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Intramolecular Cyclization of *m*-Homoprenylphenols through Oxidative Nucleophilic Aromatic Substitution

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We developed an intramolecular cyclization of *m*-homoprenylphenols and related *m*-prenylphenols to bicyclic skeletons by hypervalent iodine reagents through an oxidative nucleophilic aromatic substitution using the prenyl group as a carbon nucleophile. The reaction was applicable for the syntheses of 5/6-, 6/6-, and 7/6-fused ring systems.

Nucleophilic aromatic substitution reactions take place on electron-deficient arenes with a strong electron-withdrawing group and a good leaving group, but not on electron-rich arenes with electron-donating groups and no leaving group. However, in the presence of appropriate oxidants, electron-rich arenes can be converted to electron-deficient cationic intermediates, which undergo nucleophilic aromatic substitution by nucleophiles (Figure 1A). By this methodology, various nucleophiles can be incorporated into electron-rich arenes even without pre-installation of a leaving group on the arenes.[1] Carbon-carbon bond formation reactions by this methodology using carbon nucleophiles also have been developed. However, the employed carbon nucleophiles were limited to only electron-rich arenes and enols.[2,3] In most of the examples, arenes including heterocycles were used as nucleophiles for synthesizing biaryl compounds. Extension of the scope of carbon nucleophiles and substrates expands the utility of this approach for the construction of more molecular carbon skeletons.

Given this background, we focused on homoprenylarenes and related compounds as the substrates and the prenyl group as the carbon nucleophile in the oxidative nucleophilic aromatic substitution reaction (Figure 1B). Homoprenyl, homogeranyl, and related polyenylarenes have been employed as substrates for biomimetic electrophilic cyclization (Figure 1C)[4,5] to imitate the biogenetic cyclization of polyenes to isoprenoids. In these

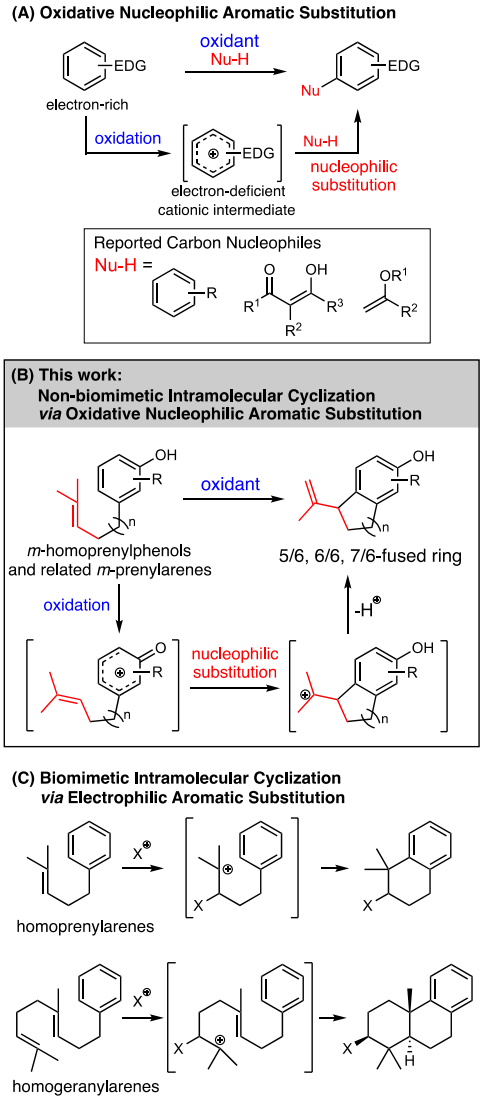

Figure 1 (A) Oxidative nucleophilic aromatic substitution reaction. (B) Non-biomimetic intramolecular cyclization of m-homoprenyl and related prenylarenes through oxidative nucleophilic aromatic substitution. (C) Biomimetic cyclization of homoprenyl and homogeranylarenes through electrophilic aromatic substitution.

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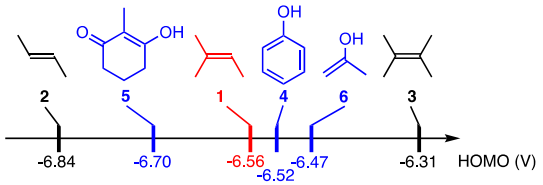


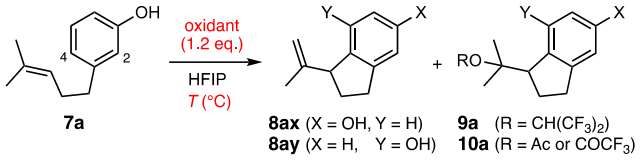
Figure 2 Calculated HOMO levels for alkenes 1-3, phenol 4, and enols 5, 6 [PBE0/6-31+G(d)].

electrophilic reactions, a stable cation is generated from the alkenes, which then undergoes electrophilic cyclization with electron-rich arenes, furnishing terpenoid skeletons with 6/6- or 6/6/6-fused ring systems. A substantial number of such electrophilic reactions using various reagents or catalysts has been developed by many groups to date. In contrast to this biomimetic cyclization to terpenoid skeletons, we designed a new non-biomimetic cyclization from *m*-homoprenylphenols and related prenylphenols to terpenoid skeletons through oxidative nucleophilic aromatic substitution (Figure 1B). In this proposed reaction, intramolecular nucleophilic substitution by a prenyl group on a cationic intermediate generated from the *m*-homoprenylphenols under oxidative conditions was followed by deprotonation to afford bicyclic skeletons. This reaction would allow us to construct different bicyclic terpenoid skeletons possessing a smaller ring size with a propenyl substituent from homoprenylphenols similar to those of the biomimetic cyclization. Here, we report the non-biomimetic cyclization from *m*-homoprenyl and related prenylphenols to bicyclic skeletons with 5/6-, 6/6-, and 7/6-fused ring systems (Figure 1B).

Since simple alkylalkenes have not been used as nucleophiles in oxidative nucleophilic aromatic substitution, calculated HOMO levels of alkylalkenes **1**-**3** were compared with those of reported carbon nucleophiles, phenol **4** and enols **5**, **6**, as an index of nucleophilicity before experimental screening (Figure 2). The calculated HOMO level of trisubstituted alkene **1** (-6.56 V) was located between those of enols **5**, **6**, and phenol **4** (-6.70, -6.47, -6.52 V), which suggested the prenyl group to be a potential nucleophile.

For screening the reaction conditions, *m*-homoprenylphenol **7a** was chosen as the substrate (Table 1). Based on the oxidative aromatic substitution reactions with arenes and enols as nucleophiles by Kita *et al.*,[2a,d] hypervalent iodine reagents and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were used as the oxidant and solvent, respectively. Under conditions using 1.2 eq. of phenyliodine diacetate (PIDA) in HFIP at 0 °C for 5 min (entry 1), the expected cyclization proceeded, giving **8a** (= **8ax**+**8ay**) in 19% yield in **8ax**:**8ay** = 1:1 ratio. Products **8ax** and **8ay** were regioisomers formed by cyclization at the C4 and C2 positions, respectively. As by-products, **9a** (= **9ax**+**9ay**) with $OCH(CF_3)_2$ and **10a** (= **10ax**+**10ay**) with OAc were also obtained in 8% and 32% yields. It is inferred that these by-products were formed by the desired cyclization followed by the addition of HFIP or AcOH from PIDA to an intermediate cation instead of the elimination of a proton. Using phenyliodine ditrifluoroacetate (PIFA) (entry 2) and pentafluorophenyliodine ditrifluoroacetate (FPIFA) (entry 3), the yields of **8a** were decreased to 7% and 14%,

Table 1. Screening of oxidants and temperatures[a]



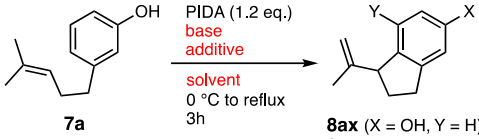
7a

8ax (X = OH, Y = H) **9a** (R = $CH(CF_3)_2$)
8ay (X = H, Y = OH) **10a** (R = Ac or $COCF_3$)

entry	oxidant	*T* (°C)	time	yield (%)[b]			
				8a	**9a**	**10a**	**7a**
1	PIDA	0	5 min	19	8	32	10
2	PIFA	0	5 min	7	5	37	8
3	FPIFA	0	5 min	14	7	22	13
4	PIDA	0 to reflux	3 h	47	5	14	0

[a]**7a** (0.30 mmol), oxidant (0.36 mmol), HFIP (15 mL). [b]Combined yield of regioisomers. The ratios of regioisomers were 1:1.

Table 2. Screening of bases, additive, and solvents[a]



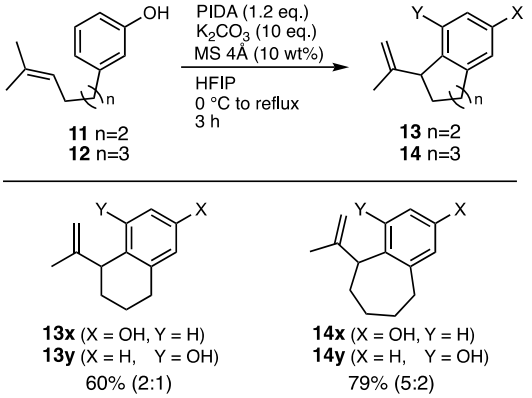
7a

8ax (X = OH, Y = H)
8ay (X = H, Y = OH)

entry	base	additive	solvent	yield (%)[b]
1	Na_2CO_3 (3 eq.)	-	HFIP	61
2	K_2CO_3 (3 eq.)	-	HFIP	70
3	Cs_2CO_3 (3 eq.)	-	HFIP	30
4	MgO (3 eq.)	-	HFIP	58
5	K_2CO_3 (10 eq.)	-	HFIP	72
6	K_2CO_3 (10 eq.)	MS 4Å[c]	HFIP	84
7	-	MS 4Å[c]	HFIP	55
8	K_2CO_3 (10 eq.)	MS 4Å[c]	CF_3CH_2OH	65
9	K_2CO_3 (10 eq.)	MS 4Å[c]	CH_2Cl_2	43
10	K_2CO_3 (10 eq.)	MS 4Å[c]	$(CH_2Cl)_2$	43
11	K_2CO_3 (10 eq.)	MS 4Å[c]	$CHCl_3$	36

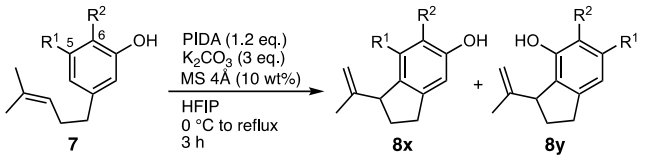
[a]**7a** (0.30 mmol), oxidant (0.36 mmol), solvent (15 mL). [b]Combined yield of **8ax** and **8ay**. The ratio of **8ax** and **8ay** was 1:1. [c]10 wt%

respectively. By-products **10a** with $OCOCF_3$ were also formed in 37% and 22% yields with 5% and 7% yields of **9a**. In entries 1-3, **7a** was recovered in 8 to 13% yields. In entry 4, the reaction temperature was raised to the reflux temperature (60 °C) after addition of PIDA at 0 °C and stirring was performed for 3 h. The yield of **8a** was improved to 47% along with the complete consumption of **7a** and decrease of **10a**. To improve the yield of **8a**, base, additive, and solvent were further screened (Table 2). In entries 1-4, 3 eq. of Na_2CO_3, K_2CO_3, Cs_2CO_3, or MgO was used to convert the remaining by-products **9a** and **10a** to **8a**. Except for Cs_2CO_3, the yield of **8a** was improved and the highest 70% yield was obtained by K_2CO_3 with 3% of **10a**. By-products **9a** and **10a** were completely consumed by 10 eq. of K_2CO_3 (entry 5), giving 72% yield of **8a**. The yield of **8a** was further improved to 84% by using 10 wt% of MS 4Å (entry 6). Although the effect of MS 4Å is unclear, the amount of other unidentified by-products was reduced. Without K_2CO_3 in the presence of MS 4Å (entry 7),



Scheme 1 Scope of ring sizes.[a] [a]Combined yield of regioisomers.

Table 3. Scope of substituents

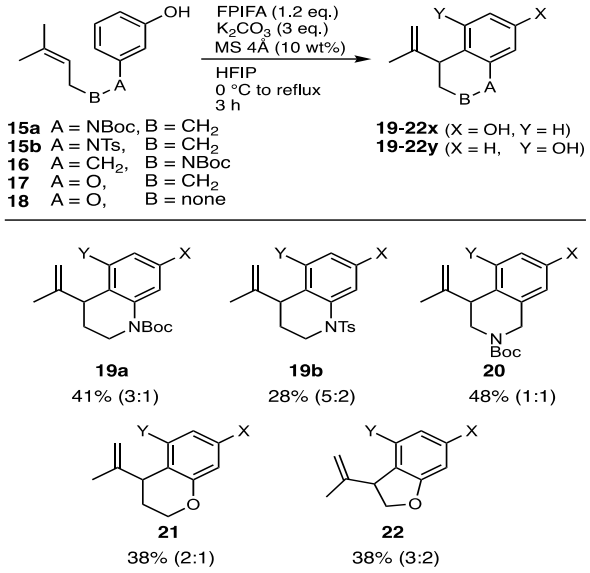


entry	compounds	R^1	R^2	yield (%)[a]	**8x** : **8y**
1	**b**	Br	H	65	9 : 2
2	**c**	Cl	H	62	3 : 1
3	**d**	F	H	32	0 : 1
4	**e**	CF_3	H	79	0 : 1
5	**f**	Me	H	64	2 : 1
6	**g**	OMe	H	49	1 : 1
7	**h**	H	I	60	1 : 2
8	**i**	H	Br	40	3 : 2
9	**j**	H	Cl	45	2 : 1
10	**k**	H	F	24	1 : 1
11	**l**	H	CF_3	64	1 : 1
12	**m**	H	Me	45	1 : 1

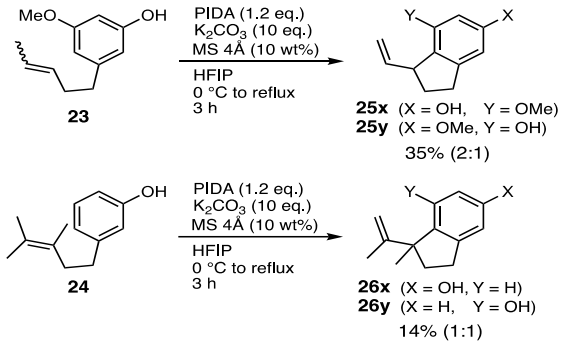
[a]Combined yield of the regioisomers of **8x** and **8y**.

the yield of **8a** was decreased. In entries 8-11, other solvents were investigated but HFIP was the best solvent.

With the optimized conditions in hand, the scope of the reaction was investigated. The reaction was applied to the cyclization of **11** and **12** with longer alkyl side chains (Scheme 1). Desired compounds **13** with a 6-membered ring and **14** with a 7-membered ring were obtained in 60% and 79% yields with 2:1 and 5:2 ratios. Thus, the reaction was applicable for the formation of larger ring sizes. The applicability to *m*-homoprenylphenols **7** substituted at C5 and C6 is shown in Table 3. Cyclization of **7b**-**d** (entries 1-3) and **7h**-**k** (entries 7-10) with halogens atoms, I, Br, Cl, and F, afforded the cyclized products **8** in 65-24% yields. The yields were higher in the order of I > Br ≈ Cl > F. The major by-products were assumed to be biaryl compounds formed through [3,3] sigmatropic rearrangement between PIDA and substates,[6] although the by-products were not fully identified. In the case of the reactions of **7d** and **7k** with a F atom, **7d** and **7k** were recovered in 14% and 39% yields, and the yields of **8d** and **8k** significantly reduced.



Scheme 2 Scope of heterocycles[a] [a]Combined yield of regioisomers.

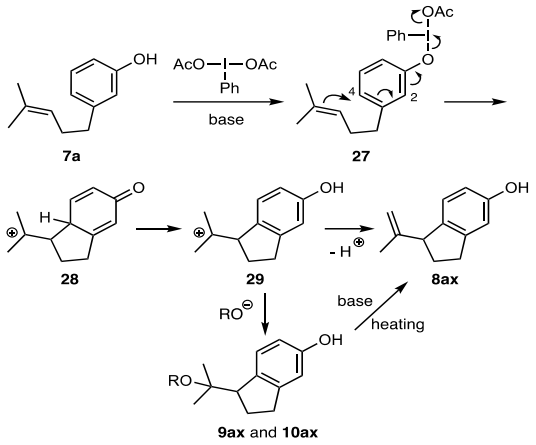


Scheme 3 Scope of alkenes[a] [a]Combined yield of regioisomers.

In contrast, cyclization of **7e** and **7l** with a trifluoromethyl group afforded **8e** and **8l** in good 79% and 64% yields (entries 4 and 11). It is also noteworthy that high regioselectivity was observed for **8b** with a Br atom (9:2) and **8e** with a trifluoromethyl group (0:1) at C5. Cyclization of **7f** and **7m** with a methyl group and **7g** with a methoxy group afforded 64%, 45%, and 48% yields (entries 5, 12, and 6), respectively.

We also applied the reaction to the formation of heterocycles from **15**-**18** to **19**-**22** as shown in Scheme 2. First, the optimized conditions using PIDA were applied. However, by-products through [3,3] sigmatropic rearrangement[6] were formed. Thus, FPIFA was used as the oxidant to prevent the rearrangement. Tetrahydroquinoline, tetrahydroisoquinoline, chromane, and dihydrobenzofuran skeletons were constructed, giving **19a**, **19b**, **20**, **21**, **22** in moderate or low 48-28% yields.

Judging from the comparison of calculated HOMO levels as an index of nucleophilicity in Figure 2, a disubstituted alkene would not be suitable as a nucleophile. The steric hindrance of a tetrasubstituted alkene would also be a problem, although the



Scheme 4 Plausible reaction mechanism

HOMO level for a tetrasubstituted alkene is higher than that for the others. To verify the reactivity, cyclization of **23** with a disubstituted alkene and **24** with a tetrasubstituted one was tested (Scheme 3). Under optimized conditions using PIDA, cyclized products **25** and **26** were formed in 35% and 14% yields, both of which were lower than of those for the homoprenylphenols. The lower yields are attributed to the lower nucleophilicity and the steric hindrance.

Based on the mechanism for oxidative coupling of phenols with arenes as nucleophiles using hypervalent iodine reagents proposed by Kita *et al*.,[2f,g] a plausible mechanism for our reaction is shown in Scheme 4. Phenol **7a** reacts with PIDA to form an intermediate **27**. Elimination of the hypervalent iodine and nucleophilic attack of the prenyl group to the electron-deficient benzene ring at the C4 position give the cation **28**. Aromatization followed by elimination of proton affords **8ax**. Although **9ax** and **10ax** are formed through the addition of $(CF_3)_2CHO^-$ or AcO^-, they are converted to **8ax** through elimination by a base by heating. **8ay** is also formed through cyclization at the C2 position. Since the addition of TEMPO did not affect the yield of **8a**, a radical reaction mechanism is not indicated. Although the origin of the observed regioselectivity at the C4 and C2 positions in the reactions of substituted homoprenylphenols was not fully elucidated, the electronic effect of the substituents on the benzene ring, the steric hindrance, and the through-space effect of the prenyl group could cause the selectivity.

In summary, we succeeded in developing an intramolecular cyclization process for *m*-homoprenyl and related prenylphenols to bicyclic skeletons through an oxidative nucleophilic aromatic substitution using hypervalent iodine as the oxidant. Based on predictions by DFT calculations, a trisubstituted alkene was proven to be an effective carbon nucleophile in the oxidative nucleophilic aromatic substitution reaction. The reaction was applicable for the syntheses of 5/6-, 6/6-, and 7/6-fused ring systems, and the scope of substituents on the phenol, formation of heterocycles, and alkenes were also elucidated. In contrast to the biomimetic electrophilic cyclization of homoprenylphenols, this non-biomimetic nucleophilic cyclization allows us to construct different bicyclic terpenoid skeletons from similar homoprenylphenols. Although the regioselectivity of the cyclization could still be improved, this type of cyclization is promising for synthesis of terpenoids.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) P. Kovacic and M.B. Jones, *Chem. Rev.*, **1987**, *87*, 357-379. (b) Q. Ding, Y. Ye and R. Fan, R., *Synthesis*, **2013**, *45*, 1-16. (c) S. Quideau, D. Deffieux and L. Pouysegu, *Comprehensive Organic Synthesis (Second Edition)*., **2014**, *3*, 656-740. (d) K. Morimoto, T. Dohi and Y. Kita, *Synlett*, **2017**, *28*, 1680-1694. (e) Z. Huang and J. P. Lumb, *ACS. Catal.*, **2019**, *9*, 521-555. (f) P. Pal, J. Waser, and K. R. Nandi, *Heterocycles.*, **2021**, *103*, 555-591. (g) A. Bauer and N. Maulide, *Chem. Sci.*, **2021**, *12*, 853-864.

2 (a) Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai and S. Oka, *J. Am. Chem. Soc.*, **1994**, *116*, 3684-3691. (b) T. Takada, M. Arisawa, M. Gyoten, R. Hamada, H. Tohma and Y. Kita, *J. Org. Chem.*, **1998**, *63*, 7698-7706. (c) M. Arisawa, N. G. Ramesh, M. Nakajima, H. Tohma, and Y. Kita, *J. Org. Chem.*, **2001**, *66*, 59-65. (d) K. Morimoto, T. Nakae, N. Yamaoka, T Dohi and Y. Kita, *Eur. J. Org. Chem.*, **2011**, 6326-6334. (e) T. C. Turner, K. Shibayama and D. L. Boger, *Org. Lett.*, **2013**, *15*, 1100-1103. (f) K. Morimoto, K. Sakamoto, Y. Ohnishi, T. Miyamoto, M. Ito, T. Dohi and Y. Kita, *Chem. Eur. J.*, **2013**, *19*, 8726-8731. (g) K. Morimoto, K. Sakamoto, T. Ohshika, T. Dohi and Y. Kita, *Angew. Chem. Int. Ed.*, **2016**, *55*, 3652-3656. (h) K. Morimoto, D. Koseki, T. Dohi, and Y. Kita, *Synlett.*, **2017**, *28*, 2941-2945. (i) S. D. Holmbo and S. V. Pronin, *J. Am. Chem., Soc.* **2018**, *140*, 5065-5068.

3 (a) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, **2014**, *114*, 9219-9280. (b) R. Narayan, K. Matcha and A. P. Antonchick, *Chem. Eur. J.*, **2015**, *21*, 14678-14693.

4 (a) E. Edstrom and T. Livinghouse, *J. Am. Chem. Soc.*, **1986**, *108*, 1334-1336. (b) R. L. Danheiser, D. S. Casebier and F. Firooznia, *J. Org. Chem.*, **1995**, *60*, 8341-8350. (c) K. Ishihara, H. Ishibashi and H. Yamamoto, *J. Am. Chem. Soc.*, **2001**, *123*, 1505-1506. (d) B. D. Dangel, K. Godula, S. W. Youn, B. Sezen and D. Sames, *J. Am. Chem. Soc.*, **2002**, *124*, 11856-11857. (e) S. W. Youn, S. J. Pastine and D. Sames, *Org. Lett.*, **2004**, *6*, 581-584. (f) A. Sakakura, A. Ukai and K. Ishihara, *Nature*, **2007**, *445*, 900-903. (g) R. R. Knowles, S. Lin and E. N. Jacobsen, *J. Am. Chem. Soc.*, **2010**, *132*, 5030-5032. (h) S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.*, **2010**, *132*, 8276-8277. (i) S. A. Snyder, D. S. Treitler and A. P. Brucks, *J. Am.Chem. Soc.*, **2010**, *132*, 14303-14314. (j) M. A. Schafroth, D. Sarlah, S. Krautwald, and E. M. Carreira, *J. Am. Chem. Soc.*, **2012**, *134*, 20276-20278. (k) K. Surendra and E. J. Corey, *J. Am. Chem. Soc.*, **2012**, *134*, 11992-11994. (l) S. E. Denmark and A. Jaunet, *J. Am. Chem. Soc.*, **2013**, *135*, 6419-6422. (m) B. R. Rosen, E. W. Werner, A. G. O'Brien and P. S. Baran, *J. Am. Chem. Soc.*, **2014**, *136*, 5571-5574.

5 (a) R. A. Yoder and J. N. Johnston, *Chem. Rev.*, **2005**, *105*, 4730-4756. (b) C. N. Ungarean, E. H. Southgate and D. Sarlah, *Org. Biomol. Chem.*, **2016**, *14*, 5454-5467. (c) A. Barrett, T.-K. Ma and T. Mies, *Synthesis*, 2019, **51**, 67–82.

6 M. Hori, J.-D. Guo, T. Yanagi, K. Nogi, T. Sasamori and H. Yorimitsu, *Angew. Chem. Int. Ed.*, **2018**, *57*, 4663-4667.