18.4.26

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Form 7／様式 7

外国人特別研究員作成／By Fellow

2018 / 04 / 24
(YYYY) (MM) (DD)

JSPS Fellow's
Signature (Handwritten only) : Ramesh Chandra Samanta

Research Report (by Fellow)
(Cover Page)

I hereby submit the research report of my fellowship.

1. Name (Print) : SAMANTA Ramesh Chandra
2. Nationality : INDIA
3. Host Institution : CHUBU UNIVERSITY
4. Host Researcher : Professor Hisashi YAMAMOTO
5. Title of Research in Japan : DEVELOPMENT OF NEW METHOD FOR CATALYTIC ASYMMETRIC ELECTROPHILIC HALOGENATIONS REACTIONS
6. Fellowship Tenure : From 2016/ 04 / 01 To 2018 / 03 / 31
(YYYY) (MM) (DD) (YYYY) (MM) (DD)

***Notes for writing the Research Report**
***Type this form except the date and the signature.**
Please prepare your Research Report in English or Japanese within three to ten pages including this page. The contents should include:

7. Background of Research
8. Research methodology
9. Results/impacts

Note: As much as possible, describe the contents and results of your research in a manner that is easily understandable to a non-specialist in your field. Provide a concrete description if (1) papers related to your work have been published in major academic journals, (2) particularly outstanding research results were achieved, or (3) patent applications have been made or other tangible outcomes achieved through the research.

10. Research Presentations during the period of the fellowship (Name of the conference, title, place, date)
Poster Presentation at HALCHEM VIII, The 8th International Meeting on Halogen Chemistry, Inuyama (September 15th 2017)

11. A list of paper published during or after the period of the fellowship, and the names of the journals in which they appeared (Please fill in the format below). Attach a copy of each article if available.

Author(s)	Title	Name of Journal	Volume	Page	Date	Note
Ramesh C. Samanta, Hisashi Yamamoto	Catalytic Asymmetric Bromocyclization of Polyenes	Journal of The American Chemical Society	139	1460-1463	January 6, 2017	

12. Awards during the period of the fellowship (Name of the award, Institution, date etc.)

HALCHEM VIII Young Scientist Poster Award at the 8th International Meeting on Halogen Chemistry, Inuyama, Japan (September 15th 2017)

13.Future Contact Information

JSPS would like to keep in touch with all of you and provide with our English newsletter, "JSPS Quarterly". It contains the latest information on JSPS programs. In addition, the existing JSPS Alumni Associations and those in the process of being established would like to welcome you as a new member. If you are interested in being involved in the JSPS alumni activities, please check the following boxes. JSPS will provide the information to the alumni association in your country or region.

[✓] Yes, JSPS may forward my contact information to the relevant alumni association.

※If you don't wish your contact information to be forwarded to the relevant alumni association, please erase the check mark.

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Considering JSPS former Fellows to be valuable assets in advancing research between Japan and its counterpart countries, JSPS places great importance on follow-up activities aimed at retaining contact and communication with and among them. Since 1995, JSPS has supported to organize JSPS Alumni Associations and so far 18 associations are officially established. Among 24,000 JSPS former Fellows in total, 7,400 Fellows are now members of alumni associations in their countries or areas. In cooperation with JSPS, they actively hold academic symposium, general assemblies among members annually, maintain website and publish useful newsletters regularly. Please visit our homepage and check which association is suitable for you!

URL: https://www.jsps.go.jp/english/e-plaza/20_alumni.html

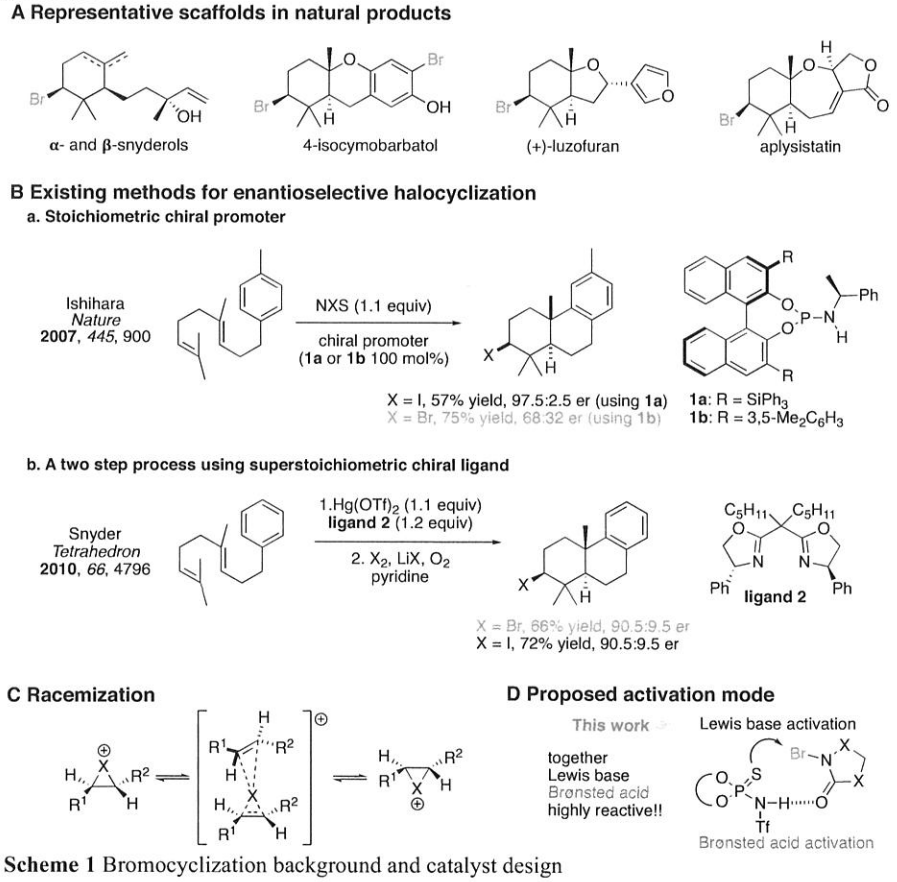
Note: This form must be submitted along with your Host's Form 8 within one month of the end of your fellowship tenure.

Research Report
Development of New Method for Catalytic Asymmetric Electrophilic Halogenations Reactions

Dr. Ramesh C. Samanta (ID No.: P16041)
Host Researcher: Professor Hisashi Yamamoto
Molecular Catalyst Research Center, Chubu University, Kasugai, Japan

Background:

Halogen containing compounds are frequently found in nature. Carbocycles and heterocycles containing one or more halogen atoms appeared as the key structure of several natural products.[1-4] Mother nature synthesizes such molecules mostly by enzymes halo peroxidase and the reaction is initiated by an addition of an electrophilic halogen onto a double bond.[5] Synthesis of halogenated polycyclic compounds can be done by halonium ion induced polyene cyclization. However in laboratory controlling stereochemistry in halocyclization reactions is very challenging. We were involved in searching for a new halogenation catalyst for halocyclization reactions. Bromopolyene cyclization was chosen as our target reaction. While searching in literature, only two reports appeared prior to our study; 1. Ishihara group reported an iodopolyene cyclization by using a stoichiometric chiral phosphoramidate as a promoter in good yield and selectivity. However, this method was limited for iodocyclization and did not work effectively for bromo and chlorocyclization reactions.[6] 2. Snyder group developed a two steps method for the synthesis of such compounds using a superstoichiometric amount of chiral ligand to make the mercurated compound subsequent halodemercuration generated the product.[7]

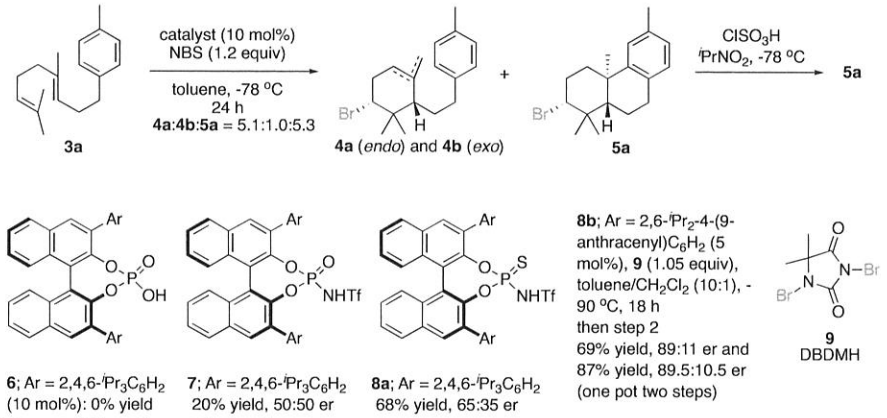


Scheme 1 Bromocyclization background and catalyst design

No suitable catalytic method was available until then. Major problem is the racemization via olefin-to-olefin halonium ion transfer prior to the cyclization. We are the first to develop a catalytic bromopolyene cyclization using a chiral binol derived thiophosphoramide catalyst acting in a bifunctional mode to deliver the products in good yield and selectivities.

Our experiment started with homogeranyl benzene **3a** as substrate and *N*-bromosuccinimide as electrophilic bromine source. We tested chiral phosphoric acids and phosphoric acid derivatives having potential for bifunctional catalyst. The reaction did not proceed at all using chiral phosphoric acid. However, switching to more acidic phosphoramide the reaction proceeded to give the desired cyclization product **5a** together with partially cyclization products **4a** and **4b**, further treatment by chlorosulfonic acid converged to the complete cyclization product **5a** in 20% yield but no enantioselectivity was obtained. Surprisingly using chiral thiophosphoramide **8a** the product was obtained in 68% yield and 30% ee. After rigorous screening of reaction conditions, halogen source and catalyst modification; catalyst **8b** in combination with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as electrophilic bromine source and toluene/CH_2Cl_2 (10:1,v/v) solvent at -90 °C and additional treatment with $ClSO_3H$ delivered the product in 69% yield and 89:11 enantiomeric ratio (er).

C Optimization of bromocyclization reaction



Scheme 2 Reaction optimization

Differently substituted homogeranyl benzene derivatives were reacted under optimized reaction conditions to deliver the products in good yields and diastereo and enantioselctivities. In the case of highly electron rich olefin further cyclization step was not required and the product was obtained in high yield and high enantioseectivity (94% ee).

Geranyl phenols are difficult substrate for halocyclization reactions as it is associated with both low diastereo and enantioselectivity. Under our optimized conditions geranyl phenol was cyclized to give a single diastereomer in good yield and enantioselectivity. Furter cyclization step was not required. This reaction was pretty general for different geranyl phenol derivatives. In the case of highly electron rich substituents on the aromatic ring a different outcome was obtained in high yield and excellent enantioselectivity (99:1 er).

Table 1 Scope of bromocyclization for homogeranyl benzene derivatives

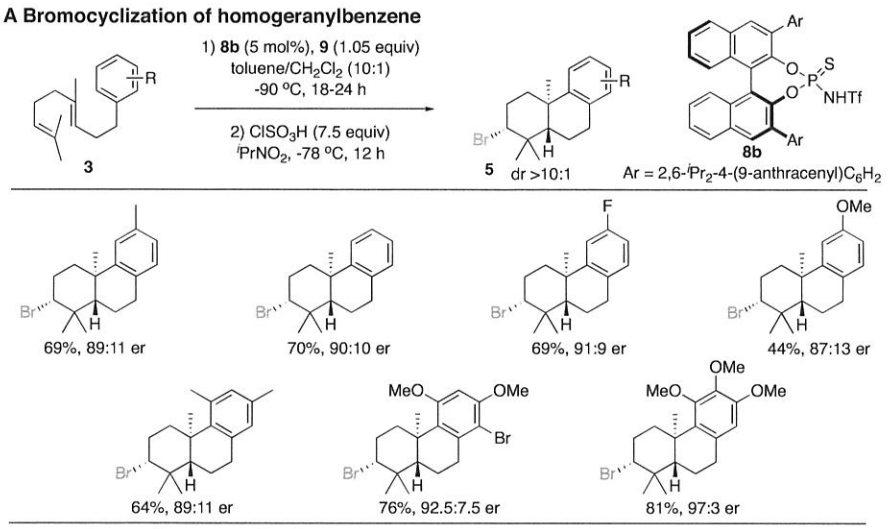
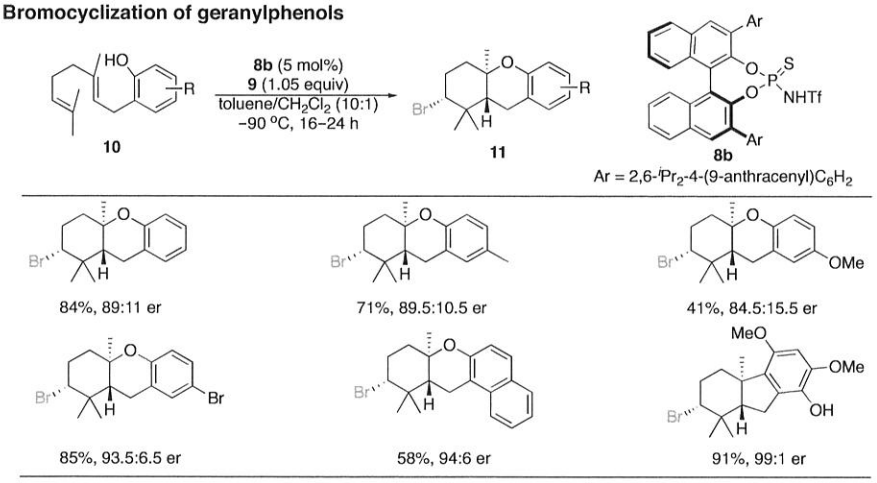
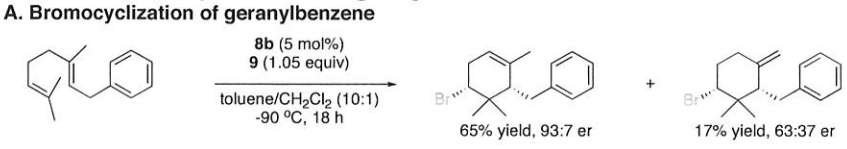
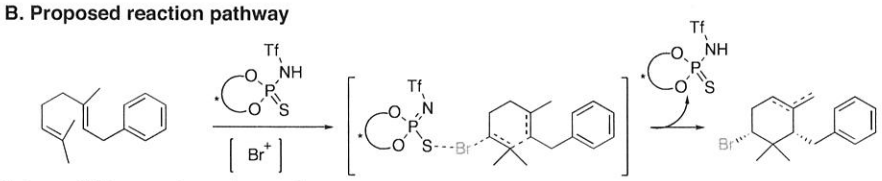


Table 2 Scope of bromocyclization reactions for geranyl phenol derivatives



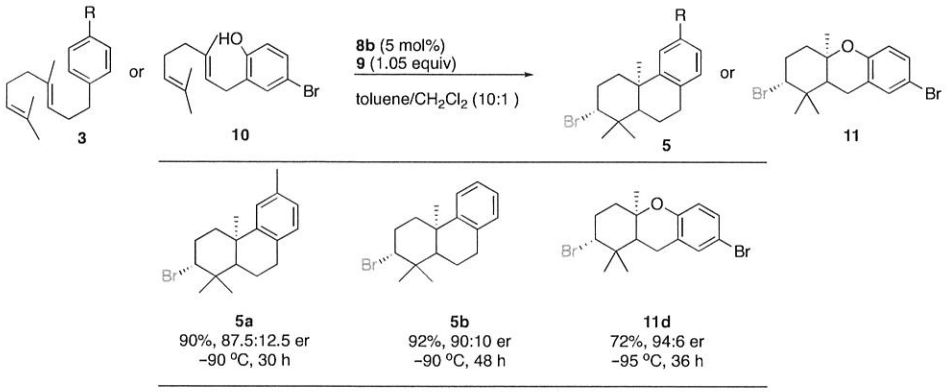
When geranyl benzene was reacted under bromocyclization conditions two different products were obtained with different selectivities. Therefore we propose a concerted mechanism for this reaction and bromonium ion formation can not be the enantioselectivity determining step.





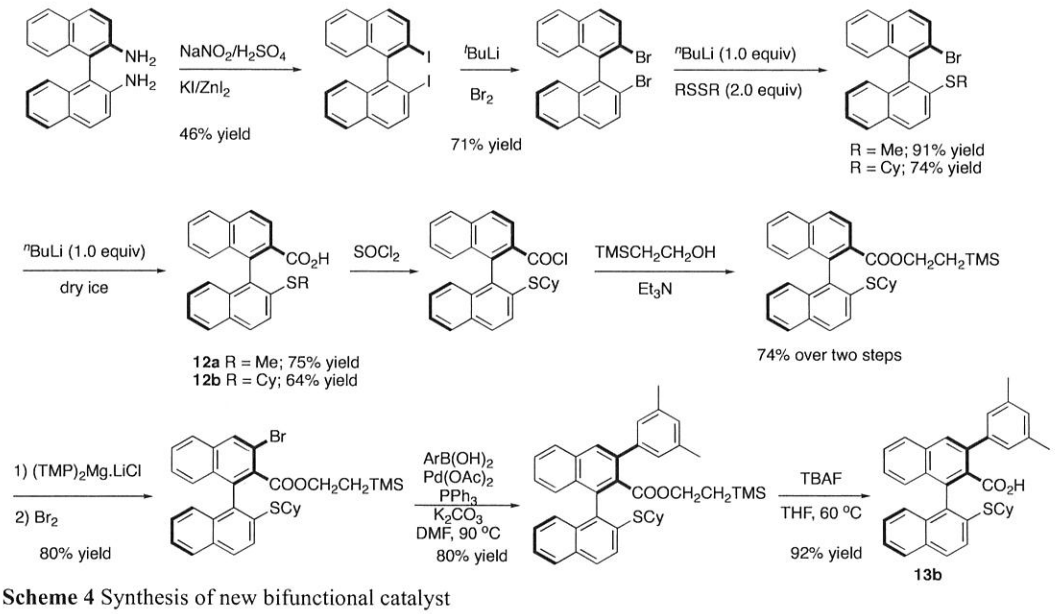
Scheme 3 Proposed reaction pathway

Table 3 Scale up experiments



In order to vouchsafe the synthetic utility, the reaction was performed in 1 mmol scale for several substrates without significant loss of ether yield or selectivities. Detail mechanistic studies and applications are currently under investigation.

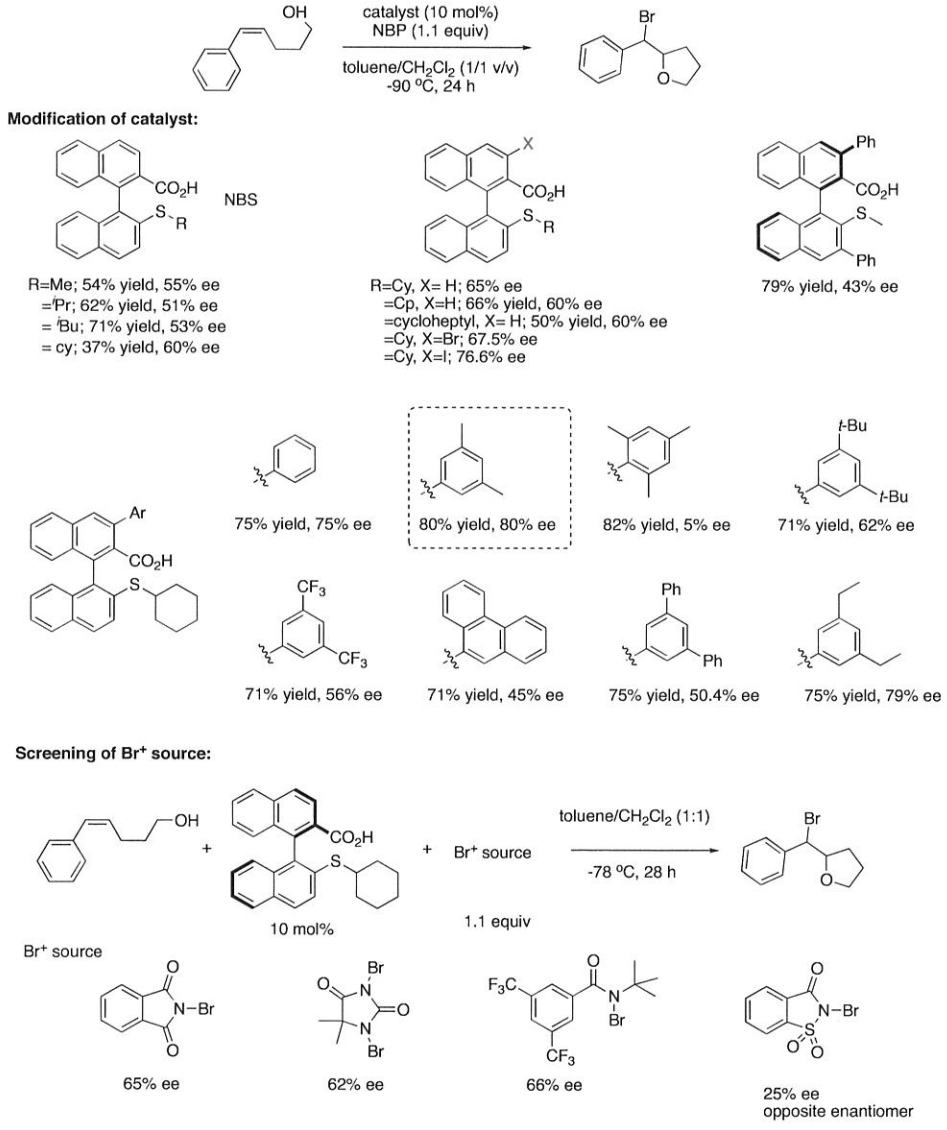
Although there is not enough evidence for the proposed bifunctional mode of this thiophosphoramide catalyst which is responsible for high selectivity in bromopolyene cyclization. We were interested to design a truly bifunctional catalyst for halocyclization reactions. Chiral sulfides and selenides have been used as catalyst for bromocyclization reactions. However, the reactivity of these catalysts was very poor and required several days (5day) to complete the reaction.[8] Pleasingly, the use of stoichiometric amount of strong Brønsted acids (methane sulfonic acid; MsOH) accelerates the rate of these reactions to certain extent.[9] The use of catalytic chiral Brønsted acids together with an achiral sulfide as co-catalyst facilitates the reaction in good yield and selectivity within reasonable reaction time (24 h).[10] We envisaged that if we could install the acid and sulfide in the same molecule that can react in a cooperative fashion might be more efficient in terms of both in reactivity and selectivity.



Scheme 4 Synthesis of new bifunctional catalyst

Carboxylic acid; a very weak Brønsted acid at 2-position and a methyl sulfide at 2' position of a chiral binaphthyl core was synthesized and employed as a catalyst for bromoetherification reaction of a *cis*-5-phenyl pent 4-ene-1-ol. Synthesis of the catalyst **12a** was started from chiral binaphthyl amine (scheme 4). The catalysis reaction proceeded smoothly at -78 °C and 5-exo-trig cyclization product was selectively formed in 75% yield and 65% ee. The modification of catalyst showed that substituents at 3-position has strong influence on selectivity. However, the catalyst with 3,3' disphenyl substituents resulted lower selectivity. Substituents at 3-position and as well at sulfur were then varied. Further modification of the catalyst is demonstrated in scheme 4. A 3,5-dimethyl phenyl group at 3-position and a cyclohexyl substituent at sulfur turned out to be the best catalyst **13b** to deliver the bromoetherification product in 79% yield and with 80% ee. Scope of this reaction is currently under investigation.

Table 4 Optimization for bromoetherification reaction



Conclusion:

We have successfully developed the first catalytic asymmetric bromopolyene cyclization using a chiral binol derived thiophosphoramide catalyst and 1,3-dibromo-

5,5-dimethylhydantoin (DBDMH) as electrophilic bromine source. Homogeranyl benzene derivatives and geranyl phenols were cyclized in good yields and with good selectivities. The reaction could be scaled up to 1 mmol scale without significant loss of yield or selectivities. We believe that this method will have high impact in natural product synthesis. A truly bifunctional catalyst has been developed and showed good catalytic activity for bromoetherification reaction. Expansion of substrate scope and application for other transformations is currently ongoing.

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1. Gribble, G. W. *J. Nat. Prod.* **1992**, *55*, 1353. 2. Craigie, J. S.;Gruenig, D. E. *Science* **1967**, *157*, 1058. 3. Wang, B.-G.; Gloer, J. B.; Ji, N. Y.; Zhao, J.-C. *Chem. Rev.* **2013**, *113*, 3632. 4. Chung, W.-J.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2016**, *55*, 4396. 5. Bulter, A.; Carter-Franklin, J. N. *Nat. Prod. Rep.* **2004**, *21*, 180. 6. Sakakura, A. Ukai, A. Ishihara, K. *Nature* **2007**, *445*, 900. 7. Snyder, S. A.; Treitler, D. S.; Schall, A. *Tetrahedron* **2010**, *66*, 4796. 8. Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232. 9. Ke, Z.; Tan, C. K.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2014**, *136*, 5627. 10. Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256.