Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2019, **10**, 2773

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 20th December 2018
Accepted 15th January 2019

DOI: 10.1039/c8sc05702h

rsc.li/chemical-science

Open Access Article. Published on 17 2019. Downloaded on 08-07-2025 13:55:34.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Chiral cyclopentadienyl Rh^{III}-catalyzed enantioselective cyclopropanation of electron-deficient olefins enable rapid access to UPF-648 and oxylipin natural products†

Coralie Duchemin and Nicolai Cramer *

Chiral cyclopentadienyl Rh^{III} complexes efficiently catalyze enantioselective cyclopropanations of electron-deficient olefins with *N*-enoxysuccinimides as the C1 unit. Excellent asymmetric inductions and high diastereoselectivities can be obtained for a wide range of substrate combinations. The reaction proceeds under mild conditions without precautions to exclude air and water. Moreover, the synthetic utility of the developed method is demonstrated by concise syntheses of members of the oxylipin natural products family and the KMO inhibitor UPF-648.

Introduction

Chiral cyclopropanes are important structural motifs frequently found in a diverse range of natural products and biologically active compounds.[1] Cyclopropanes are attractive building blocks for drug discovery due to their rigid structure with defined three-dimensional vectors and their good metabolic stability.[2] Moreover, they are versatile intermediates for synthesis as ring-opening reactions opens access to useful building blocks.[3] Synthetically, the most practical strategy to build the cyclopropane motif consists of an enantioselective cycloaddition between an olefin and a suitable C1 unit.[4] For instance, transition-metal catalyzed reactions[5] – metal-carbenoid mediated transformations[5a] and the ring closure of π-allylpalladium species,[5b] Lewis-acid catalyzed Simmons–Smith reactions[6] as well as radical processes[7] have proven to be powerful methods for the asymmetric cyclopropanations of electron-rich olefins. Complementary, asymmetric Michael-initiated ring-closure (MIRC) reactions have been shown to be an attractive cyclopropanation method for electron-deficient olefins.[8–10] Moreover, tailored transition-metal catalysts enable enantioselective cyclopropanations of electron-deficient olefins with diazo compounds.[11] However, these transformations still have limitations in scope and frequently require potentially hazardous reactants. Therefore, the development of novel and efficient catalytic cyclopropanation strategies using complementary substrates remain an attractive and important task. In this respect, Rovis and co-workers recently reported a unique cyclopropanation using *N*-enoxyphthalimides and Michael acceptors as substrates (Fig. 1).[12] Tailored achiral cyclopentadienyl Rh^{III} catalysts enabled this transformation and moreover allowed to efficiently control its diastereoselectivity.[12b] Given our longstanding focus on the development of chiral cyclopentadienyl (Cp^x) metal catalysts[13] for challenging asymmetric transformations,[14] we felt prompted to explore the feasibility of an enantioselective Rovis-cyclopropanation. This is

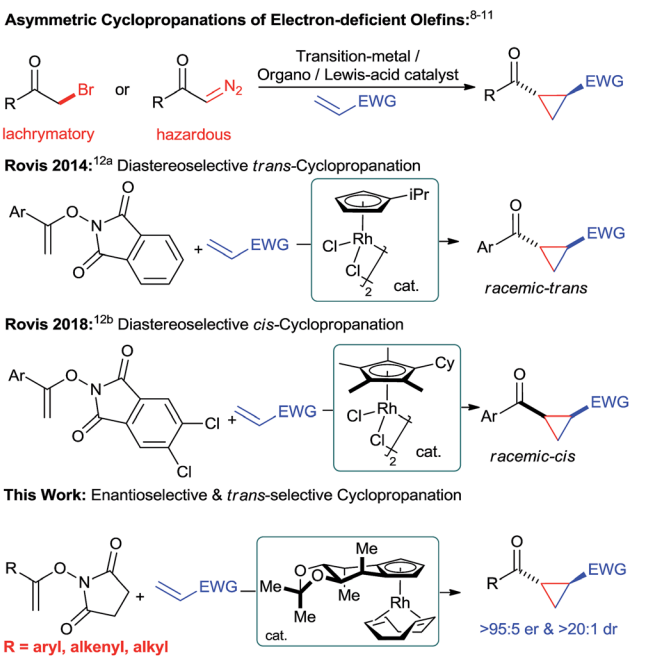


Fig. 1 Catalytic methods for the selective cyclopropanation of electron-deficient olefins.

Laboratory of Asymmetric Catalysis and Synthesis, EPFL SB ISIC LCSA, BCH 4305, CH-1015 Lausanne, Switzerland. E-mail: nicolai.cramer@epfl.ch

† Electronic supplementary information (ESI) available: Experimental procedures and characterization of all new compounds. See DOI: 10.1039/c8sc05702h

Open Access Article. Published on 17 2019. Downloaded on 08-07-2025 13:55:34.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

a formidable challenge to expand the current boundaries of asymmetric Cp^xRh^{III} catalysis beyond functionalizations of aryl C_{sp2}–H bonds.[15] Despite ample precedence with achiral Cp^*Rh^{III} complexes,[16] the corresponding asymmetric functionalization of alkenyl C_{sp2}–H bonds with Cp^xRh^{III} catalysts remained so far elusive.[17]

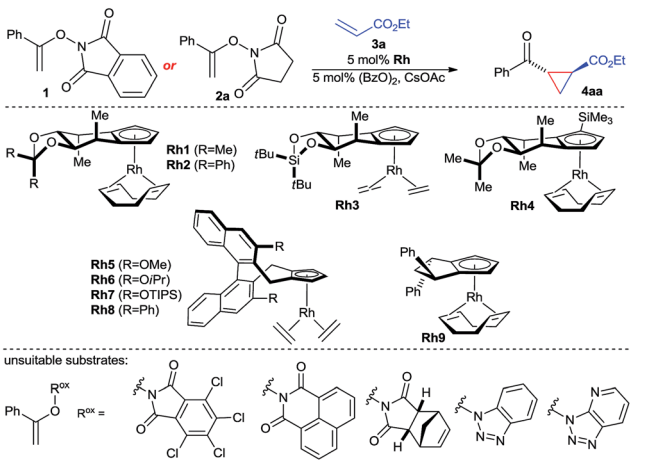
Herein, we report a highly enantioselective alkenyl C–H bond functionalization providing access to chiral cyclopropanes under mild conditions.

Results and discussion

The envisioned enantioselective cyclopropanation was investigated with *N*-enoxyphthalimide **1** and ethyl acrylate (Table 1). **Rh1** featuring our simplest first generation Cp^x design[13b] provided desired cyclopropane **4aa** in 71% yield, >20 : 1 *trans*/*cis* ratio and 93.5 : 6.5 er (entry 1). Increasing of the size of the backwall using a diphenyl acetal (**Rh2**) or a silyl bridge (**Rh3**) reduced the enantioselectivity (entries 2 and 3). Complex **Rh4** with a trisubstituted TMS-bearing Cp^x ligand[13g] was as well inferior (entry 4). Binaphthyl-derived ligands (**Rh5–Rh8**)[13c] are not suited and gave a general poor performance concerning yield, diastereo- and enantioselectivity (entries 5–8). Moreover, usage of **Rh9** with a cyclopentyl-backbone Cp^x ligand[13f] formed cyclopropane **4aa** in negligible amounts (entry 9). The solvent has a large influence. Replacement of TFE by either ethanol or HFIP gave dramatically lower yields (entries 10 and 11). A lower reaction temperature (0 °C) caused a sluggish reaction with no discernible increase in enantioselectivity (entry 12), whereas heating to 50 °C triggered slight erosion in yield and selectivity (entry 13). A short premixing period between the rhodium catalyst and the oxidant increased the yield to 76% while maintaining an enantiomeric ratio of 93.5 : 6.5 (entry 14). The nature of the imide of the oxidizing directing group was important. A range of other oxidizing directing group R^{ox} failed to provide the desired reactivity which was attributed to poor solubility. However, replacement of **1** by enoxysuccinimide **2a** resulted in a cleaner and faster reaction, giving **4aa** in 78% isolated yield with an improved excellent enantioselectivity of 97 : 3, although with a lower diastereoselectivity of 4 : 1 (entry 15).

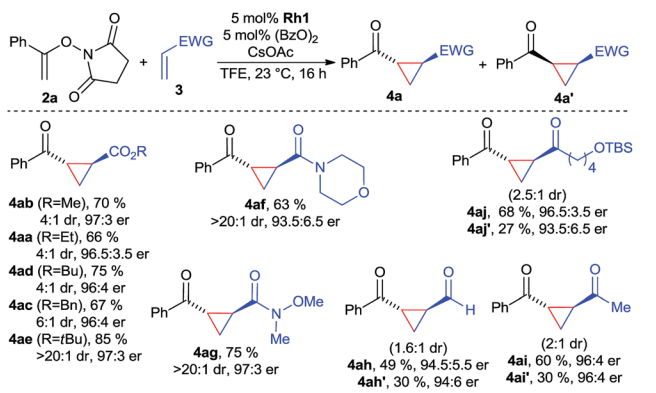
With the optimized conditions, the scope of the reaction was investigated (Scheme 1). A variety of acrylic esters were tested. Commonly used methyl, ethyl, butyl and benzyl esters gave the cyclopropane products with good yields, >95 : 5 er and useful diastereomeric ratios between 4 : 1 and 6 : 1. Notably, *tert*-butyl acrylate provided in all aspects superior results, giving **4ae** in 85% yield with >20 : 1 dr and 97 : 3 er. Moreover, acrylamide derivatives, exemplified with morpholine **3f** reacted smoothly, giving **4af** in excellent dr and suitable yields and enantioselectivity. In particular, Weinreb acrylamide proved to be well suited, giving cyclopropane **4ag** in 75% yield with >20 : 1 dr and 97 : 3 er. Surprisingly, both acrolein and MVK acceptors gave high yields of the corresponding cyclopropanes **4ah** and **4ai**,

Table 1 Optimization of the asymmetric cyclopropanation[a]



Entry	Rh	Solvent	T (°C)	% yield[b]	Trans/cis[c]	er[d]
1	**Rh1**	TFE	23	71	>20 : 1	93.5 : 6.5
2	**Rh2**	TFE	23	68	>20 : 1	84 : 16
3	**Rh3**	TFE	23	51	>20 : 1	85 : 15
4	**Rh4**	TFE	23	55	>20 : 1	78.5 : 21.5
5	**Rh5**	TFE	23	27	3.4 : 1	45 : 55
6	**Rh6**	TFE	23	15	1.1 : 1	39 : 61
7	**Rh7**	TFE	23	22	1 : 2.5	47 : 53
8	**Rh8**	TFE	23	10	4.8 : 1	73 : 27
9	**Rh9**	TFE	23	<5	—	—
10	**Rh1**	HFIP	23	<5	—	—
11	**Rh1**	EtOH	23	15	>20 : 1	87 : 13
12	**Rh1**	TFE	0	26	>20 : 1	93.5 : 6.5
13	**Rh1**	TFE	50	62	8 : 1	91.5 : 8.5
14[e]	**Rh1**	TFE	23	76	>20 : 1	93.5 : 6.5
15[e,f]	**Rh1**	TFE	23	78	4 : 1	97 : 3

[a] 0.05 mmol **1**, 0.055 mmol **3a**, 2.5 μmol **Rh**, 2.5 μmol $(BzO)_2$, 0.2 M in the indicated solvent and temperature for 16 h. [b] Isolated yield. [c] dr determined by ^{1}H-NMR of the crude product. [d] er determined by HPLC analysis with a chiral stationary phase. [e] $(BzO)_2$ and **Rh** were premixed for 2 min. [f] With **2a** instead of **1**.



Scheme 1 Suitable acceptors for the enantioselective cyclopropanation. Reaction conditions: 0.10 mmol **2a**, 5.0 μmol **Rh1**, 5.0 μmol $(BzO)_2$, 0.12 mmol **2**, 0.2 M in TFE at 23 °C for 16 h; isolated yields; dr determined by ^{1}H-NMR of the crude product; er determined by HPLC analysis with a chiral stationary phase.

This journal is © The Royal Society of Chemistry 2019

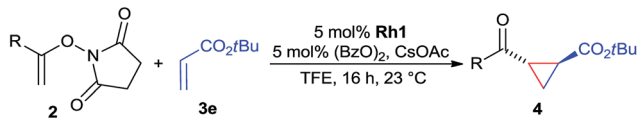
Open Access Article. Published on 17 2019. Downloaded on 08-07-2025 13:55:34.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

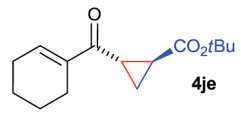
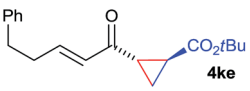
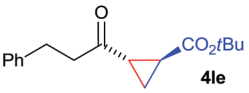
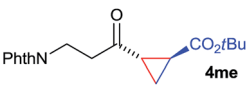
maintaining high levels of enantioselectivity. However, due to their small size, the diastereomeric ratio was with 1.6 : 1, respectively 2 : 1 lower. Interestingly, the *cis*-products were formed in approximately the same enantioselectivity. Besides MVK, similar reactivity was observed for longer chain vinyl ketone giving **4aj**. Considering the dearth of methods for enantiopure *cis*-cyclopropanes from electron-poor olefins,[18] this observation could be a starting point in the development of an enantioselective *cis*-selective variant. Heteroatom-based Michael acceptor such as phenyl vinyl sulfone/selenone or ethenesulfonyl fluoride did not undergo cyclopropanation. Acrylates with α or β-substitution were not reactive acceptors with the current catalytic system.

The range of suitable enoxy-succinimides was investigated (Table 2). We first evaluated variations of the steric and electronic properties of the aryl-substituted enoxy-succinimides. Electron-donating and withdrawing groups in the *para* position were found to have very little influence on the reaction outcome, providing high yields and enantioselectivities of the corresponding cyclopropanes **4** (entries 1–4). Along the same lines, *meta*- (**2f**) and *ortho*- (**2g**) substitution as well as heteroaryl (**2i**) and condensed aromatic substituent (**2h**) were tolerated well. Due to limited solubility in TFE, substrates having a naphthyl- (**2h**) or chloroarene substituent (**2e**) required longer reaction times. Attractively, besides aryl-substituted enoxy-succinimides, the cyclopropanation worked very well with dienenoxy substrates such as **2j** and **2k** giving enone products **4je** and **4ke** in an excellent er of 96 : 4. Notably, no competing Diels–Alder cycloaddition between the electron-rich diene and the acrylate acceptor was observed under the reaction conditions. Moreover, the reactivity, diastereo- and enantioselectivity were excellent for alkyl substituents, leading to functionalized cyclopropanes **4le** and **4me** (entries 11 and 12).

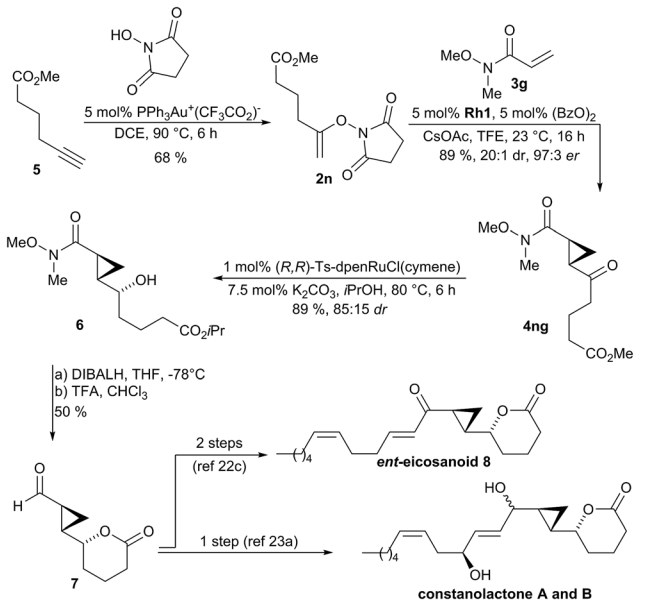
The synthetic utility of the method was demonstrated as key step in the synthesis of natural products and inhibitor UPC-648. Constanolactones[19] and *ent*-eicosanoid **8**[20] are marine oxylipins[21] containing a *trans*-cyclopropane. Previous syntheses[22,23] used lactone **7** as common intermediate which could be accessed in 6[23a] or 13 steps.[22c] In a streamlined access to required *N*-enoxysuccinimide **2n**, we developed a gold(I)-catalyzed addition of *N*-hydroxysuccinimide to terminal alkyne **5** which directly provided substrate **2n** in 68% yield (Scheme 2).[24] Subjecting **2n** to the developed optimized enantioselective cyclopropanation conditions in the presence of Weinreb acryl amide **3g** gave cyclopropane **4ng** in 89% yield, 97 : 3 enantiomeric ratio and >20 : 1 dr. The transformation was efficient for gram-scale preparation giving 1.10 g of **4ng**. Diastereoselective reduction of **4ng** with Noyori's catalyst gave secondary alcohol **6** in 89% yield and 85 : 15 dr. Reduction of the Weinreb amide over the isopropyl ester of **6** and subsequent lactonization under acidic conditions yielded intermediate **7** in 50% yield over 2 steps. This intermediate can be elaborated either in a single step operation into constanolactone A and B,[23a] or by a two-step sequence into *ent*-eicosanoid **8**.[22c]

Table 2 Variations of the *N*-enoxysuccinimide partner[a]



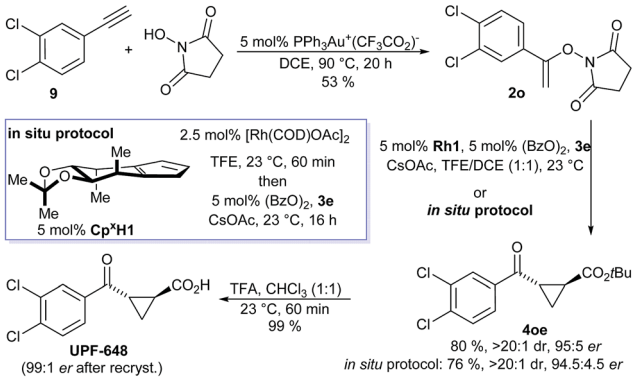
Entry	2	4 (R)	% yield[b]	dr[c]	er[d]
1	**2b**	**4be** (4-Me-C_6H_4)	85	>20 : 1	97 : 3
2	**2c**	**4ce** (4-OMe-C_6H_4)	90	>20 : 1	97.5 : 2.5
3	**2d**	**4de** (4-F-C_6H_4)	89	>20 : 1	95 : 5
4[e]	**2e**	**4ee** (4-Cl-C_6H_4)	81	>20 : 1	97 : 3
5	**2f**	**4fe** (3-MeO-C_6H_4)	85	>20 : 1	97 : 3
6	**2g**	**4ge** (2-Me-C_6H_4)	73	>20 : 1	96 : 4
7[f]	**2h**	**4he** (2-naphthyl)	83	>20 : 1	93.5 : 6.5
8	**2i**	**4ie** (3-thienyl)	69	>20 : 1	97.5 : 2.5
9	**2j**	 **4je**	87	>20 : 1	96 : 4
10	**2k**	 **4ke**	72	>20 : 1	96 : 4
11	**2l**	 **4le**	75	>20 : 1	96 : 4
12	**2m**	 **4me**	77	>20 : 1	96 : 4

[a] 0.10 mmol **2**, 5.0 μmol **Rh1**, 5.0 μmol $(BzO)_2$, 0.12 mmol **3e**, 0.20 mmol CsOAc, 0.2 M in TFE at 23 °C for 16 h. [b] Isolated yield. [c] Determined by ^{1}H-NMR of the crude product. [d] Determined by HPLC analysis with a chiral stationary phase. [e] For 40 h. [f] For 56 h.



Scheme 2 Synthetic application of the enantioselective cyclopropanation in the formal synthesis of members of oxylipin natural products family.

Open Access Article. Published on 17 2019. Downloaded on 08-07-2025 13:55:34.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



Scheme 3 Synthetic application of the enantioselective cyclopropanation in the formal synthesis of the KMO inhibitor UPF-648.

UPF-648, a potent inhibitor (IC_{50} = 40 nM) for kynurenine 3-monooxygenase (KMO),[25,26] was identified as another attractive target. Inhibition of KMO has therapeutic potential for several neurodegenerative disorders, including Huntington's disease.[27] The two reported syntheses of UPF-648 are long and use a stoichiometric chiral auxiliary[28] or involve a resolution.[29] Therefore, a short catalytic enantioselective route represents significant synthetic value. Our synthesis starts with a gold-catalyzed addition of *N*-hydroxy succinimide to 3,4-dichloro phenyl acetylene (**9**) affording *N*-enoxysuccinimide **2o** in 53% yield (Scheme 3). The enantioselective cyclopropanation was conducted without any precaution to exclude moisture or oxygen, giving cyclopropane **4oe** in 80% yield and 95 : 5 er. Alternatively, application of our recently developed *in situ* Cp^xRh catalyst preparation[13g] provided **4oe** in 76% yield and 94.5 : 4.5 er. Cleavage of the *tert*-butyl ester gave UPF-648 ester. A subsequent recrystallization increased its optical purity to 99 : 1 er. Overall, UPF-648 could be synthesized in 3 steps in a catalytic enantioselective fashion with an overall yield of 39%.

Conclusions

In summary, we have developed a highly enantioselective and diastereoselective cyclopropanation of electron-deficient olefins using enoxysuccinimides as the one-carbon component. The transformation is catalyzed by chiral Cp^xRh^{III} complexes and operates under mild and open-flask reaction conditions. We applied the transformation as a key step in the synthesis of the oxylipin family of natural products and the kynurenine 3-monooxygenase inhibitor UPF-648, showcasing its synthetic utility.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work is supported by the Swiss National Science Foundation (no. 157741).

Notes and references

1 (*a*) A. de Meijere, S. I. Kozhushkov and H. Schill, *Chem. Rev.*, 2006, **106**, 4926; (*b*) J. Pietruszka, *Chem. Rev.*, 2003, **103**, 1051.
2 (*a*) L. A. Wessjohann, W. Brandt and T. Thiemann, *Chem. Rev.*, 2003, **103**, 1625; (*b*) T. T. Talele, *J. Med. Chem.*, 2016, **59**, 8712.
3 (*a*) D. C. Nonhebel, *Chem. Soc. Rev.*, 1993, **22**, 347; (*b*) C. Ebner and E. M. Carreira, *Chem. Rev.*, 2017, **117**, 11651.
4 (*a*) H. Lebel, J.-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977; (*b*) H. Pellissier, *Tetrahedron*, 2008, **64**, 7041; (*c*) W. Wu, Z. Lin and H. Jiang, *Org. Biomol. Chem.*, 2018, **16**, 7315.
5 (*a*) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115**, 9981; (*b*) J.-Q. Huang, W. Liu, B.-H. Zheng, X. Y. Liu, Z. Yang, C.-H. Ding, H. Li, Q. Peng and X.-L. Hou, *ACS Catal.*, 2018, **8**, 1964.
6 A. B. Charette, C. Molinaro and C. Brochu, *J. Am. Chem. Soc.*, 2001, **123**, 12168.
7 L. Ye, Q.-S. Gu, Y. Tian, X. Meng, G.-C. Chen and X.-Y. Liu, *Nat. Commun.*, 2018, **9**, 227.
8 (*a*) C. D. Papageorgiou, M. A. Cubillo de Dios, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2004, **43**, 4641; (*b*) C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2006, **45**, 6024.
9 (*a*) V. K. Aggarwal, H. W. Smith, R. V. H. Jones and R. Fieldhouse, *Chem. Commun.*, 1997, 1785; (*b*) V. K. Aggarwal, H. W. Smith, G. Hynd, R. V. H. Jones, R. Fieldhouse and S. E. Spey, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3267; (*c*) V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd and M. Porcelloni, *Angew. Chem., Int. Ed.*, 2001, **40**, 1433.
10 (*a*) L. Gao, G.-S. Hwang and D. H. Ryu, *J. Am. Chem. Soc.*, 2011, **133**, 20708; (*b*) S. Y. Shim, J. Y. Kim, M. Nam, G.-S. Hwang and D. H. Ryu, *Org. Lett.*, 2016, **18**, 160; (*c*) G.-J. Sun, J. Gong and Q. Kang, *J. Org. Chem.*, 2017, **82**, 796; (*d*) X. Zhong, J. Lv and S. Luo, *Org. Lett.*, 2017, **19**, 3331.
11 (*a*) J. A. Miller, W. Jin and S. T. Nguyen, *Angew. Chem., Int. Ed.*, 2002, **41**, 2953; (*b*) Y. Chen, J. V. Ruppel and X. P. Zhang, *J. Am. Chem. Soc.*, 2007, **129**, 12074; (*c*) S. Zhu, X. Xu, J. A. Perman and X. P. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 12796; (*d*) H. Wang, D. M. Guptill, A. Varela-Alvarez, D. G. Musaev and H. M. L. Davies, *Chem. Sci.*, 2013, **4**, 2844; (*e*) X. Xu, Y. Wang, X. Cui, L. Wojtas and X. P. Zhang, *Chem. Sci.*, 2017, **8**, 4347.
12 (*a*) T. Piou and T. Rovis, *J. Am. Chem. Soc.*, 2014, **136**, 11292; (*b*) T. Piou, F. Romanov-Michailidis, M. A. Ashley, M. Romanova-Michaelides and T. Rovis, *J. Am. Chem. Soc.*, 2018, **140**, 9587; (*c*) T. Piou and T. Rovis, *Acc. Chem. Res.*, 2018, **51**, 170; (*d*) S. Vásquez-Céspedes, X. Wang and F. Glorius, *ACS Catal.*, 2018, **8**, 242.
13 (*a*) C. G. Newton, D. Kossler and N. Cramer, *J. Am. Chem. Soc.*, 2016, **138**, 3935; (*b*) B. Ye and N. Cramer, *Science*, 2012, **338**, 504; (*c*) B. Ye and N. Cramer, *J. Am. Chem. Soc.*, 2013, **135**, 636; (*d*) D. Kossler and N. Cramer, *J. Am. Chem.*

 This journal is © The Royal Society of Chemistry 2019

Open Access Article. Published on 17 2019. Downloaded on 08-07-2025 13:55:34.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Soc., 2015, **137**, 12478; (*e*) B. Ye and N. Cramer, *Acc. Chem. Res.*, 2015, **48**, 1308; (*f*) S.-G. Wang, S. H. Park and N. Cramer, *Angew. Chem., Int. Ed.*, 2018, **57**, 5459; (*g*) B. Audic, M. D. Wodrich and N. Cramer, *Chem. Sci.*, 2019, **10**, 781.

14 (*a*) C. Zheng and S.-L. You, *RSC Adv.*, 2014, **4**, 6173; (*b*) C. G. Newton, S.-G. Wang, C. C. Oliveira and N. Cramer, *Chem. Rev.*, 2017, **117**, 8908; (*c*) T. G. Saint-Denis, R.-Y. Zhu, G. Chen, Q.-F. Wu and J.-Q. Yu, *Science*, 2018, **359**, 759.

15 (*a*) T. K. Hyster, L. Knörr, T. R. Ward and T. Rovis, *Science*, 2012, **338**, 500; (*b*) B. Ye, P. A. Donets and N. Cramer, *Angew. Chem., Int. Ed.*, 2013, **53**, 507; (*c*) B. Ye and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 7896; (*d*) J. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2014, **53**, 13244; (*e*) B. Ye and N. Cramer, *Synlett*, 2015, **26**, 1490; (*f*) J. Zheng, S.-B. Wang, C. Zheng and S.-L. You, *J. Am. Chem. Soc.*, 2015, **137**, 4880; (*g*) S. Reddy Chidipudi, D. J. Burns, I. Khan and H. W. Lam, *Angew. Chem., Int. Ed.*, 2015, **54**, 13975; (*h*) M. V. Pham and N. Cramer, *Chem.–Eur. J.*, 2015, **22**, 2270; (*i*) J. Zheng, W.-J. Cui, C. Zheng and S.-L. You, *J. Am. Chem. Soc.*, 2016, **138**, 5242; (*j*) Y. Sun and N. Cramer, *Angew. Chem., Int. Ed.*, 2016, **56**, 364; (*k*) T. J. Potter, D. N. Kamber, B. Q. Mercado and J. A. Ellman, *ACS Catal.*, 2017, **7**, 150; (*l*) Z.-J. Jia, C. Merten, R. Gontla, C. G. Daniliuc, A. P. Antonchick and H. Waldmann, *Angew. Chem., Int. Ed.*, 2017, **56**, 2429; (*m*) J. Zheng, S.-B. Wang, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2017, **56**, 4540; (*n*) Y. Sun and N. Cramer, *Chem. Sci.*, 2018, **9**, 2981; (*o*) E. A. Trifonova, N. M. Ankudinov, A. A. Mikhaylov, D. A. Chusov, Y. V. Nelyubina and D. S. Perekalin, *Angew. Chem., Int. Ed.*, 2018, **57**, 7714; (*p*) G. Shan, J. Flegel, H. Li, C. Merten, S. Ziegler, A. P. Antonchick and H. Waldmann, *Angew. Chem., Int. Ed.*, 2018, **57**, 14250; (*q*) B. Shen, B. Wan and X. Li, *Angew. Chem., Int. Ed.*, 2018, **57**, 15534; (*r*) N. Cramer and Y. Sun, *Angew. Chem., Int. Ed.*, 2018, **57**, 15539.

16 (*a*) J. M. Neely and T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 66; (*b*) T. Piou and T. Rovis, *Nature*, 2015, **527**, 86; (*c*) F. Xie, Z. Qi, S. Yu and X. Li, *J. Am. Chem. Soc.*, 2014, **136**, 4780; (*d*) M. Boultadakis-Arapinis, M. N. Hopkinson and F. Glorius, *Org. Lett.*, 2014, **16**, 1630; (*e*) K. D. Collins, F. Lied and F. Glorius, *Chem. Commun.*, 2014, **50**, 4459; (*f*) C. Feng, D. Feng and T.-P. Loh, *Chem. Commun.*, 2014, **50**, 9865; (*g*) C. Feng, D. Feng, Y. Luo and T.-P. Loh, *Org. Lett.*, 2014, **16**, 5956.

17 (*a*) N. Fujii, F. Kakiuchi, A. Yamada, N. Chatani and S. Murai, *Chem. Lett.*, 1997, **26**, 425; (*b*) K. Tsuchikama, Y. Kuwata, Y.-k. Tahara, Y. Yoshinami and T. Shibata, *Org. Lett.*, 2007, **9**, 3097; (*c*) D. F. Fernández, M. Gulías, J. L. Mascareñas and F. López, *Angew. Chem., Int. Ed.*, 2017, **56**, 9541.

18 (*a*) S. Bachmann, M. Furler and A. Mezzetti, *Organometallics*, 2001, **20**, 2102; (*b*) W. Hu, D. J. Timmons and M. P. Doyle, *Org. Lett.*, 2002, **4**, 901; (*c*) M. J. Johansson, D. J. Gorin, S. T. Staben and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 18002; (*d*) H. Suematsu, S. Kanchiku, T. Uchida and T. Katsuki, *J. Am. Chem. Soc.*, 2008, **130**, 10327; (*e*) B. Herlé, P. M. Holstein and A. M. Echavarren, *ACS Catal.*, 2017, **7**, 3668; (*f*) O. F. Brandenberg, C. K. Prier, K. Chen, A. M. Knight, Z. Wu and F. H. Arnold, *ACS Catal.*, 2018, **8**, 2629.

19 D. G. Nagle and W. H. Gerwick, *Tetrahedron Lett.*, 1990, **31**, 2995.

20 S. W. Baertschi, A. R. Brash and T. M. Harris, *J. Am. Chem. Soc.*, 1989, **111**, 5003.

21 W. H. Gerwick, *Chem. Rev.*, 1993, **93**, 1807.

22 (*a*) J. D. White and M. S. Jensen, *J. Am. Chem. Soc.*, 1993, **115**, 2970; (*b*) T. Nagasawa, Y. Handa, Y. Onoguchi and K. Suzuki, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 31; (*c*) G. Kumaraswamy and M. Padmaja, *J. Org. Chem.*, 2008, **73**, 5198; (*d*) V. Angamuthu, W.-J. Chang and D.-R. Hou, *ACS Omega*, 2017, **2**, 4088.

23 (*a*) J. D. White and M. S. Jensen, *J. Am. Chem. Soc.*, 1995, **117**, 6224; (*b*) J. Yu, J.-Y. Lai, J. Ye, N. Balu, L. M. Reddy, W. Duan, E. R. Fogel, J. H. Capdevila and J. R. Falck, *Tetrahedron Lett.*, 2002, **43**, 3939; (*c*) J. Pietruszka and T. Wilhelm, *Synlett*, 2003, 1698.

24 C. Duchemin and N. Cramer, *Org. Chem. Front.*, 2019, **6**, 209.

25 L. Vécsei, L. Szalárdy, F. Fülöp and J. Toldi, *Nat. Rev. Drug Discovery*, 2012, **12**, 64.

26 M. Amaral, C. Levy, D. J. Heyes, P. Lafite, T. F. Outeiro, F. Giorgini, D. Leys and N. S. Scrutton, *Nature*, 2013, **496**, 382.

27 M. T. Sapko, P. Guidetti, P. Yu, D. A. Tagle, R. Pellicciari and R. Schwarcz, *Exp. Neurol.*, 2006, **197**, 31.

28 L. Benatti, R. Fariello, P. Salvati, R. Pellicciari and C. Caccia, EP1475385 A1, 2004.

29 M. Varasi, A. Giordani, P. Pevarello, R. Pellicciari and C. Speciale, WO 9840344, 1991.