

Cite this: *Chem. Sci.*, 2020, **11**, 2175

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

Received 12th November 2019  
Accepted 23rd December 2019

DOI: 10.1039/c9sc05738b  
[rsc.li/chemical-science](http://rsc.li/chemical-science)

## Introduction

Over the course of the past several years, pyrone-based Diels–Alder reactions have served as a valuable tool to generate diverse molecules, including structurally complex natural products.<sup>1,2</sup> Indeed, not only can they lead directly to the [2.2.2]-bicyclic lactones found in targets such as basilioide C (**1**, Fig. 1)<sup>3</sup> and scholarisine A (**2**),<sup>4</sup> but their functionality can also be converted into a number of other patterning. Those changes include the highlighted domains of  $\alpha$ -lycorane (**3**),<sup>5</sup> chatancin (**4**),<sup>6</sup> and gracilamine (**5**)<sup>7</sup> as achieved through ring openings, as well as the aromatized systems of rufescine (**6**)<sup>8</sup> and cavicularin (**7**)<sup>9</sup> formed *via* retro-Diels–Alder reactions expelling CO<sub>2</sub>.<sup>10</sup> Despite this collated potential, however, none of the cycloadditions leading to these diverse products served as the enantioselective step in their sequences. That result likely reflects the fact that few catalytic, asymmetric variants have been developed to date,<sup>11</sup> perhaps due to the pyrone unit itself precluding traditional strategies that activate and facially differentiate dienophiles. Key exceptions shown in Scheme 1 include (1) work by the Posner group<sup>12</sup> using stoichiometric TADDOL Lewis acid complexes to achieve asymmetric inverse demand Diels–Alder reactions between 3-carbomethoxy-2-pyrones and aryl vinyl ethers and (2) precedent by Deng,<sup>13</sup> built upon by Wang,<sup>14</sup> in which the 3-hydroxy motif of pyrones **8** and **10** enabled hydrogen-bonding catalysis with cinchona-derived amino alcohol or amino thiourea promoters to deliver **9** and **11** with high stereochemical control in a normal demand version. Herein, we highlight a new approach to achieve catalytic,

enantioselective pyrone Diels–Alder chemistry with distinct substrate scope fueled by activating  $\alpha,\beta$ -unsaturated aldehydes (**19**) as their dienamine counterparts. This process affords an array of structurally useful [2.2.2]-bicyclic lactones with good to excellent diastereo- and enantiocontrol.

Recent precedent from Chen and co-workers<sup>15,16</sup> showed that the use of the proline-derived promoter **13** (Scheme 1)<sup>17</sup> was able to effect Diels–Alder reactions between a variety of substrates, including the electron deficient dienes and crotonaldehyde, to forge highly substituted cyclohexene systems. We wondered whether mechanistically similar chemistry could be achieved with an array of substituted pyrones (**18**) with diverse aldehyde-

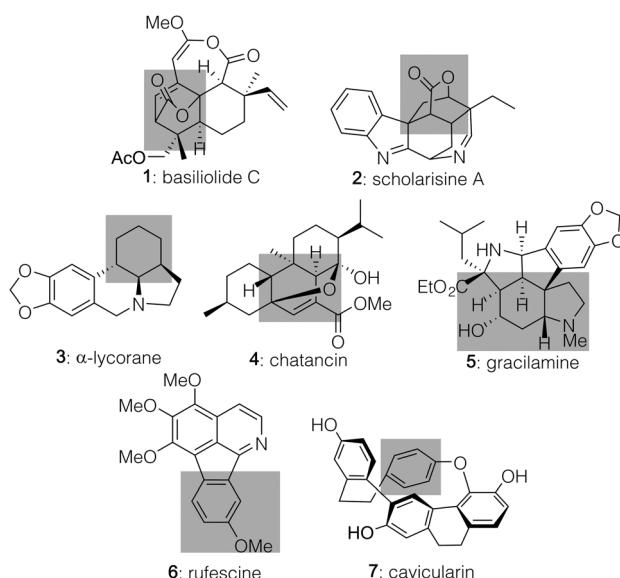
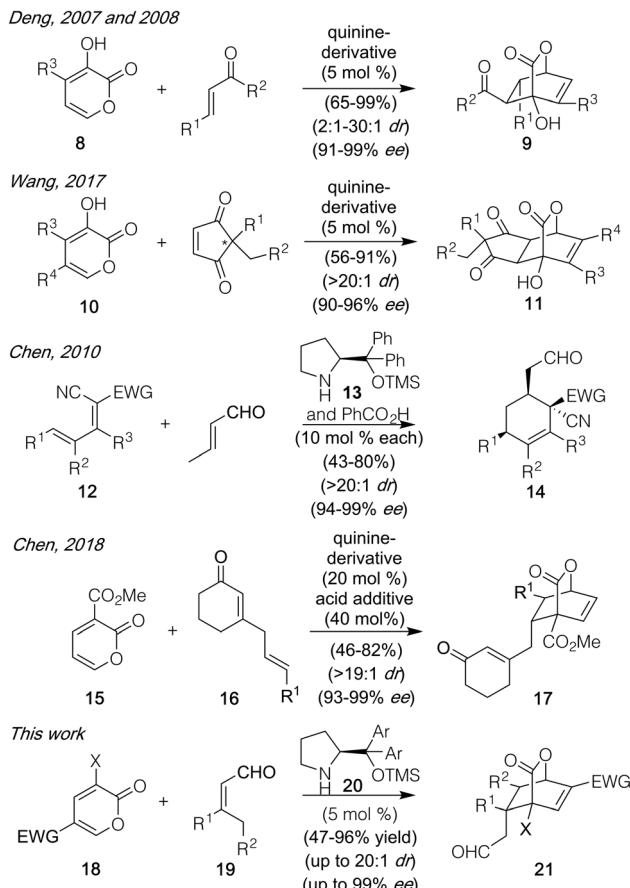


Fig. 1 Selected natural products synthesized through pyrone Diels–Alder reactions.





**Scheme 1** Examples of asymmetric pyrone Diels–Alder reactions, and the development of a new variant of such a process using dienamine catalysis.

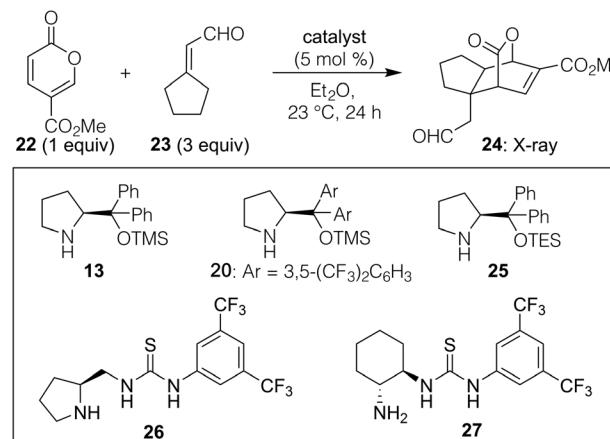
derived dienophiles (**19**) to generate chiral [2.2.2]-bicyclic products. If so, then arguably greater reaction scope could be achieved *versus* existing precedent, particularly in terms of the pyrone partner, since the specific structural requirements critical to the Posner, Deng, and Wang designs would not be required given the distinct mode of activation. Questioning that assumption was a report<sup>18</sup> issued after our studies began which revealed that one such Diels–Alder process could be achieved, though only under more forcing conditions<sup>16</sup> (50 °C, 20 mol% promoter, 40 mol% acid) and restricted to a single pyrone (**15**) and dienophile class in which a cyclic enone coupled with an allyl substituent (in the form of **16**) was needed to generate the competent reaction partner. Herein, we show that it is possible to achieve significant breadth in this reaction process, under milder conditions which allow for low catalyst loadings (25 °C, 5 mol% promoter, no additive), using an array of pyrones (**18**) and simple  $\alpha,\beta$ -unsaturated materials (**19**) as the dienophile precursor.

## Results and discussion

Our explorations began by using methyl coumalate (**22**, Table 1) as the pyrone-based diene given its documented success in

Diels–Alder chemistry<sup>19</sup> along with a variety of  $\alpha,\beta$ -unsaturated aldehydes to determine what patterning, if any, could afford reasonably high reactivity and stereoselectivity. That screen showed that in  $\text{Et}_2\text{O}$  as solvent at 23 °C,<sup>20</sup> 3,3'-disubstituted enals were by far the most effective partners (see ESI† for full details) when used as the model dienophile for further optimizations. As shown in Table 1, we found that Chen's original catalyst (**13**) in combination with equimolar benzoic acid additive could afford some of the desired *endo* product (**24**) containing a fused ring and a new quaternary carbon (entry 1; structure verified by X-ray analysis)<sup>21</sup> with fairly good selectivity over its undrawn *exo* alternative. However, using the 3,5-bis(trifluoromethyl) phenyl variant **20** at only a 5 mol% loading (entry 2), improved yield (56%) and selectivity [5.7 : 1 dr, 93% ee for the major diastereomer drawn, ee values determined by HPLC analysis of the UV-active homologated methyl ester formed *via* reaction of the aldehyde with methyl (triphenylphosphoranylidene)acetate] were obtained. Given that most reactions involving dienamines typically require catalyst loadings around 20 mol%,<sup>16</sup> we next tested whether the acidic or basic additives, which are often used to ensure high conversion and stereoselectivity, were needed. As indicated in entry 4, that turned out not to be the case, as the absence of such a promoter using catalyst **20** led to a significant increase in yield to 93% and an improved dr of 6.7 : 1.<sup>22</sup> No other catalyst screened, including several thioureas,<sup>23</sup> provided superior results. It

**Table 1** Screening of conditions and promoters for a dienamine-catalyzed asymmetric pyrone Diels–Alder reaction of **22** and **23**



Entry	Additive	Catalyst	Yield (%)	dr	ee <sup>c</sup> (%)
1 <sup>a</sup>	$\text{PhCO}_2\text{H}^a$	<b>13</b>	52	4.9 : 1	87
2	$\text{PhCO}_2\text{H}^b$	<b>20</b>	56	5.7 : 1	93
3	$\text{Et}_3\text{N}^b$	<b>20</b>	13	4.9 : 1	n.d.
4	—	<b>20</b>	93	6.7 : 1	94
5	—	<b>13</b>	70	2.3 : 1	90
6	—	<b>25</b>	64	3.5 : 1	92
7	—	<b>26</b>	10	3.0 : 1	20
8	—	<b>27</b>	—	n.d.	n.d.

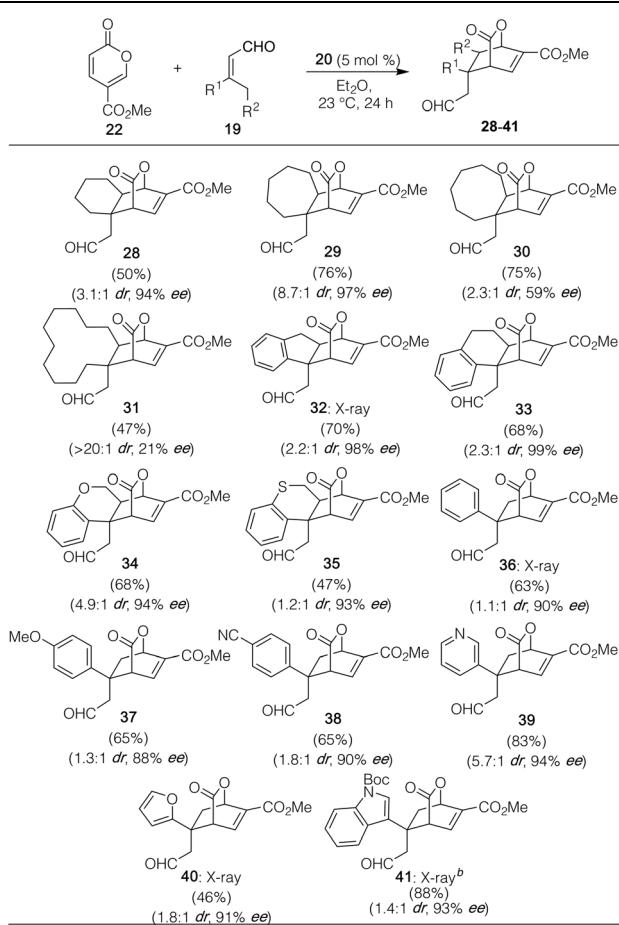
<sup>a</sup> 10 mol% loading of both catalyst and benzoic acid. <sup>b</sup> 0.1 equiv. added.

<sup>c</sup> Measured for major diastereomer.

should be noted that upon resubjection of the products to the reaction conditions (5 mol% **20** in  $\text{Et}_2\text{O}$ ), no change in *dr* was observed, suggesting that cycloreversion/equilibration is not taking place.

With these optimized conditions in hand, we then probed the dienophile scope with a number of cyclic and acyclic 3,3'-disubstituted enals. As shown in Table 2, rings of varied size, including 6-, 7-, and 8-membered carbocycles, could be readily fused onto pyrone **22** to deliver **28–30**. Quite pleasingly, the ring size could even be expanded to include the 12-membered carbocycle of **31**, albeit with modest enantioselectivity, though in near perfect diastereoselectivity. Similarly, a number of aryl-containing products, arising from indanone, tetralone, chromanone, thiochromanone, and a variety of aryl and heteroaryl-containing precursors succeeded smoothly as well irrespective of being electron-rich or electron-poor. In all of these cases, enantioselectivity for the major drawn diastereomer (with several such as **32**, **36**, **40**, and **41** verified *via* X-ray crystallographic analysis) was high, though diastereorecontrol was more modest than the fully aliphatic examples (*vide infra*).<sup>24</sup> In the

**Table 2** Scope of the inverse electron-demand pyrone Diels–Alder reaction by varying the enal partner<sup>a</sup>



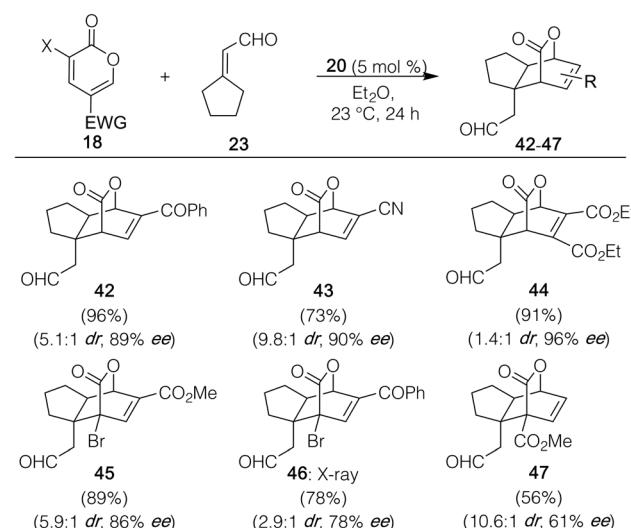
<sup>a</sup> Reactions were performed with **22** (0.3 mmol) and enal (0.9 mmol) in  $\text{Et}_2\text{O}$  (0.2 M) open to air. <sup>b</sup> X-ray obtained of the undrawn *exo*-**41** as well; see ESI.

case of the furanyl substituted enal leading to **40**, we attribute the slightly lower yield as being the result of the reactive furan moiety itself serving as a diene partner. Of note, the use of 3,3'-disubstituted enals is essential to the reaction's success; concurrent with our studies, Liu and Zu showed that under similar modes of catalysis with pyrone **22**, a variety of differentially substituted 3-aryl  $\alpha,\beta$ -unsaturated aldehydes participated in Rauhut–Currier reactions instead.<sup>25</sup>

We next explored variations in the pyrone partner in its reaction with cyclopentylidene carboxaldehyde (**23**). As shown in Table 3, both 5-substituted ketone and nitrile-containing substrates provided the desired products (**42** and **43**), the latter with far superior *dr* (9.8:1) *versus* the other counterparts probed. A 4,5-diester variant also succeeded to afford **44**. A 3-bromomethyl coumalate starting material, as well as its phenyl ketone analog, worked as well to deliver **45** and **46**; their bridgehead bromide atom is of potential synthetic use to enable further functionalizations. Finally, 2-pyrone substrates containing a single methyl ester group at different positions on the ring were also explored; however, besides methyl coumalate, only the 3-carbomethoxy-2-pyrone was capable of undergoing the desired transformation to provide **47**, albeit with reduced enantioselectivity. It should be noted that a similar trend was observed by Liu and Zu.<sup>25</sup> These final examples (**45–47**) collectively reveal the ability of the method to construct optically active products containing two fully substituted vicinal carbon atoms in a single step.<sup>26</sup>

With this body of results in hand, a transition state analysis to account for the stereoselection observed for the process is provided in Fig. 2; here, we have focused in particular on explaining the variations in *dr* observed based on the structural differences in the two respective partners. For aliphatic-containing substrates, we reason that transition state *endo* **48**,

**Table 3** Scope of the inverse electron-demand pyrone Diels–Alder reaction by varying the pyrone partner<sup>a</sup>



<sup>a</sup> Reactions were performed with pyrones (0.3 mmol) and **23** (0.9 mmol) in  $\text{Et}_2\text{O}$  (0.2 M) open to air.



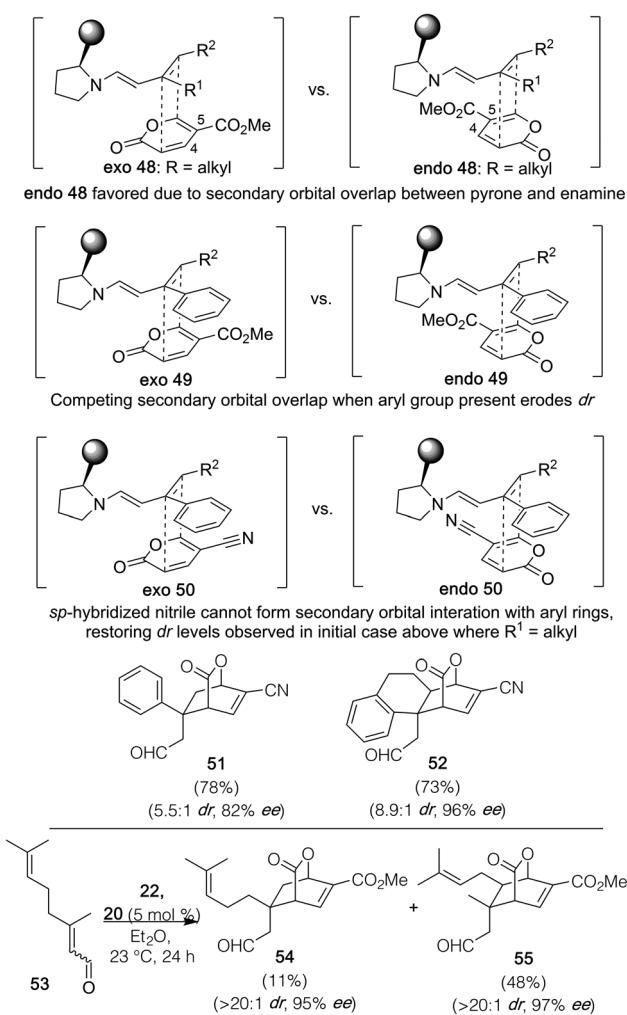
leading to the observed major diastereomer in each case, is favored over transition state *exo* 48, due to secondary orbital overlap between the 4,5-position of the pyrone and the formed enamine. When aryl-containing substrates are deployed, that diastereoselectivity bias is eroded due to competing secondary orbital overlap present in both transition states. By contrast, when a nitrile group is attached to the pyrone at the 5-position instead of an ester, the geometry imposed by its sp hybridization prevents effective secondary orbital overlap with added aryl rings in transition state *exo* 50, and generally would seem to favor transition state *endo* 50 through the similar stabilization of the 4,5-positions on the diene partner even if the dienophile contains only aliphatic substituents.

In support of that assertion, both products **51** and **52** were formed in significantly superior levels of dr *versus* the corresponding analogs generated with pyrone **22** at the price of a very small drop in enantioselection; thus, if high dr is a significant concern over enantiocontrol, the use of a nitrile-containing pyrone reactant might be the better choice given these observations. Finally, for dienophile precursors where both kinetic

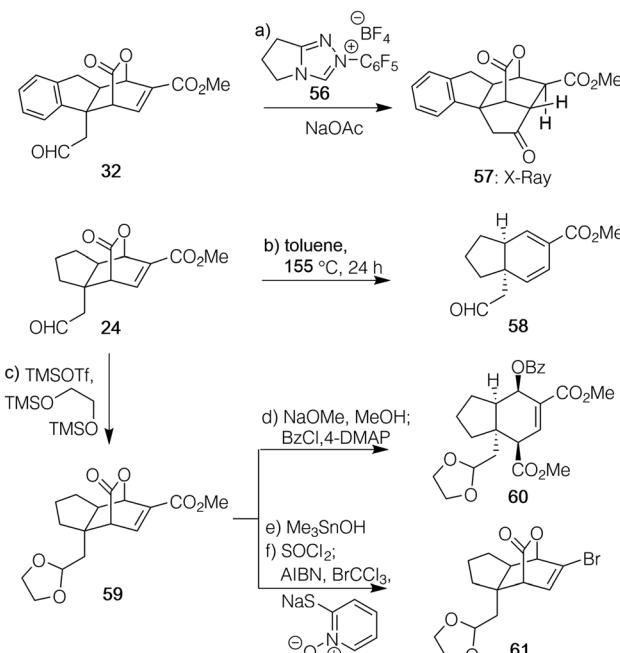
and thermodynamic dienamines could potentially react, as in substrate 53, the conditions allow for the preferential reaction of the thermodynamic dienamine given the formation of 55 in an  $\sim 4 : 1$  ratio with the separable 54.

Finally, to further illustrate the value of the developed reaction and its overall scope, a number of additional transformations were effected along the lines indicated in Scheme 2. First, as shown with [2.2.2]-bicycle 32, a Stetter reaction<sup>15b</sup> promoted by triazolium salt 56 can enable coupling of the enoate with the pendant aldehyde on the quaternary carbon to generate the new fused ring system of 57 in 91% yield as a single diastereomer about the ester. This example highlights the asymmetric construction of a fully substituted cyclohexane ring in 2 steps, thus demonstrating the ability of the approach to rapidly build congested molecular complexity.

Second, upon subjection to thermal conditions, the strained bicyclic lactone of **24** underwent a retro-Diels–Alder reaction expelling CO<sub>2</sub> that generated an electron-poor diene with functionality suitable for further elaboration in the form of **58**; the pre-generated quaternary carbon of the initial product prevented aromatization to allow access to this atypical, pyrone-derived material. Third, following protection of the aldehyde within **24** as its ethylene glycol acetal (to generate **59**), methanolysis of the lactone followed by *in situ* benzoyl protection of the resultant alcohol afforded a highly-substituted hydrindane



**Fig. 2** Proposed transition state analysis to account for observed drug trends.<sup>27</sup>



**Scheme 2** Selected transformations of pyrone Diels–Alder products to afford additional compounds of value. (a) 56 (20 mol%), NaOAc (1.2 equiv.), CHCl<sub>3</sub>, 40 °C, 30 min, 91%, 96% ee; (b) toluene, 155 °C, 24 h, sealed tube, 67%, 95% ee; (c) 1,2-bis(trimethoxysilyl)ethane (2.0 equiv.), TMSOTf (0.1 equiv.), 0 °C, 1 h, 98%; (d) NaOMe (2.0 equiv.), MeOH, 0 °C, 2 h; BzCl (2.0 equiv.), Et<sub>3</sub>N (2.0 equiv.), 4-DMAP (2.0 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 1 h, 67% over 2 steps, 95% ee; (e) Me<sub>3</sub>SnOH (3.0 equiv.), ClCH<sub>2</sub>CH<sub>2</sub>Cl, 80 °C, 16 h; (f) SOCl<sub>2</sub> (5.0 equiv.), toluene, 23 °C, 24 h; AIBN (0.1 equiv.), mercaptopyridine *N*-oxide sodium salt (1.1 equiv.), BrCCl<sub>3</sub>, 100 °C, 1 h, 38% over 3 steps, 92% ee.

core (**60**) in 67% yield over two steps. Alternatively, it is possible to differentially functionalize the exocyclic methyl ester over the potentially more strained lactone *via* controlled methanolysis of **59** as effected with  $\text{Me}_3\text{SnOH}$ .<sup>28</sup> This event was followed by a Hunsdiecker-type reaction<sup>29</sup> using a Barton thiohydroximate ester intermediate and  $\text{CBrCl}_3$  to generate **61** in 38% yield over three steps. Not only is the resultant bromide a handle for further diversification, but the material formally reflects the Diels–Alder product of 5-bromo-2-pyrone,<sup>30</sup> a notoriously challenging diene to engage in cycloaddition chemistry to afford products in racemic format, let alone the asymmetric version obtained here.<sup>31</sup>

## Conclusions

In conclusion, we have developed a novel catalytic asymmetric inverse electron demand pyrone Diels–Alder reaction that has a unique scope relative to previously developed alternatives; indeed, to the best of our knowledge, all compounds prepared constitute new molecular entities.<sup>32</sup> The reaction process is operationally simple, non-sensitive to air or moisture, and can be conducted with very low catalyst loadings (5 mol%) in the absence of additional additives typical of other transformations involving dienamines. As highlighted by the products formed, an array of synthetically valuable and structurally distinct [2.2.2]-bicyclic lactones can be accessed in moderate to good yields with effective diastereo- and high enantiocontrol. Applications to the synthesis of complex natural products and other materials, as well as the extension of the general protocol to other substrate types, is the subject of current endeavors.

## Author contributions

S. A. S. and C. J. F. C. conceived the project. S. A. S directed the research, and S. A. S. and C. J. F. C. composed the manuscript and the ESI† section; all authors commented on the manuscript. C. J. F. C. developed the initial reaction and explored substrate scope, while L. F. completed the synthesis of several pyrone starting materials and contributed significantly to the substrate tables.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We thank Dr Alexander Filatov and Mr Andrew McNeece for X-ray analysis of our crystalline intermediates, and Dr Antoni Jurkiewicz and Dr C. Jin Qin for assistance with NMR and mass spectrometry, respectively. We also thank Ms Lindsey Jay and Ms Jenna Reisler for the preparation and purification of some of the starting materials. Financial support for this work came from the University of Chicago (start-up funds and graduate fellowships to C. J. F. C.) and CONACyT (postdoctoral fellowship to L. F.).

## Notes and references

- For selected reviews of the Diels–Alder reaction, see: (a) E. J. Corey, *Angew. Chem., Int. Ed.*, 2002, **41**, 1650; (b) K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2002, **41**, 1668.
- For reviews of pyrone Diels–Alder reactions, see: (a) K. Afarinkia, V. Vinader, T. D. Nelson and G. H. Posner, *Tetrahedron*, 1992, **48**, 9111; (b) B. T. Woodard and G. H. Posner, *Adv. Cycloaddit.*, 1999, **5**, 47.
- J. R. Gordon, H. M. Nelson, S. C. Virgil and B. M. Stoltz, *J. Org. Chem.*, 2014, **79**, 9740.
- M. W. Smith and S. A. Snyder, *J. Am. Chem. Soc.*, 2013, **135**, 12964.
- Y.-G. Jung, S.-C. Lee, H.-K. Cho, N. B. Darvatkar, J.-Y. Song and C.-G. Cho, *Org. Lett.*, 2012, **15**, 132.
- Y. M. Zhao and T. J. Maimone, *Angew. Chem., Int. Ed.*, 2015, **54**, 1223.
- P. Gan, M. W. Smith, N. R. Braffman and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2016, **55**, 3625.
- (a) D. L. Boger and C. E. Brotherton, *J. Org. Chem.*, 1984, **49**, 4050; (b) D. L. Boger and K. Takahashi, *J. Am. Chem. Soc.*, 1995, **117**, 12452.
- P. Zhao and C. M. Beaudry, *Org. Lett.*, 2013, **15**, 402.
- For other examples of pyrone Diels–Alder reactions in total synthesis, see: (a) G. H. Posner and D. G. Wetzlaufer, *J. Am. Chem. Soc.*, 1986, **108**, 7373; (b) G. H. Posner and C. M. Kinter, *J. Org. Chem.*, 1990, **55**, 3967; (c) H. Shimizu, H. Okamura, T. Iwagawa and M. Nakatani, *Tetrahedron*, 2001, **57**, 1903; (d) P. S. Baran and N. Z. Burns, *J. Am. Chem. Soc.*, 2006, **128**, 3908; (e) I.-J. Shin, E.-S. Choi and C.-G. Cho, *Angew. Chem., Int. Ed.*, 2007, **46**, 2303; (f) N. T. Tam and C.-G. Cho, *Org. Lett.*, 2008, **10**, 601; (g) H. M. Nelson, K. Murakami, S. C. Virgil and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2011, **50**, 3688; (h) L. Min, Y. Zhang, X. Liang, J. Huang, W. Bao and C.-S. Lee, *Angew. Chem., Int. Ed.*, 2014, **53**, 11294; (i) X. Yu, L. Xiao, Z. Wang and T. Luo, *J. Am. Chem. Soc.*, 2019, **141**, 3440.
- For examples utilizing chiral auxiliaries, see: (a) I. E. Markó and G. R. Evans, *Tetrahedron Lett.*, 1994, **35**, 2767; (b) H. Okamura, K. Morishige, T. Iwagawa and M. Nakatani, *Tetrahedron Lett.*, 1998, **39**, 1211; (c) G. H. Posner and D. G. Wetzlaufer, *Tetrahedron Lett.*, 1986, **27**, 667.
- (a) G. H. Posner, J.-C. Carry, J. K. Lee, D. S. Bull and H. Dai, *Tetrahedron Lett.*, 1994, **35**, 1321; (b) I. E. Markó, G. R. Evans and J.-P. Declercq, *Tetrahedron*, 1994, **50**, 4557; (c) G. H. Posner, H. Dai, D. S. Bull, J.-K. Lee, F. Eydoux, Y. Ishihara, W. Welsh, N. Pryor and S. Petr, *J. Org. Chem.*, 1996, **61**, 671; (d) I. E. Markó, I. Chellé-Regnaut, B. Leroy and S. L. Warriner, *Tetrahedron Lett.*, 1997, **38**, 4269; (e) Y. Hashimoto, R. Abe, N. Morita and O. Tamura, *Org. Biomol. Chem.*, 2018, **16**, 8913; (f) X.-W. Liang, Y. Zhao, X.-G. Si, M.-M. Xu, J.-H. Tan, Z.-M. Zhang, C.-G. Zheng, C. Zheng and Q. Cai, *Angew. Chem., Int. Ed.*, 2019, **58**, 14562.
- (a) Y. Wang, H. Li, Y.-Q. Wang, Y. Liu, B. M. Foxman and L. Deng, *J. Am. Chem. Soc.*, 2007, **129**, 6364; (b) R. P. Singh,





K. Bartelson, Y. Wang, H. Su, X. Lu and L. Deng, *J. Am. Chem. Soc.*, 2008, **130**, 2422.

14 L.-M. Shi, W.-W. Dong, H.-Y. Tao, X.-Q. Dong and C.-J. Wang, *Org. Lett.*, 2017, **19**, 4532.

15 (a) J.-L. Li, T.-R. Kang, S.-L. Zhou, R. Li, L. Wu and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2010, **49**, 6418; (b) J.-L. Li, S.-L. Zhou, P.-Q. Chen, L. Dong, T.-Y. Liu and Y.-C. Chen, *Chem. Sci.*, 2012, **3**, 1879.

16 For recent reviews of dienamine catalysis in organic transformations, see: (a) S. Mukherjee, J. W. Yang, S. Hoffman and B. List, *Chem. Rev.*, 2007, **107**, 5471; (b) A. Moyano and R. Rios, *Chem. Rev.*, 2011, **111**, 4703; (c) J.-L. Li, T.-Y. Liu and Y.-C. Chen, *Acc. Chem. Res.*, 2012, **45**, 1491; (d) E. Arceo and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2012, **51**, 2012; (e) D. B. Ramachary and Y. V. Reddy, *Eur. J. Org. Chem.*, 2012, 865; (f) I. D. Jurberg, I. Chatterjee, R. Tannert and P. Melchiorre, *Chem. Commun.*, 2013, **49**, 4869; (g) H. Jiang, L. Albrecht and K. A. Jørgensen, *Chem. Sci.*, 2013, **4**, 2287; (h) X. Jiang and R. Wang, *Chem. Rev.*, 2013, **113**, 5515; (i) V. Marcos and J. Alemán, *Chem. Soc. Rev.*, 2016, **45**, 6812; (j) F. E. Held and S. B. Tsogoeva, *Catal. Sci. Technol.*, 2016, **6**, 645; (k) L. Klier, F. Tur, P. Poulsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2017, **46**, 1080. For reviews on computational studies of dienamine catalyzed transformations, see: (l) K. Halskov, B. S. Donslund, B. M. Paz and K. A. Jørgensen, *Acc. Chem. Res.*, 2016, **49**, 974; (m) P. Renzi, J. Hioe and R. M. Gschwind, *Acc. Chem. Res.*, 2017, **50**, 2936.

17 (a) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212; (b) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 18296. For reviews, see: (c) A. Mieglo and C. Palomo, *Chem.-Asian J.*, 2008, **3**, 922; (d) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht and K. A. Jørgensen, *Acc. Chem. Res.*, 2012, **45**, 248; (e) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2015, **54**, 13860; (f) G. J. Reyes-Rodríguez, N. M. Rezayee, A. Vidal-Albalat and K. A. Jørgensen, *Chem. Rev.*, 2019, **119**, 4221.

18 Y. Zhou, Z. Zhou, W. Du and Y.-C. Chen, *Acta Chim. Sin.*, 2018, **76**, 382.

19 (a) T. Imagawa, N. Sueda and M. Kawanisi, *Tetrahedron*, 1974, **30**, 2227; (b) M. E. Jung, L. J. Street and Y. Usui, *J. Am. Chem. Soc.*, 1986, **108**, 6810; (c) I. E. Markó and G. R. Evans, *Tetrahedron Lett.*, 1993, **34**, 7309; (d) G. A. Kraus and S. Wang, *RSC Adv.*, 2017, **89**, 56760; (e) H. Yu and G. A. Kraus, *Tetrahedron Lett.*, 2018, **59**, 4008.

20 Although reactions were conducted under an argon atmosphere, strict exclusion of air and water was not essential to its success.

21 All crystals obtained for diffraction analysis in this study were racemates; no ee measurements were taken of the resultant mother liquors to determine the degree of enhancement. The absolute configuration of **24** as drawn was determined using a copper source.

22 Based on crude NMR analysis, acidic additives seem to promote undesired pathways, as reaction profiles in their presence were never clean. For a review on the importance of additives in such transformations, see: L. Hong, W. Sun, D. Yang, G. Li and R. Wang, *Chem. Rev.*, 2016, **116**, 4006.

23 (a) S. Bertelsen, M. Marigo, S. Brandes, P. Diner and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 12973; (b) L. Albrecht, G. Dickmeiss, C. F. Weise, C. Rodríguez-Esrich and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2012, **51**, 13109; (c) C. F. Weise, V. H. Lauridsen, R. S. Rambo, E. H. Iversen, M.-L. Olsen and K. A. Jørgensen, *J. Org. Chem.*, 2014, **79**, 3537; (d) B. S. Donslund, A. Monleón, J. Larsen, L. Ibsen and K. A. Jørgensen, *Chem. Commun.*, 2015, **51**, 13666.

24 All ee values for the minor diastereomers are provided in the ESI† section. In addition, we were able to obtain an X-ray crystal structure of *exo* **41** which enabled us to assign its configuration in relative terms. Given the generally low ee values for the *exo* products, we have been unable to obtain a suitable crystal structure to determine absolute configuration despite significant effort.

25 Q. Liu and L. Zu, *Angew. Chem., Int. Ed.*, 2018, **57**, 9505.

26 G. H. Posner, T. D. Nelson, C. M. Kinter and K. Afarinkia, *Tetrahedron Lett.*, 1991, **32**, 5295.

27 Note that the *s-cis* conformation presented in the proposed transition state analysis is based on the absolute stereochemistry of the products as obtained by X-ray crystallographic analysis of *endo* **41** and *exo* **41**. It is believed that the *s-cis* configuration is preferred due to the A<sup>1,3</sup> steric interaction present in the *s-trans* conformation as well as the additional frontier molecular orbital stabilization when in the *s-cis* conformation. We thank a referee for his/her comments which provoked further thought on the proposed transition state structures.

28 K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee and B. S. Safina, *Angew. Chem., Int. Ed.*, 2005, **44**, 1378.

29 D. H. R. Barton, D. Crich and W. B. Motherwell, *Tetrahedron*, 1985, **41**, 3901.

30 K. Afarinkia and G. H. Posner, *Tetrahedron Lett.*, 1992, **33**, 7839.

31 In all cases, the ee of the initial Diels–Alder products was retained in the subsequent transformations.

32 As judged by using standard search engines in early November, 2019.