Enantioselective radical cascade cyclization via Ti-catalyzed redox relay

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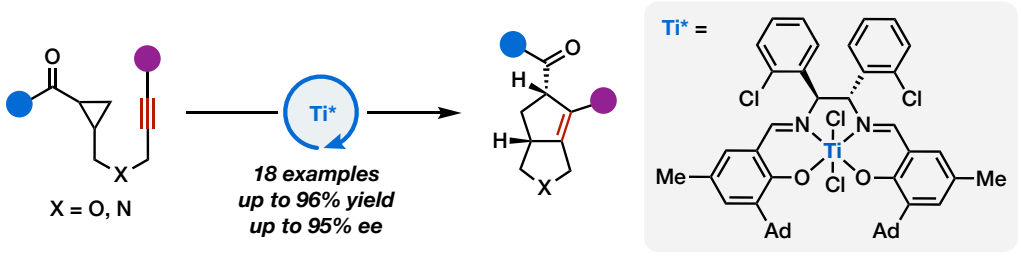
Graphical Abstract



Abstract

Radical cascade cyclization reactions provide an efficient method for the construction of polycyclic architectures with multiple stereogenic centers. However, achieving enantioselectivity control of this type of reaction is a challenging task. Here, we report an enantioselective cyclization of polyfunctional substrates containing cyclopropyl ketone and alkyne units, wherein the stereochemical outcome is directed by a chiral Ti(salen) catalyst. This transformation was proposed to proceed via a radical cascade process involving the reductive ring-opening of the cyclopropyl ketone followed by two annulation events entailing cyclization of the ensuing alkyl radical onto the alkyne and subsequent addition of the incipient vinyl radical to the Ti(IV)-enolate.

Keywords

Radical cascade cyclization, asymmetric catalysis, titanium catalysis, salen ligands, polycyclic molecules

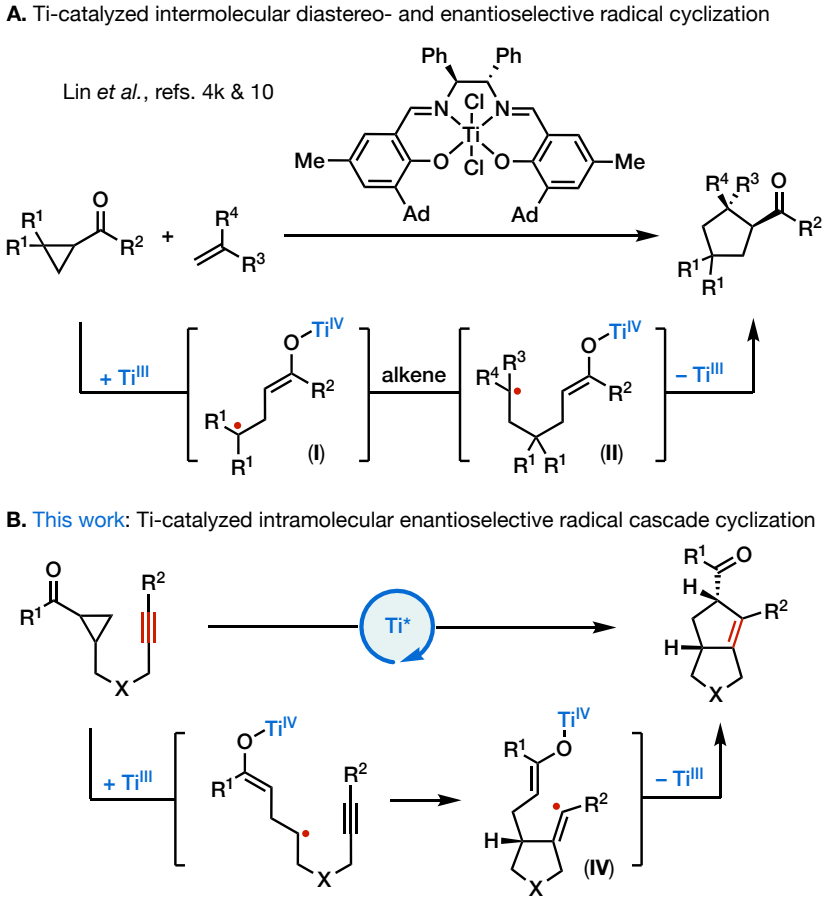
Introduction

Radical cascade cyclization reactions enable efficient access to complex polycyclic molecular scaffolds that are often encountered in biologically active molecules.[1] While numerous methods are available to achieve this type of transformations,[2] the corresponding enantioselective variants are substantially more limited in number due to challenges in regulating the stereochemical behavior of highly reactive free radical intermediates.[3] Among established strategies[4], the use of redox-active metal-based catalysts supported by chiral ligands has proven to be particularly effective in part owing to the convenience in catalyst optimization by structural modification of the chiral ligands[5]. For example, in a cobalt-catalyzed asymmetric radical cascade cyclization of 1,6-enynes with diazo compounds reported by Zhang and coworkers, precise selectivity control was achieved through fine-tuning of the structure of D2-symmetric chiral amidoporphyrin ligands, enabling the construction of multisubstituted cyclopropane-fused tetrahydrofurans with excellent stereoselectivity.[6] Despite these advances, the development of new and highly effective metal-based chiral catalysts for controlling the stereoselectivity of radical cascade cyclization reactions remains an important objective in organic synthesis.

Reductive generation of ketyl radicals via single electron transfer (SET) from reducing metal complexes to carbonyl compounds provides an efficient and versatile platform to initiate radical cascade

cyclization reactions.[7] For example, Procter and coworkers developed a series of radical-mediated cyclization reactions promoted by samarium diiodide (SmI_2), which enables the reductive generation of ketyl radicals to trigger the ring-closing cascade.[8, 2b] However, few enantioselective variants of this strategy have been reported thus far [9]. Among these limited contributions, Procter employed a combination of SmI_2 and a chiral aminodiol ligand to promote the ketyl-olefin cyclization cascade for the formation of chiral octahydropentalenes in high enantiomeric excess.[9a] Although an elegant method, it requires the use of stoichiometric amounts of both the catalyst and the ligand.

Our group has recently developed a family of chiral Ti(salen) catalysts for the diastereo- and enantioselective formal [3 + 2] cycloadditions of cyclopropyl ketones and alkenes (Scheme 1A).[4k] This reaction proceeds through the coordination of the Ti(III) complex to the cyclopropyl ketone group, which then undergoes ligand-to-metal charge transfer followed by ketyl-radical induced ring opening of the three-membered carbocycle. The resultant radical intermediate (**I**) reacts with an alkene, and the ensuing carbon-centered radical (**II**) cyclizes onto the Ti(IV)-enolate motif to close the catalytic cycle and sets the stereogenic centers in high selectivity. This final step simultaneously returns the metal complex to its active Ti(III) oxidation state, thus rendering the reaction catalytic in Ti. We aim to leverage this reactivity to achieve the desired catalytic enantioselective radical cascade cyclization. Specifically, we envisioned that by tethering a cyclopropyl ketone group and a radical acceptor π-system (e.g., an alkyne) in the same substrate, two successive radical cyclization events would give rise to a fused bicyclic product, and that by using a chiral Ti(salen) complex, this reaction could be made highly enantioselective (Scheme 1B).

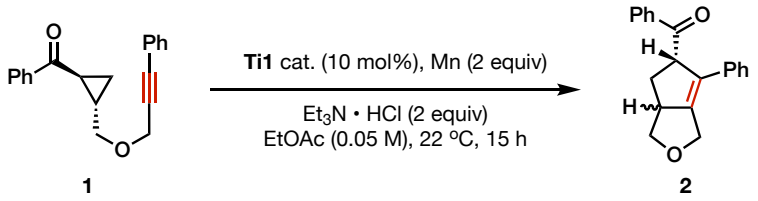


Scheme 1. Achieving stereoselectivity control in radical cascade cyclization reactions via asymmetric titanium catalysis.

Results and discussion

To test our hypothesis, we selected substrate **1** that feature a cyclopropyl ketone and an aryl alkyne connected via an ether linkage, and treated **1** with reaction conditions that were previously developed by our group for the analogous intermolecular [3+2] cycloadditions [10], which employed **Ti3** (10 mol%) as the catalyst, Mn (2 equiv) as the reductant, Et_3N•HCl (2.0 equiv) as an additive, and ethyl acetate (0.05 M) as the solvent, with the reaction carried out at room temperature (22 °C). Indeed, desired bicyclic product **2** was obtained in 83% yield as a mixture of two diastereomers (dr = 1.1:1) with 77% and 59% ee, respectively (entry 2). To further optimize this reaction, a set of Ti complexes with chiral salen ligands bearing various diamine backbones and substituted salicylaldehyde groups were evaluated (entries 2 to 7) [10]. The results showed that this radical cyclization produced the most favorable outcomes in the presence of **Ti1** featuring a 1,2-bis(2-chlorophenyl)ethane-1,2-diamine backbone and 3-admantanyl-5-methyl salicylaldehyde units (entry 1, 91% yield, 1.6:1 dr, 86% ee for major diastereomer, 72% ee for minor diastereomer). Other reaction parameters such as the reductant, additives, temperature, and solvent were also investigated. Although similar enantioselectivity was observed, the use of Zn instead of Mn as the reductant resulted in a decrease in the reaction yield (entry 8). Lowering the loading of Et_3N•HCl also led to lower yield while maintaining comparable stereoselectivity (entry 9). As expected, a catalytic amount of reductant (20 mol%)—which reduced Ti(IV) catalyst precursor to active Ti(III)—was sufficient to promote the reaction, resulting in the formation of the product in high efficiency and enantioselectivity (entry 10). However, this reaction requires a longer time for catalyst pre-activation (1 h; vs 10 min for entry 1). Decreasing the temperature to 0 °C provided marginally higher enantioselectivity (entry 11); however, temperatures lower than 0 °C was found to inhibit the desired reactivity (entry 12). Finally, other solvents such as THF and CH_3CN led to inferior yield and stereoselectivity to EtOAc (entries 13 and 14). We note that in this model system as well as all following examples discussed in this work, two diastereomeric products were obtained in comparable quantities with the dr varying between 1:1 to 2:1. This stereochemical outcome is the result of a substrate-controlled non-selective initial cyclization (from **III** to **IV**, Scheme 1) due to the long distance between the chiral catalyst and the newly formed stereogenic center and the flexible linkage that connects the two. Nevertheless, the Ti catalyst was capable of effectively controlling the stereochemistry of the final cyclization event (from **IV** to the product), thereby providing both diastereomeric products in high enantioselectivity.

Table 1. Reaction optimization[a].

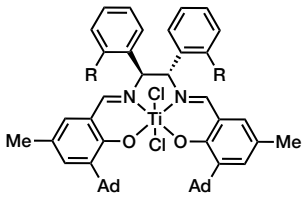


1 2

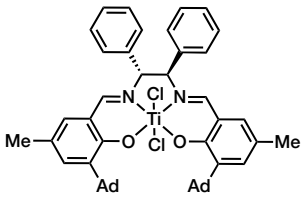
Entry	Variation from the standard conditions	Conversion of **1** (%)	Yield of **2** (%)	dr	ee (%)
1	None	100	89 (91)[b]	1.6:1	86, 72
2	**Ti3** instead of **Ti1**	100	83	1.1:1	-77, -59
3	**Ti2** instead of **Ti1**	100	89	1.6:1	85, 75
4	**Ti4** instead of **Ti1**	100	90	1.3:1	84, 68
5	**Ti5** instead of **Ti1**	100	82	1.6:1	49, 37
6	**Ti6** instead of **Ti1**	94	63	2.9:1	-10, -15
7	**Ti7** instead of **Ti1**	100	71	1:1	-16, -25
8	Zn instead of Mn	100	52	1.9:1	89, 66
9	50 mol% of Et_3N•HCl	100	76	1.5:1	86, 71

10	20 mol% Mn[c]	100	94	1.5:1	86, 72
11	0 °C instead of 22 °C	100	98	2.1:1	89, 77
12	-10 °C instead of 22 °C	<5	0	-[d]	-[d]
13	THF instead of EtOAc	100	61	1.3:1	76, 56
14	CH_3CN instead of EtOAc	88	22	1:1	35, 58

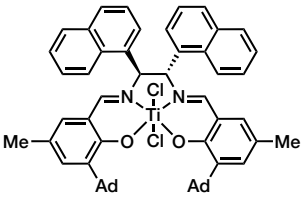
[a]Reaction conditions: **1** (0.05 mmol), Ti cat. (10 mol%), Mn (2 equiv.), Et_3N•HCl (2.0 equiv.), EtOAc (0.05 M), 22 °C, 15 h. Conversion and yield determined by ^1H NMR using CH_2Br_2 as an internal standard. dr = H/H cis: H/H trans, determined by ^1H NMR. ee determined by HPLC with a chiral stationary phase. The former is major diastereomer, the latter is minor diastereomer. [b]Isolated yield. [c]Catalyst preactivated for 1 h. [d]not applicable.



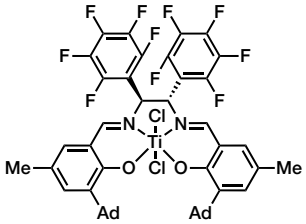
Ti1: R = Cl, Ti2: R = Me



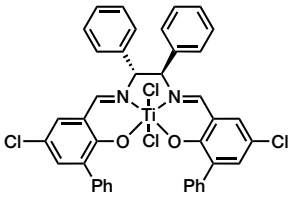
Ti3



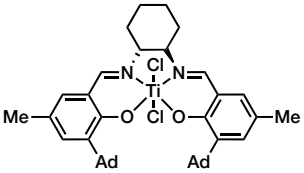
Ti4



Ti5



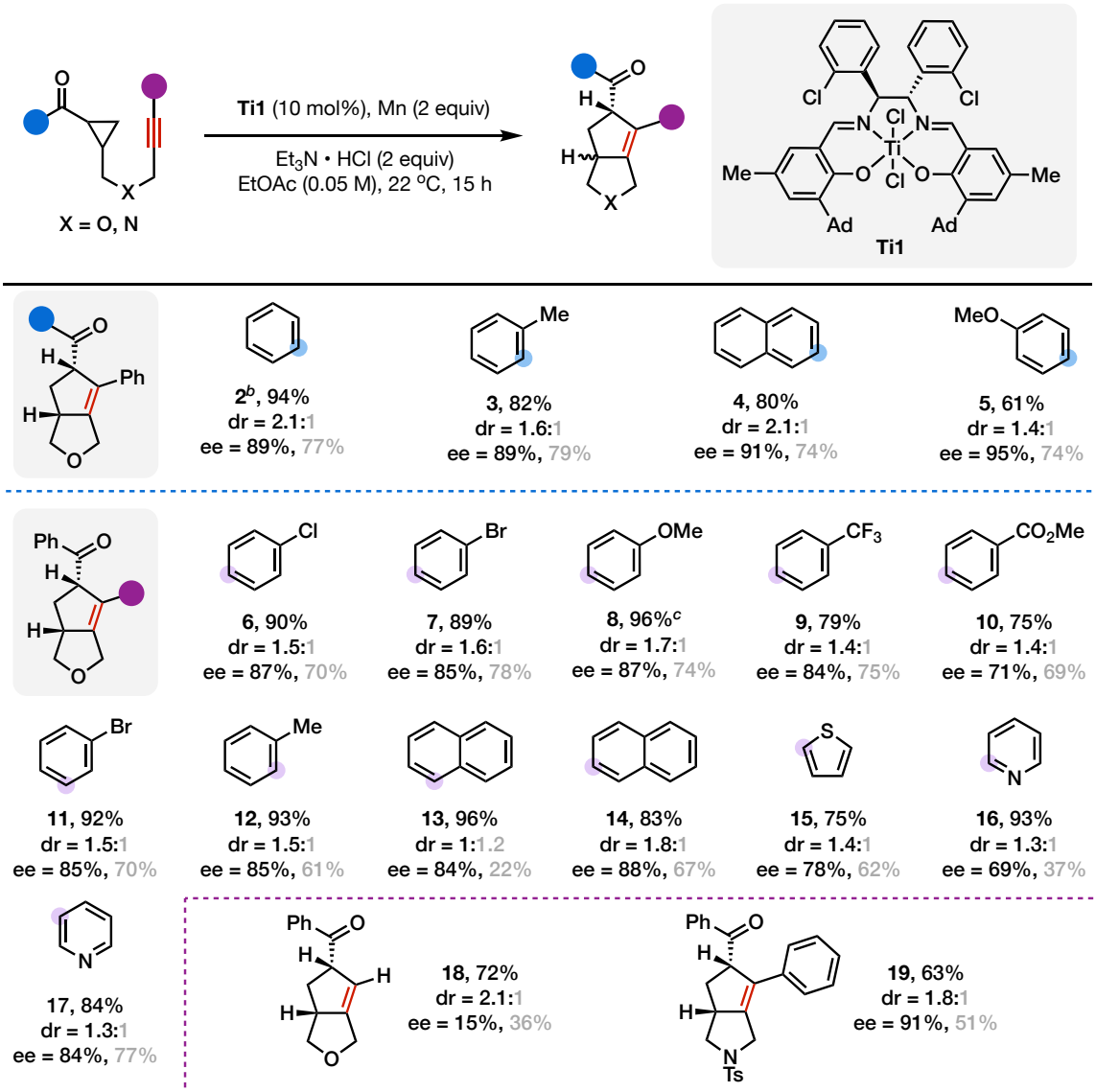
Ti6



Ti7

With the optimal conditions identified, we evaluated the scope of this radical cascade cyclization reaction (Table 2). A panel of substrates analogous to **1** and featuring cyclopropyl ketones with various aryl substituents were effectively and enantioselectively converted to the desired products (**2**–**5**). An *ortho*-substitution on the phenyl ring, which could impede the initial substrate–catalyst coordination, was tolerated (**3**). Regarding substation on the alkyne group, electron-neutral and -rich aryl groups were compatible, delivering the corresponding bicyclic products in excellent yield with high enantioselectivity (**8**, **12**, **13**, **14**). Substrates bearing haloarenes successfully participated in the reaction (**6**, **7**, **11**), producing a series of products that could be readily further functionalized via cross-coupling. Electron-poor aryl groups were also compatible (**10**, **11**), albeit giving marginally decreased yield and enantioselectivity. Several products containing heterocycles such as thiophene (**15**) and pyridine (**16, 17**) were successfully synthesized with slightly diminished enantioselectivity. Cyclization of a terminal alkyne-derived substrate showed good reactivity but the products were obtained with only 15% and 36% ee (**18**). Finally, this radical cascade cyclization was applied to a substrate bearing sulfonamide linkage, granting access to N-containing bicycles in a combined 63% yield with 91% and 50% ee for the two diastereomers (**20**).

Table 2. Substrate scope.[a]



[a]Reactions were performed on a 0.05 mmol scale with substrate (1.0 equiv), **Ti1** (10 mol%), Mn (2 equiv), Et_3N•HCl (2.0 equiv), EtOAc (0.05 M), 22 °C, 15 h. Isolated yields are reported. dr = H/H *cis* : H/H *trans*, as determined by ^{1}H NMR (see Supporting Information for stereochemistry assignments). Ee were determined using HPLC with a chiral stationary phase. The former value is for the major diastereomer and the latter is for the minor diastereomer. [b]0 °C. [c]NMR yield using CH_2Br_2 as an internal standard.

Conclusion

In summary, we have developed an enantioselective radical cascade cyclization of cyclopropyl ketones and alkynes catalyzed by a chiral Ti(salen) complex. From readily prepared precursors, this reaction provides direct access to chiral fused-bicyclic ketones featuring two stereogenic centers with high enantiomeric purity. We anticipate that a similar catalytic strategy employing chiral Ti(salen) catalysts will enable a diverse range of analogous radical cascade cyclization reactions.

Acknowledgements

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References

[1] For selected reviews on radical cascade cyclization, see: (a) Huang, H. M.; Garduno-Castro, M. H.; Morrill, C.; Procter, D. J. *Chem. Soc. Rev.* **2019**, *48*, 4626−4638. (b) Xuan, J.; Studer, A. *Chem. Soc. Rev.* **2017**, *46*, 4329−4346. (c) Liao, J.; Yang, X.; Ouyang, L.; Lai, Y.; Huang, J.; Luo, R. *Org. Chem. Front.* **2021**, *8*, 1345−1363. (d) Zhang, Y.; Sun, K.; Lv, Q.; Chen, X.; Qu, L.; Yu, B. *Chin. Chem. Lett.* **2019**, *30*, 1361−1368.

[2] (a) Hung, K.; Hu, X. R.; Maimone, T. J. *Nat. Prod. Rep*. **2018**, *35*, 174−202. (b) Huang, H. M.; McDouall, J. J. W.; Procter, D. J. *Nat. Catal.* **2019**, *2*, 211−218.

[3] (a) Mondal, S.; Dumur, F.; Gigmes, D.; Sibi, M. P.; Bertrand, M. P.; Nechab, M. *Chem. Rev.* **2022**, *122*, 5842−5976. (b) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263−3296. (c) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; Wiley-VCH: Weinheim, 1996.

[4] (a) Miyabe, H.; Asada, R.; Toyoda, A.; Takemoto, Y. *Angew. Chem., Int. Ed*. **2006**, *45*, 5863−5866. (b) Miyabe, H.; Takemoto, Y. *Chem. - Eur. J.* **2007**, *13*, 7280−7286. (c) Miyabe, H.; Toyoda, A.; Takemoto, Y. *Synlett* **2007**, *2007*, 1885−1888. (d) Jui, N. T.; Lee, E. C. Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10015−10017. (e) Yoshioka, E.; Wang, K. X.; Kohtani, S.; Miyabe, H. *Synlett* **2011**, *2011*, 2085−2089. (f) Kern, N.; Plesniak, M. P.; McDouall, J. J. W.; Procter, D. J. *Nat. Chem*. **2017**, *9*, 1198−1204. (g) Ryss, J. M.; Turek, A. K.; Miller, S. J. *Org. Lett.* **2018**, *20*, 1621−1625. (h) Wozniak, L.; Magagnano, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2018**, *57*, 1068−1072. (i) Zheng, D. Q.; Studer, A. *Angew. Chem., Int. Ed.* **2019**, *58*, 15803−15807. (j) Perego, L. A.; Bonilla, P.; Melchiorre, P. *Adv. Synth. Catal.* **2020**, *362*, 302−307. (k) Hao, W.; Harenberg, J. H.; Wu, X.; MacMillan, S. N.; Lin, S. *J. Am. Chem. Soc.* **2018**, *140*, 3514−3517. (l) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 17735−17738. (m) Du, J. N.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392−396. (n) Hashimoto, T.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2014**, *6*, 702−705.

[5] For selective reviews, see: (a) McCallum, T.; Wu, X.; Lin, S. *J. Org. Chem.* **2019**, *84*, 14369−14380. (b) Rana, S.; Biswas, J. P.; Paul, S.; Paik, A.; Maiti, D. *Chem. Soc. Rev.* **2021**, *50*, 243−472. (c) Pellissier, H. Coord. *Chem. Rev.* **2019**, *386*, 1−31. (d) Demarteau, J.; Debuigne, A.; Detrembleur, C. *Chem. Rev.* **2019**, *119*, 6906−6955. (e) Pellissier, H.; Clavier, H. *Chem. Rev.* **2014**, *114*, 2775−2823. (f) Kyne, S. H.; Lefèvre, G.; Ollivier, C.; Petit, M.; Ramis Cladera, V.-A.; Fensterbank, L. *Chem. Soc. Rev.* **2020**, *49*, 8501−8542. (g) Wu, X.; Chang, Y.; Lin, S. *Chem*. **2022**, *8*, 1805. (h) Hilche, T.; Younas, S. L.; Gansäuer, A.; Streuff, J. *ChemCatChem* **2022**, *14*, e2022005.

[6] Zhang, C.; Wang, D. S.; Lee, W. C. C.; McKillop, A. M.; Zhang, X. P. *J. Am. Chem. Soc*. **2021**, *143*, 11130−11140.

[7] (a) Lu, Z.; Shen, M.; Yoon, T. P. *J. Am. Chem. Soc*. **2011**, *133*, 1162–1164. (b) Amador, A. G.; Sherbrook, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2016**, 138, 4722–4725. (c) Amador, A. G.; Sherbrook, E. M.; Lu, Z.; Yoon, T. P. *Synthesis* **2018**, *50*, 539–547. (d) Hao, W.; Wu, X.; Sun, J. Z.; Siu, J. C.; MacMillan, S. N.; Lin, S. *J. Am. Chem. Soc.* **2017**, *139*, 12141 30. (e) Huang, X.; Lin, J.; Shen, T.; Harms, K.; Marchini, M.; Ceroni, P.; Meggers, E. *Angew. Chem., Int. Ed.* **2018**, *57*, 5454−5458. (f) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959–6039. (g) Peter, Á., Agasti, S., Knowles, O., Pye, E. & Procter, D. J. *Chem. Soc. Rev.* **2021**, *50*, 5349−5365.

[8] (a) Agasti, S.; Beattie, N. A.; McDouall, J. J. W.; Procter, D. J. *J. Am. Chem. Soc.* **2021**, *143*, 3655–3661. (b) Agasti, S.; Beltran, F.; Pye, E.; Kaltsoyannis, N.; Crisenza, G.; Procter, D. *Nat. Chem*. **2023**, *15*, 535–541.
[9] (a) Kern, N.; Plesniak, M. P.; McDouall, J. J. W.; Procter, D. J. *Nat. Chem.* **2017**, *9*, 1198−1204. (b) Wang, Y.; Zhang, W.-Y.; Yu, Z.-L.; Zheng, C.; You, S.-L. *Nat. Synth*. **2022**, *1*, 401–406. (c) Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *17*, 5382–5390. (d) Mikami, K,; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501-4504.
[10] Robinson, S. G.; Wu, X.; Jiang, B.; Sigman, M. S.; Lin, S. *J. Am. Chem. Soc*. **2020**, *142*, 18471−1848.