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Umpolung of donor–acceptor cyclopropanes *via* N-heterocyclic carbene organic catalysis†

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A carbene-catalyzed formal umpolung of donor–acceptor (D–A) cyclopropanes is disclosed. The cyclopropane moiety is connected to an acetyl aldehyde that can be activated by a carbene catalyst. The initially electrophilic carbon attached to the donor group of the D–A cyclopropane aldehyde is inverted to form a nucleophilic reaction center. A subsequent reaction with isatins *via* a formal [3 + 2] process forms lactones bearing multiple functional groups with excellent enantio- and diastereoselectivities.

Introduction

Cyclopropanes are structural moieties with unique reactivities in organic chemistry. They are useful building blocks for syntheses,[1] and can be used to probe reaction mechanisms such as those involving radical clock experiments.[2] However, despite the considerable ring strains existing in their tortuous chemical bonds, the C–C bonds in cyclopropanes are rather kinetically inert.[3] Therefore, activated cyclopropanes have been rationally designed as one class of starting materials for ring-extension and ring-opening reactions. In this regard, donor–acceptor (D–A) cyclopropanes have been extensively studied as versatile building blocks for over half a century.[4] Traditionally, D–A cyclopropanes are activated by Lewis acid catalysts,[5] transition metal catalysts[6] or organic catalysts[7] to produce zwitterionic intermediates with an electrophilic carbon attached to the donor groups and a nucleophilic carbon attached to the acceptor groups (Fig. 1, right part). D–A cyclopropanes can also be activated through radical processes and electrochemical approaches.[8] The umpolung activation of D–A cyclopropanes inverting the initial polarities of these two carbons (Fig. 1, left part), on the other hand, is much less studied. Progress in this direction has been dominated by transition metal catalysis and only a very limited number of examples have been reported to date.[9]

Organic catalysts provide robust tools for asymmetric transformations[10] and can be used in the activation of D–A cyclopropanes for various stereoselective cycloaddition reactions (Fig. 2).[7] For example, Jørgensen and co-workers disclosed the enamine-activated [2 + 2] cycloaddition reaction of D–A cyclopropanes in 2015 for the enantioselective synthesis of cyclobutanes (Fig. 2a, right part).[7c] This strategy was further developed by Vicario and co-workers in 2016 in a domino process to prepare chiral pyrroloquinoline derivatives.[7d] The stereoselective 1,3-dipolar cycloaddition reaction of D–A cyclopropanes has also been realized by Jørgensen's group in 2017, with a chiral tertiary amine/thiourea multifunctional molecule applied as the organic catalyst (Fig. 2a, left part).[7f] 1-Cyclopropylcarbaldehydes bearing multiple electron-withdrawing groups have been used as substrates in N-heterocyclic carbene (NHC) organocatalytic reactions (Fig. 2b, left part).[11] Ring-opening reactions of 1-cyclopropylcarbaldehyde molecules have been pioneered by Bode and co-workers in 2006,[11b] with the corresponding esters and amides being afforded in excellent yields. Both intra- and inter-molecular esterification reactions using 1-cyclopropylcarbaldehyde with NHC catalysis have been developed by You,[11f] Wang,[11d,e,g] Ye,[11i,k] Chi,[11h] and others in the last decade.

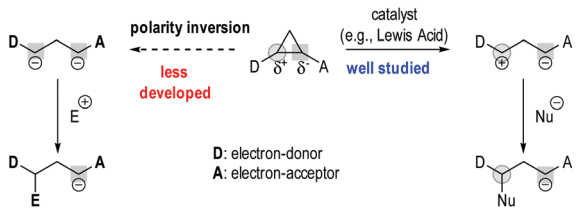

Fig. 1 Catalytic activation of donor–acceptor cyclopropanes.

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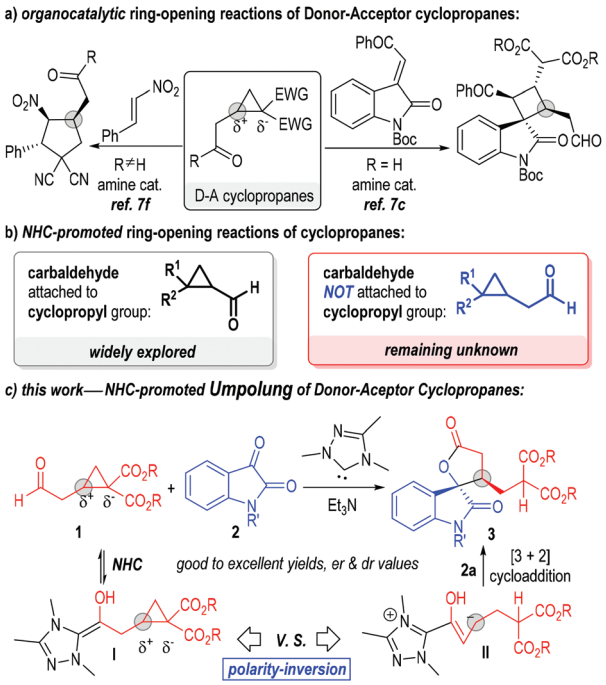


Fig. 2 Organocatalytic reactions of cyclopropanes.

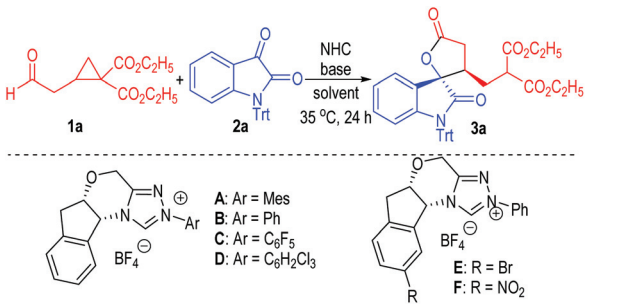
Notably, for 1-cyclopropylcarbaldehydes used in all previous NHC catalysis studies, the aldehyde moiety and cyclopropane ring are directly connected with each other. To the best of our knowledge, the carbene-catalyzed activation of D–A cyclopropanes with the carbaldehyde moiety not directly attached to the cyclopropyl rings (2-cyclopropylacetaldehydes) has not been reported (Fig. 2b, right part).

Herein, we disclose that 2-cyclopropylacetaldehyde bearing a D–A cyclopropane moiety can be efficiently activated by NHC organic catalysts and it reacts with electrophiles through asymmetric cycloaddition reactions (Fig. 2c). The β-carbon of 2-cyclopropylacetaldehyde **1** is activated as a nucleophile to react with the isatin substrate **2** through a formal [3 + 2] cycloaddition reaction and gives the lactone product **3** in good to excellent yields and stereoselectivities. In this scenario, the initially electrophilic carbon attached to the donor group of the D–A cyclopropane (*e.g.*, in substrate **1** and the Breslow intermediate **I**[12]) is formally inverted to a nucleophilic carbon through the formation of acylazolium.

Results and discussion

We started the proposed umpolung activation of the D–A cyclopropanes by using **1a** and **2a** as the model substrates (Table 1). Several NHC catalysts were found to be efficient for this process, with the desired lactone products being afforded in moderate yields and with promising stereoselectivities (Table 1, entries 1 to 6). In particular, the aminoindanol-derived NHC catalyst **F** bearing an *N*-Ph group with a NO_2 group installed on its indane unit[13] could mediate the reaction

Table 1 Optimization of the reaction conditions[a]

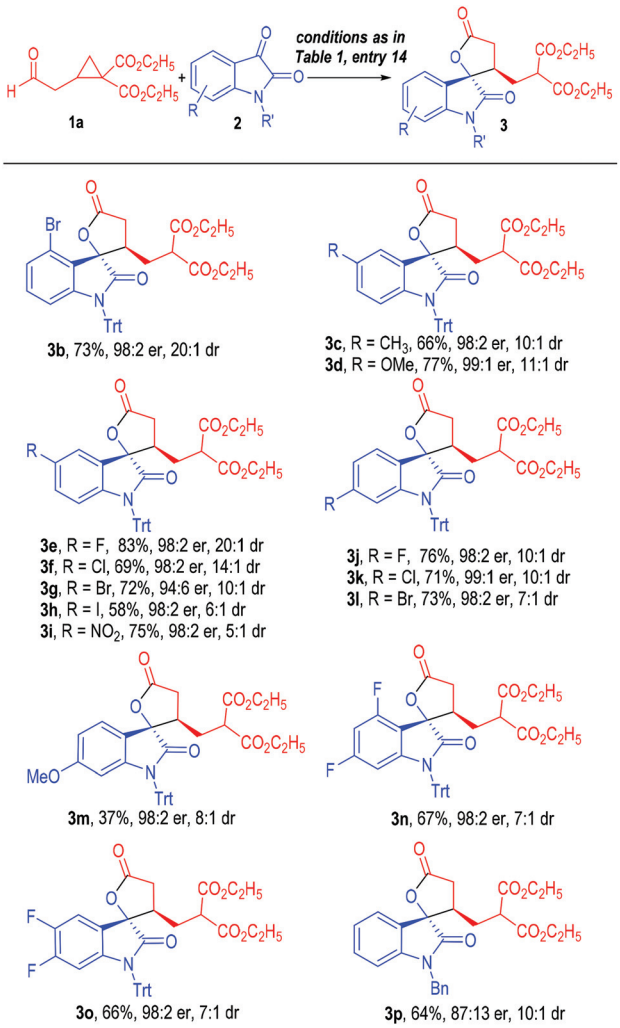


Entry	NHC	Base	Solvent	Yield[b] (%)	er[c]	dr[d]
1	**A**	Et_3N	$CHCl_3$	47	58 : 42	3 : 1
2	**B**	Et_3N	$CHCl_3$	48	81 : 19	5 : 1
3	**C**	Et_3N	$CHCl_3$	37	46 : 54	2 : 1
4	**D**	Et_3N	$CHCl_3$	30	37 : 63	2 : 1
5	**E**	Et_3N	$CHCl_3$	50	94 : 6	8 : 1
6	**F**	Et_3N	$CHCl_3$	47	98 : 2	>20 : 1
7	**F**	DMAP	$CHCl_3$	<10		
8	**F**	DABCO	$CHCl_3$	<10		
9	**F**	^{t}BuOK	$CHCl_3$	19	99 : 1	1 : 1
10	**F**	NaOAc	$CHCl_3$	16	99 : 1	2 : 1
11	**F**	Et_3N	CH_3CN	15	90 : 10	4 : 1
12	**F**	Et_3N	$PhCH_3$	<10		
13	**F**	Et_3N	CH_2Cl_2	26	94 : 6	4 : 1
14[e]	**F**	Et_3N	$CHCl_3$	82	98 : 2	>20 : 1

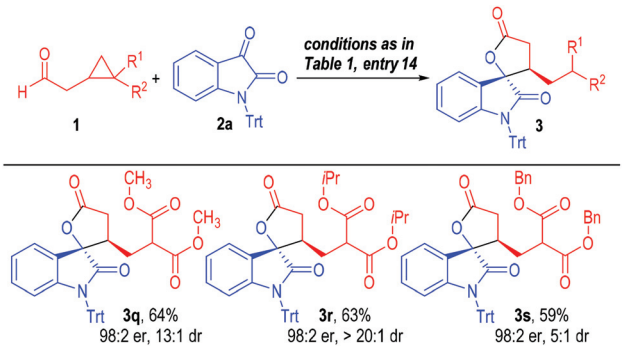
[a] General conditions (unless otherwise specified): **1a** (0.15 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), base (0.02 mmol), solvent (2.0 mL), 35 °C, 24 h. [b] Isolated yield of **3a**. [c] er was determined *via* HPLC on the chiral stationary phase. [d] dr was determined *via* ^{1}H NMR on the crude product. [e] **1a** (0.20 mmol), **2a** (0.10 mmol), **F** (0.02 mmol), Et_3N (0.02 mmol), $CHCl_3$ (0.5 mL), 35 °C, 24 h. Trt = triphenylmethyl. DMAP = 4-dimethylaminopyridine. DABCO = triethylenediamine.

to give product **3a** with excellent enantio- and diastereoselectivities (entry 6). Typical organic bases other than Et_3N tested here were inefficient for this reaction (*e.g.*, entries 7 to 8). The use of inorganic bases led to **3a** with low yields and slightly higher er values (*e.g.*, entries 9 to 10). Solvents such as CH_3CN, toluene, and CH_2Cl_2 did not perform well (*e.g.*, entries 11 to 13). Finally, the product yield could be improved to 82% when an excess amount of **1a** was used, with **3a** being formed with over 20 : 1 dr and 98 : 2 er (entry 14).

With acceptable conditions in hand, we next examined the reaction scope by using **1a** as the model D–A cyclopropane substrate to react with isatins bearing various substituents or substitution patterns (Scheme 1). Both electron-donating and electron-withdrawing groups could be installed at the 4- and 5-positions of the isatin substrates (**2**), with the corresponding lactone products **3** being afforded in moderate to good yields and with excellent enantioselectivities (**3b** to **3i**). Electron-withdrawing substituents were well tolerated at the 6-position of the isatins (**3j** to **3l**), while electron-donating substituents at the same position resulted in a decrease of the product yields (*e.g.*, **3m**). Both 4,6- and 5,6-difluoro-substituted isatins gave lactone products with excellent enantio- and diastereoselectivities (**3n** to **3o**). Replacing the *N*-Trt group with an *N*-Bn



Scheme 1 Scope of isatins. Reaction conditions as stated in Table 1, entry 14. Yields are isolated yields after purification *via* SiO_2 column chromatography. er values were determined *via* HPLC on the chiral stationary phase. dr values were determined *via* ^{1}H NMR on the crude product.



Scheme 2 Scope of D–A cyclopropanes. Reaction conditions as stated in Table 1, entry 14. Yields are isolated yields after purification *via* SiO_2 column chromatography. er values were determined *via* HPLC on the chiral stationary phase. dr values were determined *via* ^{1}H NMR on the crude product.

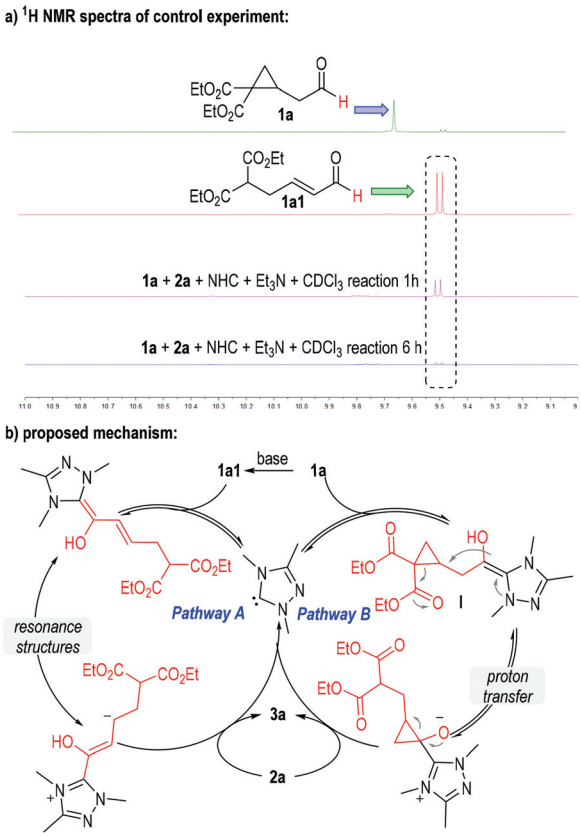


Fig. 3 ^{1}H NMR studies on the reaction system and proposed reaction mechanism.

group led to slight reduction of reaction yield and enantioselectivity (**3p**).

D–A cyclopropanes (**1**) bearing different acceptor groups were also tested (Scheme 2). The ethyl ester group in **1a** could be switched to methyl and isopropyl ester groups without reduction in the product er values, although the yields slightly dropped (**3q** to **3r**). Benzyl esters could also be installed on the D–A cyclopropane substrate to replace the ethyl esters of **1a**, with the optically enriched product **3s** being afforded with a moderate yield and diastereoselectivity. Replacing the di-ester group of **1a** with a mono-electron-withdrawing cyanide group resulted in no desired reactions.

To gain insights into the reaction mechanism, several control experiments were performed (Fig. 3). 2-Cyclopropylcarbaldehyde **1a** could isomerize into the enal **1a1** under the catalytic conditions at the beginning of the cycloaddition reaction (Fig. 3a). Therefore, our catalytic umpolung activation of 2-cyclopropylcarbaldehyde **1a** probably goes through a ring-opening/homoenolate activation cascade reaction pathway (Fig. 3b, Pathway A). However, the direct activation of the 2-cyclopropylcarbaldehyde **1a** by the NHC catalyst to provide the nucleophilic β-carbon cannot be ruled out at this stage (Fig. 3b, Pathway B).

In addition, the catalytic reaction of pre-prepared enal **1a1**[14] and **2a** gave a much lower yield than reactions using 2-cyclo-

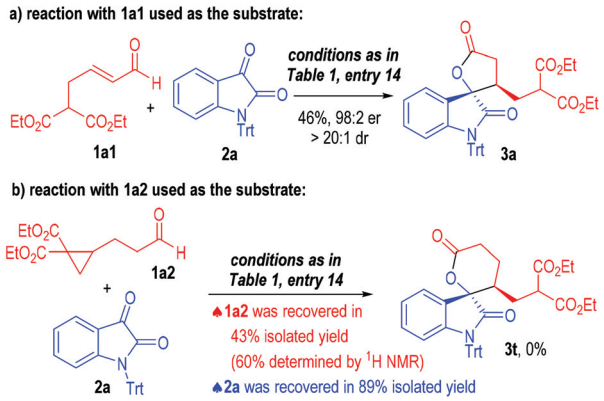


Fig. 4 Control experiments with different carbaldehydes.

propylcarbaldehyde **1a** as the substrate (Fig. 4a). Therefore, the use of the D–A cyclopropane aldehydes as the reaction substrates is practically favored for the preparation of chiral spirocyclic lactone products **3**. It is also worth mentioning that the umpolung activation of the D–A cyclopropane **1a2** was not successful under the current reaction conditions (Fig. 4b). The target lactone product **3t** was not observed, with both D–A cyclopropane **1a2** and isatin substrate **2a** being recovered in moderate to good yields. As a technical note, the D–A cyclopropane **1a2** could lead to complex side reactions and give unisolable decomposition/polymerization products in low yields.

The chiral lactone products obtained from our method possess several functional groups and are amenable for further transformations (Fig. 5). For example, the Trt protecting group on the nitrogen atom could be efficiently removed under acidic conditions to give unprotected lactam **5** in 70% yield and 95 : 5 er.[15] The free NH group on **5** could be protected by a Boc group to give product **6** with good yield and enantioselectivity.[16] The lactam **5** could also be acylated to give **7** in 94% yield with nearly no reduction in the product dr and er values.[17] The lactone ring of the chiral product **3a** could be opened by $BnNH_2$ *via* an ester-to-amide exchange to give **8** with a good yield and er value,[18] although the diastereoselectivity slightly dropped. The acidic carbon of the malonate moiety on **3a** could react with alkyl bromides[19] (products **9** and **10**) under basic conditions.

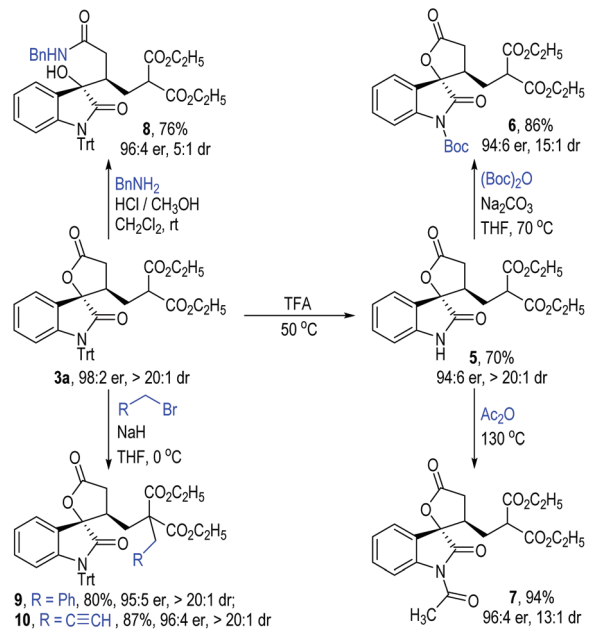


Fig. 5 Synthetic transformations.

Conclusions

In summary, we have developed a formal umpolung activation of D–A cyclopropanes bearing aldehyde moieties *via* NHC catalysis. The initially electrophilic carbon attached to the donor group of the D–A cyclopropane is activated as the nucleophilic species to react with isatins. Lactone products bearing various substituents are afforded in moderate to good yields with generally excellent enantio- and diastereoselectivities. Further investigations into D–A cyclopropane activation reactions, especially those with applications in quick construction of sophisticated functional molecules, are currently in progress in our laboratories.

Conflicts of interest

There are no conflicts to declare.

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References

1 (*a*) C. Brückner and H.-U. Reissig, Thiophene Derivatives by Novel Rearrangements of Siloxy-substituted Cyclopropanecarboxylate, *Angew. Chem., Int. Ed.*, 1985, **24**, 588–589; (*b*) E. Wenkert, Oxycyclopropanes in Organochemical Synthesis, *Acc. Chem. Res.*, 2002, **13**, 27–31; (*c*) S. Danishefsky, Electrophilic Cyclopropanes in Organic Synthesis, *Acc. Chem. Res.*, 2002, **12**, 66–72; (*d*) F. Gnad and O. Reiser, Synthesis and Applications of β -Aminocarboxylic Acids Containing a Cyclopropane Ring, *Chem. Soc. Rev.*, 2003, **103**, 1603–1623; (*e*) C. A. Carson and M. A. Kerr, Heterocycles from Cyclopropanes: Applications in Natural Product Synthesis, *Chem. Soc. Rev.*, 2009, **38**, 3051–3060.

2 (*a*) E. W. Schlag and B. S. Rabinovitch, Kinetics of the Thermal Unimolecular Isomerization Reactions of Cyclopropane-d_2[1], *J. Am. Chem. Soc.*, 1960, **82**, 5996–6000; (*b*) Z. Goldschmidt and B. Crammer, Vinylcyclopropane Rearrangements, *Chem. Soc. Rev.*, 1988, **17**, 229–267; (*c*) J. J. Gajewski, L. P. Olson and M. R. Willcott, Evidence for Concert in the Thermal Unimolecular Vinylcyclopropane to Cyclopentene Sigmatropic 1,3-Shif, *J. Am. Chem. Soc.*, 1996, **118**, 299–306; (*d*) J. E. Baldwin, Thermal Rearrangements of Vinylcyclopropanes to Cyclopentenes, *Chem. Soc. Rev.*, 2003, **103**, 1197–1212.

3 (*a*) A. De Meijere, Bindungseigenschaften des Cyclopropans und Chemische Konsequenzen, *Angew. Chem.*, 1979, **91**, 867–884; (*b*) W. R. Dolbier, Thermal Rearrangements of gem -Difluorocyclopropanes, *Acc. Chem. Res.*, 2002, **14**, 195–200.

4 (*a*) H.-U. Reissig, Donor-Acceptor-Substituted Cyclopropanes: Versatile Building Blocks in Organic Synthesis, *Angew. Chem.*, 1979, **91**, 259–278; (*b*) H. U. Reissig and R. Zimmer, Donor–Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis, *Chem. Soc. Rev.*, 2003, **103**, 1151–1196; (*c*) M. A. Cavitt, L. H. Phun and S. France, Intramolecular Donor–Acceptor Cyclopropane Ring-Opening Cyclizations, *Chem. Soc. Rev.*, 2014, **43**, 804–818; (*d*) T. F. Schneider, J. Kaschel and D. B. Werz, A New Golden Age for Donor–Acceptor Cyclopropanes, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504–5523; (*e*) D. B. Werz and A. T. Biju, Uncovering the Neglected Similarities of Arynes and Donor–Acceptor Cyclopropanes, *Angew. Chem., Int. Ed.*, 2020, **59**, 3385–3398.

5 (*a*) I. S. Young and M. A. Kerr, A Homo [3 + 2] Dipolar Cycloaddition: The Reaction of Nitrones with Cyclopropanes, *Angew. Chem., Int. Ed.*, 2003, **42**, 3023–3026; (*b*) B. Bajtos, M. Yu, H. Zhao and B. L. Pagenkopf, C-2/C-3 Annulation and C-2 Alkylation of Indoles with 2-Alkoxycyclopropanoate Esters, *J. Am. Chem. Soc.*, 2007, **129**, 9631–9634; (*c*) O. A. Ivanova, E. M. Budynina, Y. K. Grishin, I. V. Trushkov and P. V. Verteletskii, Donor–Acceptor Cyclopropanes as Three-Carbon Components in a [4 + 3] Cycloaddition Reaction with 1,3-Diphenylisobenzofuran, *Angew. Chem., Int. Ed.*, 2008, **47**, 1107–1110; (*d*) O. Lifchits and A. B. Charette, A Mild Procedure for the Lewis Acid-Catalyzed Ring-Opening of Activated Cyclopropanes with Amine Nucleophiles, *Org. Lett.*, 2008, **10**, 2809–2812; (*e*) C. L. Morales and B. L. Pagenkopf, Total Synthesis of (±)-Goniomitine via a Formal Nitrile/Donor–Acceptor Cyclopropane [3 + 2] Cyclization, *Org. Lett.*, 2008, **10**, 157–159; (*f*) A. T. Parsons and J. S. Johnson, Catalytic Enantioselective Synthesis of Tetrahydrofurans: A Dynamic Kinetic Asymmetric [3 + 2] Cycloaddition of Racemic Cyclopropanes and Aldehydes, *J. Am. Chem. Soc.*, 2009, **131**, 3122–3123; (*g*) M. Petzold, P. G. Jones and D. B. Werz, (3 + 3)-Annulation of Carbonyl Ylides with Donor–Acceptor Cyclopropanes: Synergistic Dirhodium(II) and Lewis Acid Catalysis, *Angew. Chem., Int. Ed.*, 2019, **58**, 6225–6229; (*h*) A. Kreft, A. Lucht, J. Grunenberg, P. G. Jones and D. B. Werz, Kinetic Studies of Donor–Acceptor Cyclopropanes: The Influence of Structural and Electronic Properties on the Reactivity, *Angew. Chem., Int. Ed.*, 2019, **58**, 1955–1959.

6 (*a*) H. W. Fruhauf, Metal-Assisted Cycloaddition Reactions in Organotransition Metal Chemistry, *Chem. Soc. Rev.*, 1997, **97**, 523–596; (*b*) M. Rubin, M. Rubina and V. Gevorgyan, Transition Metal Chemistry of Cyclopropenes and Cyclopropanes, *Chem. Soc. Rev.*, 2007, **107**, 3117–3179; (*c*) C. D. Schmidt, J. Kaschel, T. F. Schneider, D. Kratzert, D. Stalke and D. B. Werz, Donor-Substituted Nitrocyclopropanes: Immediate Ring-Enlargement to Cyclic Nitronates, *Org. Lett.*, 2013, **15**, 6098–6101.

7 (*a*) G. Dickmeiss, V. De Sio, J. Udmark, T. B. Poulsen, V. Marcos and K. A. Jørgensen, Organocatalytic Asymmetric Desymmetrization–Fragmentation of Cyclic Ketones, *Angew. Chem., Int. Ed.*, 2009, **48**, 6650–6653; (*b*) C. Sparr and R. Gilmour, Cyclopropyl iminium activation: reactivity umpolung in enantioselective organocatalytic reaction design, *Angew. Chem., Int. Ed.*, 2011, **50**, 8391–8395; (*c*) K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund and K. A. Jørgensen, Organocatalytic Enamine-Activation of Cyclopropanes for Highly Stereoselective Formation of Cyclobutanes, *J. Am. Chem. Soc.*, 2015, **137**, 1685–1691; (*d*) E. Sanchez-Diez, D. L. Vesga, E. Reyes, U. Uria, L. Carrillo and J. L. Vicario, Organocatalytically Generated Donor–Acceptor Cyclopropanes in Domino Reactions. One-Step Enantioselective Synthesis of Pyrrolo[1,2-*a*]quinolines, *Org. Lett.*, 2016, **18**, 1270–1273; (*e*) J. Wallbaum, L. K. Garve, P. G. Jones and D. B. Werz, Ring-Opening Regio-, Diastereo-, and Enantioselective 1,3-Chlorochalcogenation of Cyclopropyl Carbaldehydes, *Chem. – Eur. J.*, 2016, **22**, 18756–18759; (*f*) J. Blom, A. Vidal-Albalat, J. Jørgensen, C. L. Barløse, K. S. Jessen, M. V. Iversen and K. A. Jørgensen, Directing the Activation of Donor–Acceptor Cyclopropanes Towards Stereoselective 1,3-Dipolar

Cycloaddition Reactions by Brønsted Base Catalysis, *Angew. Chem., Int. Ed.*, 2017, **56**, 11831–11835.

8 (*a*) L. K. Garve, P. Barkawitz, P. G. Jones and D. B. Werz, Ring-opening 1,3-dichlorination of donor-acceptor cyclopropanes by iodobenzene dichloride, *Org. Lett.*, 2014, **16**, 5804–5807; (*b*) S. Kolb, M. Petzold, F. Brandt, P. G. Jones, C. R. Jacob and D. B. Werz, Electrocatalytic Activation of Donor-Acceptor Cyclopropanes and Cyclobutanes: An Alternative C(sp(3))-C(sp(3)) Cleavage Mode, *Angew. Chem., Int. Ed.*, 2021, **60**, 2–9.

9 (*a*) N. Selander and K. J. Szabo, Single-pot Triple Catalytic Transformations Based on Coupling of in Situ Generated Allyl Boronates with in Situ Hydrolyzed Acetals, *Chem. Commun.*, 2008, 3420–3422; (*b*) Y. Sumida, H. Yorimitsu and K. Oshima, Nickel-Catalyzed Borylative Ring-Opening Reaction of Vinylcyclopropanes with Bis(pinacolato) diboron Yielding Allylic Boronates, *Org. Lett.*, 2008, **10**, 4677–4679.

10 (*a*) B. List and J. W. Yang, The Organic Approach to Asymmetric Catalysis, *Science*, 2006, **313**, 1584–1586; (*b*) D. W. C. MacMillan, The Advent and Development of Organocatalysis, *Nature*, 2008, **455**, 304–308; (*c*) C. C. Loh and D. Enders, Exploiting the Electrophilic Properties of Indole Intermediates: New Options in Designing Asymmetric Reactions, *Angew. Chem., Int. Ed.*, 2012, **51**, 46–48; (*d*) L. C. Morrill and A. D. Smith, Organocatalytic Lewis base Functionalisation of Carboxylic Acids, Esters and Anhydrides via C1-Ammonium or Azolium Enolates, *Chem. Soc. Rev.*, 2014, **43**, 6214–6226; (*e*) S. J. Connon, Diaminocyclopropenylidene Organocatalysts: Beyond N-Heterocyclic Carbenes, *Angew. Chem., Int. Ed.*, 2014, **53**, 1203–1205; (*f*) A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. Richardson and D. J. Dixon, Organocatalytic Enantioselective Desymmetrisation, *Chem. Soc. Rev.*, 2016, **45**, 5474–5540; (*g*) S. Vellalath and D. Romo, Asymmetric Organocatalysis: The Emerging Utility of a,β-Unsaturated Acylammonium Salts, *Angew. Chem., Int. Ed.*, 2016, **55**, 13934–13943; (*h*) L. Klier, F. Tur, P. H. Poulsen and K. A. Jørgensen, Asymmetric Cycloaddition Reactions Catalysed by Diarylprolinol Silyl Ethers, *Chem. Soc. Rev.*, 2017, **46**, 1080–1102; (*i*) X. Song, Y. Zhang, P. Ji, F. Zeng, F. Bi and W. Wang, One-pot Synthesis of Salicylaldehyde Containing Biaryl Frameworks via an Aminocatalytic Diels-Alder-retro-Diels-Alder Cascade Reaction of Ynals with 2-pyrones, *Green Synth., Catal.*, 2020, **1**, 66–69.

11 (*a*) K. Y. Chow and J. W. Bode, Catalytic Generation of Activated Carboxylates: Direct, Stereoselective Synthesis of -Hydroxyesters from Epoxyaldehydes, *J. Am. Chem. Soc.*, 2004, **126**, 8126–8127; (*b*) S. S. Sohn and J. W. Bode, N-Heterocyclic Carbene Catalyzed C-C Bond Cleavage in Redox Esterifications of Chiral Formylcyclopropanes, *Angew. Chem., Int. Ed.*, 2006, **45**, 6021–6024; (*c*) J. W. Bode and S. S. Sohn, N-Heterocyclic Carbene-Catalyzed Redox Amidations of α-Functionalized Aldehydes with Amines, *J. Am. Chem. Soc.*, 2007, **129**, 13798–13799; (*d*) D. Du and Z. Wang, N-Heterocyclic Carbene-Catalyzed Domino Reactions of Formylcyclopropane 1,1-Diesters: A New Synthesis of Coumarins, *Eur. J. Org. Chem.*, 2008, **2008**, 4949–4954; (*e*) D. Du, L. Li and Z. Wang, N-Heterocyclic Carbene-Catalyzed Domino Ring-Opening/Redox Amidation/Cyclization Reactions of Formylcyclopropane 1,1-Diesters: Direct Construction of a 6–5–6 Tricyclic Hydropyrido[1,2-*a*]indole Skeleton, *J. Org. Chem.*, 2009, **74**, 4379–4382; (*f*) G. Q. Li, L. X. Dai and S. L. You, N-Heterocyclic Carbene Catalyzed Ring Expansion of Formylcyclopropanes: Synthesis of 3,4-Dihydro-α-pyrone Derivatives, *Org. Lett.*, 2009, **11**, 1623–1625; (*g*) L. Li, D. Du, J. Ren and Z. Wang, N-Heterocyclic Carbene Catalyzed Domino Reactions of Formylcyclopropane 1,1-Diesters: Construction of a 6–5–5 Tricyclic Pyrrolo[1,2-a]indole, *Eur. J. Org. Chem.*, 2011, **2011**, 614–618; (*h*) H. Lv, J. Mo, X. Fang and Y. R. Chi, Formal Diels Alder Reactions of Chalcones and Formylcyclopropanes Catalyzed by Chiral N-Heterocyclic Carbenes, *Org. Lett.*, 2011, **13**, 5366–5369; (*i*) P. Shao, L. Shen and S. Ye, Enantioselective Synthesis of Terminal 1,2-Diols from Acyl Chlorides, *Chin. J. Chem.*, 2012, **30**, 2688–2692; (*j*) J. Mahatthananchai and J. W. Bode, On the Mechanism of N-Heterocyclic Carbene Catalyzed Reactions Involving Acyl Azoliums, *Acc. Chem. Res.*, 2014, **47**, 696–707; (*k*) L. Dai and S. Ye, Photo/N-Heterocyclic Carbene Co-Catalyzed Ring Opening and γ-Alkylation of Cyclopropane Enal, *Org. Lett.*, 2020, **22**, 986–990.

12 R. Breslow, On the Mechanism of Thiamine Action. IV.1 Evidence from Studies on Model Systems, *J. Am. Chem. Soc.*, 1958, **80**, 3791–3726.

13 C. Zhao, F. Li and J. Wang, N-Heterocyclic Carbene Catalyzed Dynamic Kinetic Resolution of Pyranones, *Angew. Chem., Int. Ed.*, 2016, **55**, 1820–1824.

14 S. Bera, C. G. Daniliuc and A. Studer, Enantioselective Synthesis of Substituted *δ*-Lactones by Cooperative Oxidative N-Heterocyclic Carbene and Lewis Acid Catalysis, *Org. Lett.*, 2015, **17**, 4940–4943.

15 H. Ji, J. Xu and H. Ren, Chemoselective Intermolecular Cross-Benzoin Reaction of Aliphatic Aldehydes and Isatins via N-Heterocyclic Carbene Catalysis, *Synthesis*, 2019, **51**, 2191–2197.

16 M. D. Greenhalgh, S. M. Smith, D. M. Walden, J. E. Taylor, Z. Brice, E. R. T. Robinson, C. Fallan, D. B. Cordes, A. M. Z. Slawin, H. C. Richardson, M. A. Grove, P. H. Cheong and A. D. Smith, A C=O Isothiouronium Interaction Dictates Enantiodiscrimination in Acylative Kinetic Resolutions of Tertiary Heterocyclic Alcohols, *Angew. Chem., Int. Ed.*, 2018, **57**, 3200–3206.

17 E. Crizanto de Lima, F. S. Castelo-Branco, C. C. Maquiaveli, A. B. Farias, M. N. Renno, N. Boechat and E. R. Silva, Phenylhydrazides as Inhibitors of Leishmania Amazonensis Arginase and Antileishmanial Activity, *Bioorg. Med. Chem.*, 2019, **27**, 3853–3859.

18 N. Richy, D. Sarraf, X. Marechal, N. Janmamode, R. Le Guevel, E. Genin, M. Reboud-Ravaux and J. Vidal, Structure-based Design of Human Immuno- and

Constitutive Proteasomes Inhibitors, *Eur. J. Med. Chem.*, 2018, **145**, 570–587.

19 (*a*) I. Tellitu, I. Beitia, M. Díaz, A. Alonso, I. Moreno and E. Domínguez, An Improved Solvent-free System for the Microwave-assisted Decarboxylation of Malonate Derivatives Based on the use of Imidazole, *Tetrahedron*, 2015, **71**, 8251–8255; (*b*) D. W. P. Tay, J. D. Nobbs, C. Romain, A. J. P. White, S. Aitipamula, M. van Meurs and G. J. P. Britovsek, gem-Dialkyl Effect in Diphosphine Ligands: Synthesis, Coordination Behavior, and Application in Pd-Catalyzed Hydroformylation, *ACS Catal.*, 2019, **10**, 663–671.