Asymmetric Catalysis Hot Paper

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Nitrene-Mediated C–H Oxygenation: Catalytic Enantioselective Formation of Five-Membered Cyclic Organic Carbonates

*Xin Nie, Chen-Xi Ye, Sergei I. Ivlev, and Eric Meggers**

Abstract: The synthesis of non-racemic 5-membered cyclic carbonates from abundant alcohols is reported. Conversion of the alcohol into an azanyl carbonate is followed by a chiral-at-ruthenium catalyzed cyclization to provide chiral cyclic carbonates in yields of up to 95 % and with up to 99 % *ee*. This new synthetic method is proposed to proceed through a nitrene-mediated intramolecular C(sp^3)–H oxygenation which includes an unusual 1,7-hydrogen atom transfer within a ruthenium nitrene intermediate. The method is applicable to the synthesis of non-racemic chiral mono-, di- and trisubstituted cyclic alkylene carbonates.

Alkylene carbonates (1,3-dioxolan-2-ones), often referred to as 5-membered cyclic carbonates, are valuable synthetic building blocks for fine chemicals, bioactive molecules, pharmaceuticals and polymers.[1–4] Regarding chiral cyclic carbonates, the majority of available strategies for the synthesis of non-racemic chiral 5-membered cyclic carbonates use alkenes as the starting material, including asymmetric dihydroxylations of alkenes followed by cyclization with a carbonyl source, enantioselective epoxidations of alkenes followed by stereoretentive reaction with CO_2, and the racemic epoxidation of alkenes followed by the reaction with CO_2 under conditions of kinetic resolution (Figure 1a).[5,6] In a notable exception, a few examples of catalytic enantioselective reactions of various propargylic alcohols with CO_2 have been reported recently.[7] However, each method has their limitations and drawbacks. For example, the Sharpless catalytic asymmetric dihydroxylation requires toxic osmium,[8] while the reaction of epoxides with CO_2 has mainly been applied to mono- or 1,2-disubstituted epoxides.[5,6] New methods for the catalytic asymmetric synthesis of chiral cyclic alkylene carbonates from easily accessible starting materials are therefore of high interest.

Nitrene chemistry is traditionally used to incorporate nitrogen into a target molecule, either by nitrene addition to alkenes or by C–H amination.[9] In a recent surprising discovery, we found that nitrene chemistry can also be used as a tool to accomplish C(sp^3)–H oxygenations (Figure 1b, upper reaction).[10] The one-step conversion of readily available alcohols to their corresponding *N*-benzoyloxycarbamates was followed by a ruthenium catalyzed formation of cyclic carbonates via the proposed intermediate formation of ruthenium nitrene species. However, unfortunately, this nitrene-mediated C–H oxygenation displayed critical drawbacks. First, the cyclic carbonate formation directly competes with the formation of the cyclic carbamate via conventional C–H amination, thereby often resulting in product mixtures. Second, depending on the nature of the substrate, a racemic acyclic carbamate is formed as a side product or even as the main product, thus rendering this method not of synthetic utility. Here, we now introduce a novel catalytic enantioselective nitrene-mediated C(sp^3)–H oxygenation which provides cyclic carbonates in high yields and with high enantioselectivity. Key step is a proposed 1,7-hydrogen atom transfer (HAT) within a transition metal nitrene intermediate. This new method provides an elegant highly enantioselective method for the catalytic asymmetric synthesis of cyclic alkylidene carbonates from abundant alcohols and it

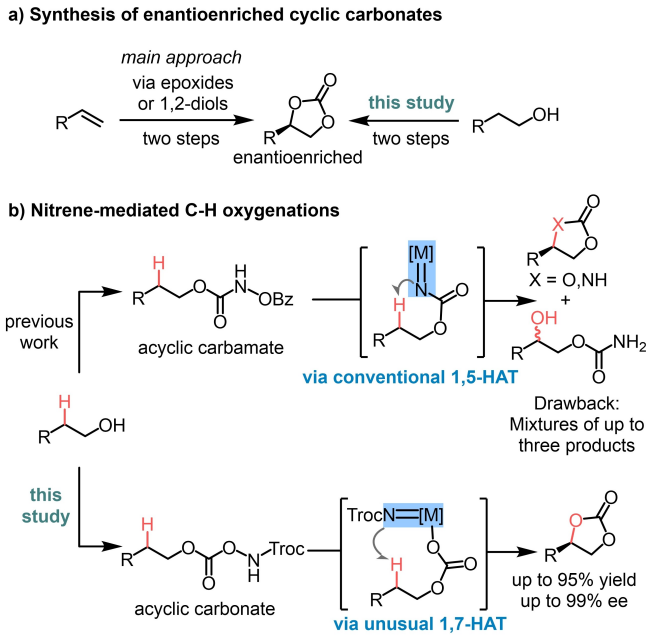

Figure 1. Synthesis of non-racemic cyclic carbonates. Previous work and this study regarding nitrene-mediated C(sp^3)–H oxygenation. Bz = benzoyl. Troc = 2,2,2-trichloroethoxycarbonyl.

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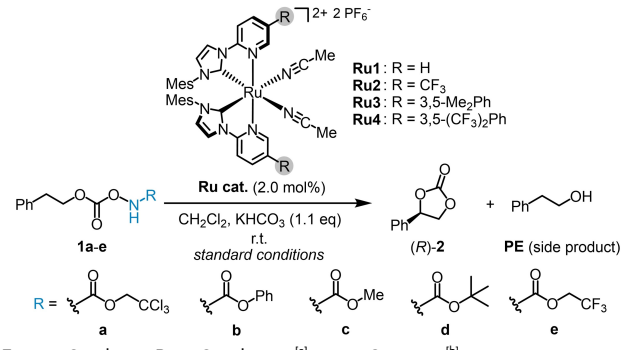
can be applied to otherwise difficult to synthesize non-racemic trisubstituted cyclic alkylene carbonates.

We commenced our study by converting 2-phenylethanol to the Troc-protected azanyl carbonate **1a** in a single step (see Supporting Information for details). We were encouraged by recent work in our lab on the use of related azanyl esters as precursors for the formation of α-amino acids via C–H amination of intermediate transition metal nitrenes.[11] We speculated that in contrast to azanyl esters, the related azanyl carbonates might undergo C–H oxygenation instead of C–H amination, due to an unfavorable 7-membered transition state for the C–N formation step. Indeed, reaction of azanyl carbonate **1a** with chiral-at-ruthenium catalyst Λ-**Ru1**[12] (2 mol %) in methylene chloride in the presence of the base K_2CO_3 (3.0 equiv) provided the desired cyclic carbonate (*R*)-**2a** in encouraging 38 % yield with 88 % *ee*, along with smaller amounts of 2-phenylethanol (**PE**, 11 %) (Table 1, entry 1). Optimization of the ruthenium catalyst (**Ru2**–**Ru4**) led to the identification of a 3,5-$(CF_3)_2$Ph moiety at the pyridine ligands as the optimal catalyst (entries 2–4). $KHCO_3$ turned out to be a slightly superior base than K_2CO_3 with 1.1 equivalent as the optimal amount of base (entries 5–6). Under these standard conditions with 2.0 mol % of Λ-**Ru4** in the presence of $KHCO_3$ (1.1 equiv) in CH_2Cl_2 at room temperature, a complete conversion was accomplished after 15 hours with 85 % isolated yield of the cyclic carbonate (*R*)-**2a** and a satisfactory enantiomeric excess of 95 % *ee* (entry 6). It is worth noting that other N-protection groups (substrates **2b–e**, entries 7–10) all provided inferior results. Furthermore, reduction of the catalyst loading from 2.0 to 1.0 mol % provided a somewhat lower yield (75 % instead of 87 % NMR yield) and lower enantioselectivity (90 % *ee* instead of 95 % *ee*) (entry 11). Control experiments revealed that base is required for the formation of the cyclic carbonate (entry 12) and that the reaction can be performed in the presence of air (entry 13).

With the optimal conditions in hand, we next performed a substrate scope under the developed standard conditions (Table 1, entry 6). First, substituents were introduced into the phenyl moiety of 2-phenylethanol-derived substrates (Figure 2). A methyl group in the *para*- or *meta*-position is well-tolerated and provided cyclic carbonates **3** and **4** with 87 % (90 % *ee*) and 82 % yield (88 % *ee*), respectively. A methyl substituent in the sterically more hindering *ortho*-

Table 1: Initial experiments and optimization.



Entry	Catalyst	R	Conditions[a]	Conv. [%]	**2**[b]	**PE** [%]	*ee* of **2** [%][c]
1	Λ-**Ru1**	**1a**	K_2CO_3 (3 equiv)	90	38	11	88
2	Λ-**Ru2**	**1a**	K_2CO_3 (3 equiv)	60	44	10	81
3	Λ-**Ru3**	**1a**	K_2CO_3 (3 equiv)	100	28	20	90
4	Λ-**Ru4**	**1a**	K_2CO_3 (3 equiv)	85	52	8	92
5	Λ-**Ru4**	**1a**	$KHCO_3$ (3 equiv)	100	80	10	95
6	Λ-**Ru4**	**1a**	standard	100	87 (85)[d]	4	95
7	Λ-**Ru4**	**1b**	standard	83	8	22	81
8	Λ-**Ru4**	**1c**	standard	100	54	2	81
9	Λ-**Ru4**	**1d**	standard	98	62	5	90
10	Λ-**Ru4**	**1e**	standard	95	70	2	82
11	Λ-**Ru4**	**1a**	1 mol % cat.	92	75	10	90
12	Λ-**Ru4**	**1a**	no base	33	< 5	5	–
13	Λ-**Ru4**	**1a**	under air	100	83	8	94

[a] Shown are the deviations from the standard reaction conditions. Standard conditions: Substrate **1** (0.10 mmol), Ru catalyst (1.0 or 2.0 mol %) in CH_2Cl_2 (1.0 mL) under the indicated conditions were stirred at room temperature for 15 hours. [b] Yields determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Enantiomeric excess determined by HPLC on chiral stationary phases. [d] Isolated yield in brackets.

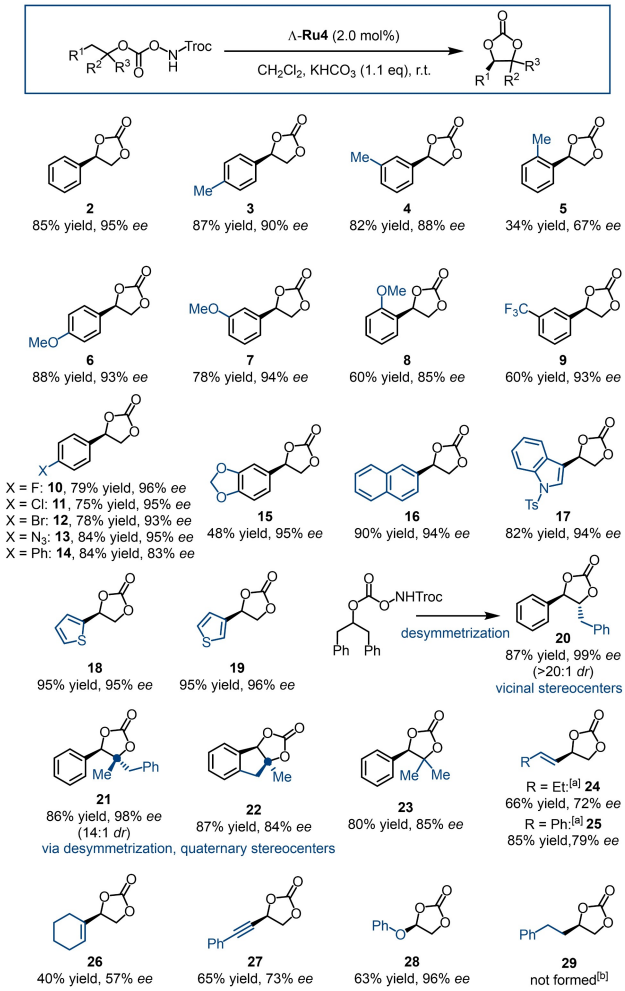


Figure 2. Substrate scope. [a] Synthesized from substrate with *E*-configuration of the alkene. [b] 4-Phenylbutanol isolated as main product (44 % yield).

position provided the cyclic carbonate **5** instead with a diminished yield of 34 % with reduced 67 % *ee*. The same trend was observed with a methoxy substituent. A methoxy group in the *para*- or *meta*-position provided satisfactory yields and enantioselectivities for the cyclic carbonates **6** and **7**, while an *ortho*-methoxy substituent reduced the yield of cyclic carbonate **8** to 60 % with 85 % *ee*. Electron-withdrawing groups are also tolerated. A CF_3-substituent, which is a common functional group in bioactive molecules,[13] afforded the cyclic carbonate **9** with 60 % yield and 93 % *ee*, and the halogenated cyclic carbonates **10**–**12** were isolated in yields of 75–79 % and with 93–96 % *ee*. The cyclic carbonate **13** containing an azide substituent suitable for click chemistry[14] was synthesized in 84 % yield and with 95 % *ee*. The biphenyl containing cyclic carbonate **14** was provided under standard conditions with 84 % yield and 83 % ee, while the 1,3-dioxole modified phenyl moiety reduced the yield of **15** to 48 % but with a satisfactory 95 % *ee*. Benzannulated and heteroaromatic substituents provided the chiral cyclic carbonates **16**–**19** in yields of 82–95 % with 94–96 % *ee*.

The new method can also be applied to desymmetrizations which leads to the simultaneous formation of two consecutive stereocenters.[15] For example the disubstituted carbonate **20** was synthesized in 87 % yield with 99 % *ee* as a single diastereomer, the trisubstituted cyclic carbonates **21** was provided with 86 % yield, 98 % *ee* and 14:1 *dr*, and the cyclic carbonate **22** was afforded in 87 % yield and with 84 % *ee* as a single diastereomer. Both **21** and **22** contain a quaternary stereocenter.[16] The trisubstituted cyclic carbonate **23** with a single stereocenter was afforded in 80 % yield with 85 % *ee*. Finally, in addition to the oxygenation of benzylic C(sp^3)–H bonds, the new method is also amenable to allylic and propargylic C–H bonds, leading to vinyl-substituted cyclic carbonates **24**–**26** and the alkynyl-substituted cyclic carbonate **27**, albeit with somewhat decreased yields (40–85 %) and enantioselectivities (57–79 % *ee*). Finally, the phenoxy-substituted cyclic carbonate **28** was synthesized in 63 % yield with 96 % *ee*, while C–H groups without any activating neighboring group are not suitable for our new method as shown for the failure to afford the cyclic carbonate **29**.[17] It is also noteworthy that this method is not suitable for the C–H oxygenation of tertiary C–H bonds (see Supporting Information for more details).

The proposed mechanism is shown in Figure 3. Upon ruthenium-induced cleavage of the weak O–N bond of the azanyl carbonate substrate, intermediate **I** is formed which contains a ruthenium-coordinated nitrene ligand in addition to a coordinated carbonate. This sets the stage for an unusual 1,7-hydrogen atom transfer (HAT)[18,19] from the β-C–H of the coordinated carbonate to the nitrene nitrogen, thereby generating the diradical **II**. In the next step, C–N bond formation apparently cannot compete with the C–O bond formation to form the cyclic carbonate product together with the amide-coordinated ruthenium catalyst **III**. Release of $TrocNH_2$ upon protonation regenerates the catalyst for a new catalytic cycle.

The proposed mechanism is consistent with a number of control experiments (Figure 4). Catalytic asymmetric intra-

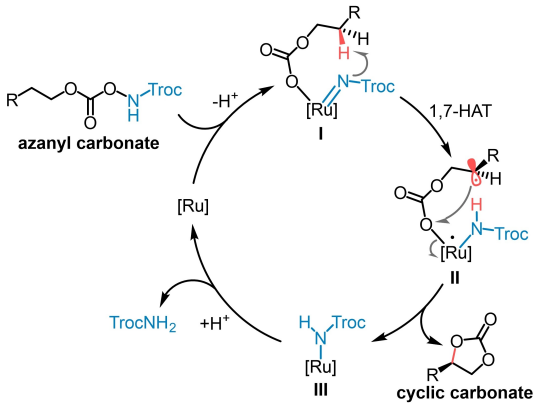


Figure 3. Proposed mechanism.

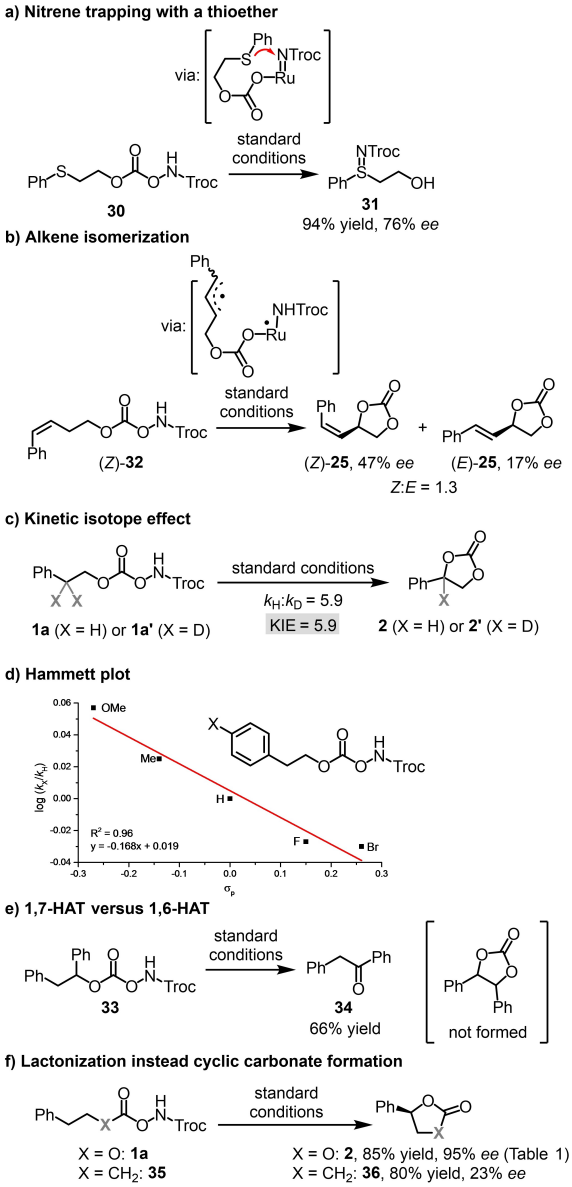


Figure 4. Mechanistic experiments.

molecular nitrene transfer to a thioether supports an intermediate ruthenium nitrene species (Figure 4a), while the $Z \rightarrow E$ isomerization of the *Z*-alkene substrate (*Z*)-**32** to product **25** as a mixture with $Z:E = 1.3$ supports a radical mechanism through an intermediate allylic radical (Figure 4b). Interestingly, the isomerized cyclic carbonate (*E*)-**25** forms almost as a racemate which suggests that it is the C–H abstraction step rather than the C–O bond formation that is the stereodetermining step. This is consistent with other C–H functionalization reactions reported using this class of chiral-at-ruthenium catalysts in which we determined that the C–H abstraction is the stereodetermining step.[11] A kinetic isotope effect (KIE) of 5.9 determined from relative rates of the non-deuterated and deuterated substrates **1a** and **1a′**, respectively, reveals that the C–H activation is the rate limiting step in the catalytic cycle (Figure 4c). A Hammett plot with substituents (X) in the *para*-position of the phenyl moiety of substrate **2** afforded a linear correlation between $\log(k_X/k_H)$ and the Hammett constants (σ_p) with a negative slope of −0.17, which is consistent with the proposed 1,7-HAT from a slightly electrophilic ruthenium nitrene intermediate (**I**), thus favoring electron rich C–H bonds (Figure 4d). The preference for the unusual 1,7-HAT versus a more common 1,6-HAT can therefore be explained with a combination of polar effects (discouraging 1,6-HAT by electron-withdrawing character of the carbonate group) and C–H bond dissociation energies (favoring 1,7-HAT by neighboring functional groups). In fact, substrate **33**, in which a phenyl moiety is added to the α-position of the phenethyl group of substrate **2**, does not provide any cyclic carbonate but instead ketone **34** (66 % yield), which is supposed to be the product of an initial 1,6-HAT (Figure 4e). Finally, it turns out that this new C–H oxygenation is also applicable to the formation of γ-lactones. Azanyl ester **35**, derived by replacing one oxygen of azanyl carbonate **1a** with a methylene group, provided lactone **36** in 80 % yield, albeit only with 23 % *ee* (Figure 4f). This demonstrates that the 1,7-HAT followed by C–O oxygenation can be expanded beyond the formation of cyclic carbonates.

Cyclic carbonates are valuable synthetic intermediates for the synthesis of fine chemicals and also natural products.[20] For example, Koert and co-workers recently reported total syntheses of the antifungal natural γ-lactones pestaphthalide A and B via an elegant anionic rearrangement of diastereomeric cyclic carbonate building blocks (4*S*,5*S*)- and (4*R*,5*S*)-**37**, which were obtained as a mixture of diastereomers from a mixture of diastereomeric diols (Figure 5).[21] Our new method offers an elegant alternative synthesis starting from the acyclic carbonate **38** which can be converted in a catalyst-controlled fashion either to (4*R*,5*S*)-**37** using Λ-**Ru4** or (4*S*,5*S*)-**37** using Δ-**Ru4** with excellent diastereoselectivities, thereby overruling the intrinsic preference of the stereocenter in the starting material.

In conclusion, we here introduced a novel method for the catalytic asymmetric synthesis of cyclic alkylene carbonates by nitrene-mediated C(sp^3)–H oxygenation. The proposed mechanism involves an unprecedented 1,7-hydrogen atom transfer within a ruthenium nitrene intermediate followed by a C–O oxygenation step. The new method expands the toolbox for accessing non-racemic chiral cyclic alkylene carbonates and might be especially interesting for the synthesis of chiral trisubstituted cyclic carbonates.

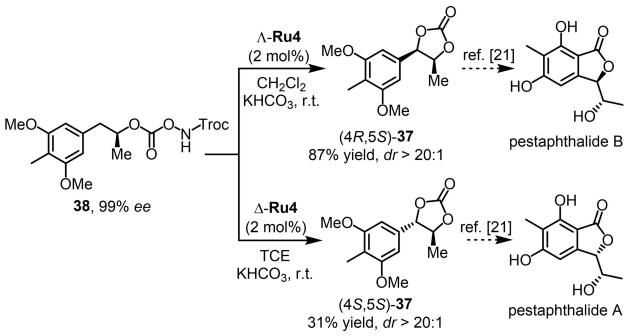


Figure 5. Catalyst-controlled stereoselectivity applied to the diastereoselective synthesis of the natural products pestaphthalide A and B. TCE = 1,1,2,2-tetrachloroethane.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Asymmetric Catalysis · C–H Oxygenation · Cyclic Carbonates · Hydrogen Atom Transfer · Nitrene

[1] J. H. Clements, *Ind. Eng. Chem. Res.* **2003**, *42*, 663–674.
[2] H. Zhang, H.-B. Liu, J.-M. Yue, *Chem. Rev.* **2014**, *114*, 883–898.
[3] W. Guo, J. E. Gómez, À. Cristòfol, J. Xie, A. W. Kleij, *Angew. Chem. Int. Ed.* **2018**, *57*, 13735–13747; *Angew. Chem.* **2018**, *130*, 13928–13941.
[4] P. Rollin, L. K. Soares, A. M. Barcellos, D. R. Araujo, E. J. Lenardao, R. G. Jacob, G. Perin, *Appl. Sci.* **2021**, *11*, 5024–5080.
[5] N. Kielland, C. J. Whiteoak, A. W. Kleij, *Adv. Synth. Catal.* **2013**, *355*, 2115–2138.
[6] J. E. Gómez, A. W. Kleij, *Curr. Opin. Green Sustainable Chem.* **2017**, *3*, 55–60.
[7] C.-K. Ran, X.-W. Chen, Y.-Y. Gui, J. Liu, L. Song, K. Ren, D.-G. Yu, *Sci. China Chem.* **2020**, *63*, 1336–1351.
[8] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
[9] G. Dequirez, V. Pons, P. Dauban, *Angew. Chem. Int. Ed.* **2012**, *51*, 7384–7395; *Angew. Chem.* **2012**, *124*, 7498–7510.
[10] Y. Tan, S. Chen, Z. Zhou, Y. Hong, S. Ivlev, K. N. Houk, E. Meggers, *Angew. Chem. Int. Ed.* **2020**, *59*, 21706–21710; *Angew. Chem.* **2020**, *132*, 21890–21894.
[11] C.-X. Ye, X. Shen, S. Chen, E. Meggers, *Nat. Chem.* **2022**, *14*, 566–573.

[12] Y. Zheng, Y. Tan, K. Harms, M. Marsch, R. Riedel, L. Zhang, E. Meggers, *J. Am. Chem. Soc.* **2017**, *139*, 4322–4325.
[13] E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315–8359.
[14] P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905–4979.
[15] C. Nájera, F. Foubelo, J. M. Sansano, M. Yus, *Tetrahedron* **2022**, *106–107*, 132629.
[16] Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740–751.
[17] Interestingly, while this method is amenable to benzylic, allylic and propargyl C–H bonds and also to C–H bonds that are activated by an ether, a neighboring electron-deficient carboxylic ester does not provide any cyclic carbonate product. See Supporting Information for more details.
[18] For an overview of less common 1, n-radical translocations, see: M. Nechab, S. Mondal, M. P. Bertrand, *Chem. Eur. J.* **2014**, *20*, 16034–16059.
[19] a) J. C. K. Chu, T. Rovis, *Angew. Chem. Int. Ed.* **2018**, *57*, 62–101; *Angew. Chem.* **2018**, *130*, 64–105; b) L. M. Stateman, K. M. Nakafuku, D. A. Nagib, *Synthesis* **2018**, *50*, 1569–1586; c) G. Kumar, S. Pradhan, I. Chatterjee, *Chem. Asian J.* **2020**, *15*, 651–672; d) S. Sarkar, K. P. S. Cheung, V. Gevorgyan, *Chem. Sci.* **2020**, *11*, 12974–12993; e) M. A. Short, J. M. Blackburn, J. L. Roizen, *Synlett* **2020**, *31*, 102–116.
[20] Cyclic carbonates can be hydrolyzed to 1,2-diols. For a related directed method to access 1,2-diols, see for example: Z. Ren, F. Mo, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 16991–16994.
[21] J. Schwaben, J. Cordes, K. Harms, U. Koert, *Synthesis* **2011**, 2929–2934.

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