)	96	**13f**	<10	nd[b]	nd[b]

[a] Isolated yield. [b] nd: Not determined.

substrate gave the desired product (**15f**) in diminished yield. Tricyclic enol ethers were formed efficiently (e.g., **15g**). Various alkyne substituents were also well tolerated, with alkyl, ethereal, and heteroaryl substitution all giving the cyclopropane products in good yields and high stereospecificity. Importantly, this level of generality with O-tethered enynes has not been observed with approaches based on asymmetric catalysis.[18]

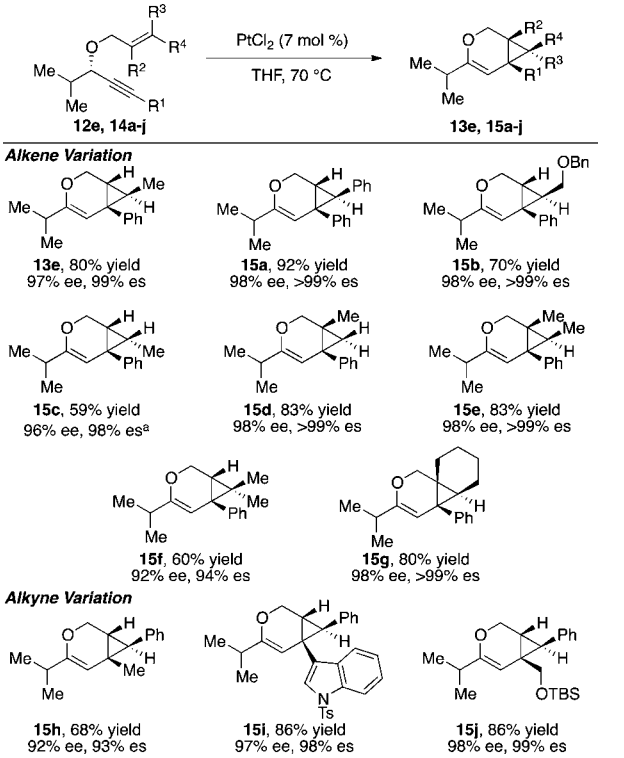


Figure 1. Enantiospecific cycloisomerization to form bicyclo[4.1.0]heptene derivatives. [a]Reaction performed at 75 °C.

The absolute stereochemistry of the product cyclopropanes was readily confirmed from the cycloisomerization of enyne **14k** (Scheme 4). Like the previous examples,

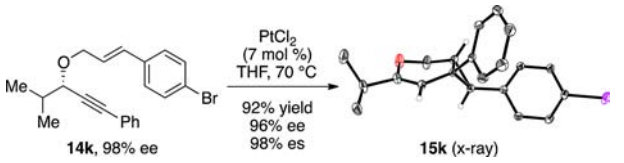
(15) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245.

(16) The increase to 7 mol % catalyst was to ensure reaction completion, which we observed did not occur uniformly at 5 mol % across all substrates. We also opted to use $PtCl_2$, as we had observed a lack of uniform reactivity across all substrates when using Zeise's dimer ($[(C_2H_4)PtCl_2]_2$).

(17) Because of the excellent efficiency of the isopropyl group in chirality transfer, enynes based on this aliphatic moiety were evaluated. The trends observed in Table 2 indicate that other groups would provide synthetically useful levels of enantioenriched products as well.

cycloisomerization of **14k** proceeded efficiently to form cyclopropane **15k** in 92% yield. An X-ray crystal structure was obtained, establishing the absolute stereochemistry as illustrated.[19]

Scheme 4. Cycloisomerization of Ether **14k**



Based on this stereochemical outcome, we have developed a working model for rationalizing the transfer of chirality (Figure 2). The enyne substrate is oriented in a boat-like conformation; the basis for this orientation is derived from related calculations by Soriano et al.[7] After the propargylic substituent is placed in a favorable pseudoequatorial position, the metal catalyst coordinates the alkyne as drawn in structure **16**. An *anti* nucleophilic attack by the alkene, in an orientation perpendicular to the alkyne, establishes the stereochemistry of the cyclopropanation. The subsequent mechanistic steps ultimately produce ether **15k**. Potentially reactive conformations that would produce the opposite enantiomer are unlikely. Conformation **14k-B** is sterically destabilized by the pseudoaxial isopropyl group, while conformation **14k-C** is stereoelectronically disfavored, with insufficient overlap of the nucleophilic π-bond with the electrophilic alkyne carbon. Albeit a preliminary model,[20] this picture is consistent with the impact of the size of the propargylic substituent on the overall stereospecificity.

An attractive aspect of this enantiospecific transformation is the synthetic utility of the oxabicycloheptene derivatives. Enol ether **15a**, when subjected to oxidative cleavage conditions,[21] was cleanly converted to cyclopropane **18** (Scheme 5). Cyclopropanes are useful intermediates in organic synthesis,[22] and new methods for generating stereodefined, highly substituted cyclopropanes are therefore valuable.[23]

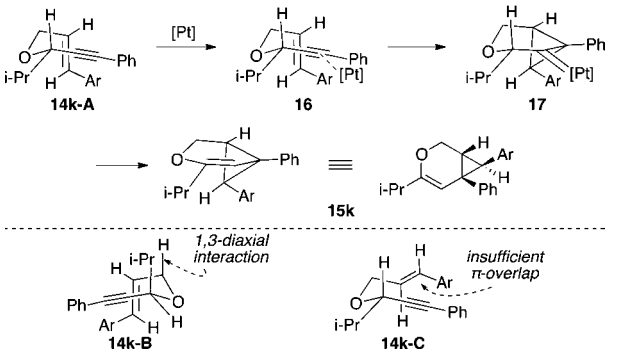
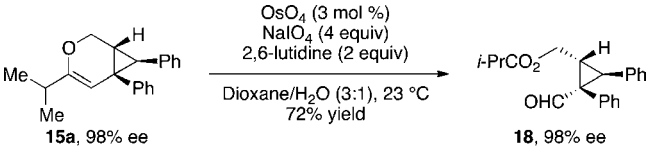


Figure 2. Stereochemical rationalization.

The generation of the aldehyde and ester functional groups in this process offers versatile synthetic handles for further manipulation.

Scheme 5. Synthetic Utility: Oxidative Cleavage



In summary, we have observed chirality transfer in the cycloisomerization of oxygen-tethered 1,6-enynes with catalytic $PtCl_2$. The process is highly enantiospecific and tolerates diverse substitutions on both alkene and alkyne. Importantly, we can generate the breadth of stereogenicity in these cycloisomerization products through this enantiospecific process from chiral propargylic alcohols, which are trivial to access. Additionally, these results experimentally reinforce the validity of the proposed mechanism for this type of cycloisomerization. A model of stereochemical relay was developed on the basis of the product absolute configuration. We are currently pursuing the use of this method in natural product synthesis, in addition to exploring this overall strategy toward chirality transfer in novel alkyne π-activation processes.

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Supporting Information Available. Experimental procedures, spectroscopic data, spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(18) (a) The toluenesulfonamide-tethered enyne substrates, more commonly used in asymmetric catalytic systems, also showed measurable enantiospecificity via this approach. With a substrate bearing a methyl group in the propargylic position, 82% enantiospecificity was observed. See the SI for details. (b) Enynes featuring tetrasubstituted alkenes remain challenging for this process. Preliminary experiments have shown marginal reactivity with these systems (approximately 10% bicyclic product), but other reaction products have been observed in these cases.

(19) The absolute configurations of all other oxabicyclo[4.1.0]heptene products were assigned by analogy.

(20) It has been observed that stereoselective processes in catalytic alkyne π-activation can be influenced by remarkably subtle effects. See: (a) Nieto Faza, O.; de Lera, A. R. *Top. Curr. Chem.* **2011**, *302*, 81–130. (b) Reference 10e. (c) Computational efforts to validate our proposed model are ongoing.

(21) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.

(22) (a) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 899–970. (b) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203–5223. (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198.

(23) (a) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041–7095. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–936.