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An asymmetric approach to bicyclo[2.2.1]heptane-1-carboxylates *via* a formal [4 + 2] cycloaddition reaction enabled by organocatalysis†

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An organocatalytic formal [4 + 2] cycloaddition reaction has been realized that permits rapid access to a wide range of bicyclo[2.2.1] heptane-1-carboxylates in a highly enantioselective manner from simple starting materials under mild and operationally simple conditions.

A bicyclo[2.2.1]heptane scaffold is a privileged molecular structure embedded in numerous compounds with various functions (Fig. 1). Camphor,[1] sordarins,[2] α-santalol and β-santalol[3,4] are bioactive natural products that contain this structural moiety. In addition, bicyclo[2.2.1]heptane is featured by drug candidates such as LMV-601[5] and AMG 221.[6] Moreover, the bicyclo[2.2.1]heptane scaffold provides the basis for asymmetric synthesis and catalysis. Bornanesultam is a well-known chiral auxiliary,[7] while dibenzyldiene[8] and diphonane[9] are effective chiral ligands for transition-metal catalysis. The development of enantioselective approaches to functionalized bicyclo[2.2.1]heptanes is critical for target-oriented and diversity-oriented syntheses of related biologically significant molecules, and therefore it is highly desirable for relevant drug discovery.

From the perspective of molecular architecture, the molecules depicted in Fig. 1 may be classified into two main groups contingent on whether or not a bridgehead carbon is present. In this regard, camphor, sordarins, and bornanesultam belong to the same group. We are interested in the development of a synthetic approach that would allow direct access to bicyclo-[2.2.1]heptanes with a functionalized bridgehead, particularly in view of the absence of such a method so far.[10] We envisaged an enantioselective approach to bicyclo[2.2.1]heptane-1-carboxylates *via* a formal [4 + 2] cycloaddition reaction, with an understanding of the carboxylate group being a versatile function amenable to various transformations (Scheme 1). Mechanistically distinct from the preceding methods, which involve enamine catalysis[10a–c] or Brønsted acid catalysis,[10d] this reaction would be effected through a hydrogen bond catalysis.[11,12] To this end, a chiral tertiary amine would be employed as the catalyst. Herein, we present the asymmetric approach to bicyclo[2.2.1]heptane-1-carboxylates by the reaction of α′-ethoxycarbonyl cyclopentenones with nitroolefins (Scheme 1).

Our research commenced with investigating the reaction between **1a** and **2a**. When 10 mol% **A** was employed as the catalyst, a stepwise incomplete reaction was observed that produced a mixture containing both the Diels–Alder product and the Michael addition product.[12] This problem was solved successfully by the addition of DBU after consumption of **1a** to promote the second Michael addition reaction.[13] Various reaction parameters were evaluated and selected results are listed in Table 1. The reaction of **1a** and **2a** catalyzed by 10 mol% **A** at room temperature produced a 2.3/1 diastereomeric
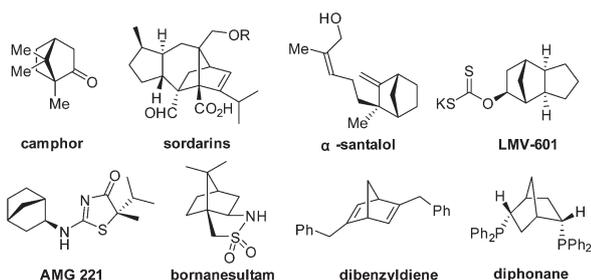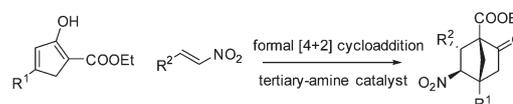

Fig. 1 Selected compounds containing a [2.2.1] bicyclic core.

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Scheme 1 Formal [4 + 2] cycloaddition reaction.

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Table 1 Conditions screening for the reaction of **1a** and **2a**[a]

Entry	Cat.	Solv.	Temp.	Yld.[b] (%)	dr[c]	ee[d] (%)
1	A	DCM	R.T.	82	2.3/1	88
2	A	DCM	0	83	2.4/1	90
3	A	DCM	−20	81	2.8/1	91
4	B	DCM	R.T.	86	3.2/1	81
5	B	DCM	−20	80	5.6/1	84
6	B	DCM	−40	82	7.1/1	87
7	B	DCM	−60	69	3.7/1	69
8	C	DCM	−40	84	3.2/1	94
9	C	DCM	−60	73	2.5/1	75
10	D	DCM	−40	77	2.0 : 1	−81
11	E	DCM	−40	77	3.3/1	94
12	C	PhMe	−40	34	3.5/1	93
13	C	MeCN	−40	61	4.0/1	92
14	C	THF	−40	41	2.5/1	95

[a] **1a** (0.20 mmol), **2a** (0.24 mmol), 10 mol% catalyst, and 1 mL of solvent were employed. After **1a** was consumed as indicated by a TLC test, DBU (0.10 mmol) was added to the reaction mixture. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by chiral HPLC analysis.

Table 2 The formal [4 + 2] reaction between **1a** and β-arylnitroalkenes[a]

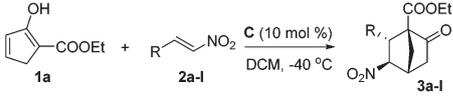| Entry[a]	R	Yld.[b] (%)	dr[c]	ee[d] (%)
1	Ph (**2a**)	84	3.2/1	94
2	4-MeC$_6$H$_4$ (**2b**)	78	3.1/1	95
3	4-MeOC$_6$H$_4$ (**2c**)	74	2.0/1	92
4	2-MeOC$_6$H$_4$ (**2d**)	75	2.6/1	94
5	4-BrC$_6$H$_4$ (**2e**)	84	3.5/1	97
6	2-BrC$_6$H$_4$ (**2f**)	80	4.0/1	98
7	3-ClC$_6$H$_4$ (**2g**)	84	4.7/1	98
8	4-FC$_6$H$_4$ (**2h**)	86	2.8/1	96
9	3-NO$_2$C$_6$H$_4$ (**2i**)	82	4.2/1	99
10	4-CF$_3$C$_6$H$_4$ (**2j**)	80	4.2/1	97
11	2-Furyl (**2k**)	73	1.3/1	92
12	2-Naphthyl (**2l**)	77	1.9/1	81

[a] **1a** (0.20 mmol), **2** (0.24 mmol), **C** (10 mol%), and 1 mL of DCM were employed. After **1a** was consumed as indicated by a TLC test, DBU (0.10 mmol) was added to the reaction mixture. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by chiral HPLC analysis.

mixture in 82% yield, with the major diastereomer **3a** bearing an enantiopurity of 88% ee (entry 1). Lower temperatures of 0 °C and −20 °C appeared to give slightly higher diastereo-selectivities and enantioselectivities (entries 2 and 3). The same reaction with catalyst **B** gave the best result at −40 °C, with 82% yield, 7.1/1 dr and 87% ee being achieved, however, further decreasing the temperature to −60 °C resulted in eroded selectivities (entries 4–7). The same was observed for catalyst **C**, which achieved the highest selectivities at −40 °C with the product being obtained in 84% yield with 3.2/1 dr and 94% ee (entries 8 and 9). Therefore, reactions with other catalysts were further tested at −40 °C. At this temperature, while the reaction with catalyst **D** was considerably less stereo-selective, the enantioselectivity obtained with catalyst **E** was similar to that with **C** (entries 10 and 11). In light of these results, **C** was determined as the catalyst of choice and the solvent effect was then evaluated with this catalyst. The reactions in toluene, CH$_3$CN, and THF, respectively, were similarly enantioselective as compared to that in dichloromethane. However, the diastereoselectivities and yields with these solvents were significantly lower (entries 12–14).

With the optimal conditions in hand, we moved on to identify the substrate scope. β-Arylnitroalkenes **2b–2l** were first examined as the electrophile (Table 2). Generally good yield, moderate diastereoselectivity and excellent enantioselectivity could be obtained for various nitrostyrenes bearing either electron donating or electron withdrawing groups (entries 2–10). The electron withdrawing groups appeared to be more favor-
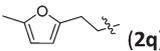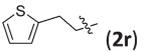
able for the reaction to achieve higher yields and stereoselec-tivities (entries 2–4 *vs.* entries 5–10). The steric effect of the substituent did not play a significant role (entry 3 *vs.* entry 4, entry 5 *vs.* entry 6). For nitroolefins **2k** and **2l** bearing other aromatic substituents, the diastereoselectivity as well as the enantioselectivity dropped considerably (entries 11 and 12). Based on these results, it may be concluded for β-arylnitro-alkene substrates that more electron-deficient nitroolefins are better substrates. Considering that more electron-deficient nitroolefins are more reactive electrophiles, it became a logical deduction for us that more reactive nitroolefins are better sub-strates for this reaction.

Accordingly, we then studied the reaction of **1a** with β-alkyl-nitroalkenes. As summarized in Table 3, the various sterically undemanding β-alkylnitroalkenes are excellent substrates for this formal cycloaddition reaction. Nitroolefins with a satu-rated hydrocarbon chain provided the [2.2.1] bicyclic products in excellent yield with *ca.* 20/1 dr and extremely high ee (entries 1–3). An aromatic ring at the distal end of the chain was tolerable (entries 4–6). Importantly, nitroolefins with func-tional groups were excellent substrates for this reaction, pro-viding the [2.2.1] products amenable for further elaborations (entries 7–10). Interestingly, **2w** bearing a cyclopropyl group was also an effective substrate (entry 11). As the bulkiness of the substituent increased, the reactivity as well as the enantio-selectivity dropped considerably (entry 12).

We further examined the reaction between **1b** and various 2-alkyl-1-nitroethenes (Table 4). With **1b** being employed as the nucleophile, products with the [2.2.1] bicyclic core deco-rated with two all-carbon quaternary stereocenters were expected to be garnered. To our delight, the reactions between **1b** and **2** underwent smoothly and furnished the formal cyclo-

Table 3 The formal [4 + 2] reaction between **1a** and β-alkylnitroalkenes[a]

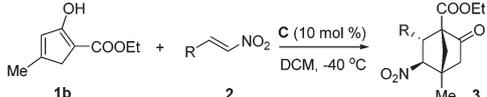| Entry	R	Yld.[b] (%)	dr[c]	ee[d] (%)
1	n-Pr (**2m**)	83	18/1	98
2	n-Bu (**2n**)	90	17/1	99
3	i-Bu (**2o**)	86	>20/1	98
4	Ph (**2p**)	88	>20/1	99
5	(**2q**)	84	>20/1	99
6	(**2r**)	90	20/1	99
7	C₅H₁₁ (**2s**)	90	>20/1	99
8	BnO (**2t**)	83	>20/1	98
9	BnO (**2u**)	88	20/1	98
10	Cl (**2v**)	89	>20/1	99
11	(**2w**)	73	10/1	95
12	i-Pr (**2x**)	69	10/1	46

[a] **1a** (0.20 mmol), **2** (0.24 mmol), **C** (10 mol%), and 1 mL of DCM were employed. After **1a** was consumed as indicated by a TLC test, DBU (0.10 mmol) was added to the reaction mixture. [b] Isolated yield. [c] Determined by ¹H NMR analysis of the crude product. [d] Determined by chiral HPLC analysis.

Table 4 The formal [4 + 2] cycloaddition reaction between **1b** and β-alkylnitroalkenes[a]

Entry	R	Prod.	Yld.[b] (%)	dr[c]	ee[d] (%)
1	i-Bu (**2o**)	**3ob**	78	6/1	84
2	Ph (**2p**)	**3pb**	73	6.5/1	84
3	(**2q**)	**3qb**	80	13/1	95
4	(**2r**)	**3rb**	74	8/1	88
5	C₅H₁₁ (**2s**)	**3sb**	74	6.3/1	83
6	BnO (**2t**)	**3tb**	76	8/1	75
7	Cl (**2v**)	**3vb**	79	>20/1	92

[a] **1b** (0.20 mmol), **2** (0.24 mmol), **C** (10 mol%), and 1 mL of DCM were employed. After **1a** was consumed as indicated by a TLC test, DBU (0.10 mmol) was added to the reaction mixture. [b] Isolated yield. [c] Determined by ¹H NMR analysis of the crude product. [d] Determined by chiral HPLC analysis.

Fig. 2 X-ray structure of **3rb** (ORTEP drawing with thermal ellipsoids at 30% probability level).
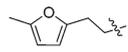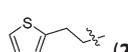
addition products in good yields with satisfactory selectivities (entries 1–7).

The structure as well as the absolute configuration of **3rb** was established unambiguously through X-ray crystallographic analysis (Fig. 2).[14]
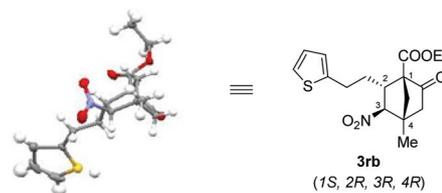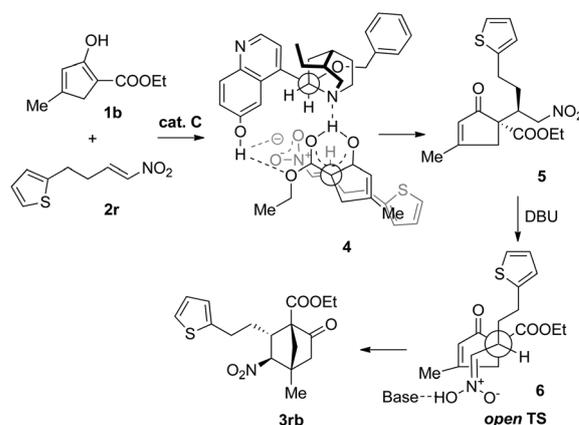
Based on the preceding results and in the light of our previous proposal,[13] the stereochemical outcome of the tandem reaction could be rationalized, as exemplified by the reaction of **1b** with **2r** (Scheme 2). In the first step, **1b** may form a complex with **C** via hydrogen-bonding interactions, thereby discriminating between the two faces of the enol. Directed by the hydrogen bonding interactions developing between the nitro and the quinolinol groups, the nitroolefin approaches the enol selectively from the α-face with the substituents of the two bond-forming carbons positioned in a staggered arrangement (**4**), leading to the formation of the intermediate compound **5**. In the second step where DBU is used as the base, the open transition state **6** should be operative to minimize the steric repulsion between the nitro and the alkyl groups, delivering **3rb** as the major product.
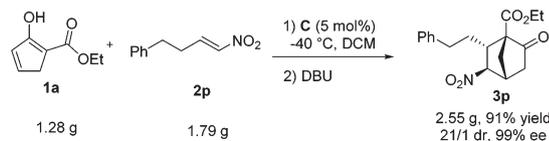
Eventually, to demonstrate the efficiency and synthetic utility of this newly developed formal [4 + 2] cycloaddition reaction, a gram-scale reaction was performed with **1a** and **2p**

Scheme 2 Proposed mechanism of the reaction.

Scheme 3 A gram-scale synthesis of **3p** via the formal [4 + 2] cyclo-addition reaction of **1a** and **2p**.

(Scheme 3). Thus, the reaction with 1.28 g of **1a** (1.0 equiv.) and 1.79 g of **2p** (1.2 equiv.) catalyzed by **C** (5 mol%) and DBU (0.5 equiv.) produced 2.55 gram of **3p** in a yield of 91% with >20/1 dr and 99% ee.

Conclusions

In summary, an organocatalytic formal [4 + 2] cycloaddition reaction has been realized that permits rapid access to a wide range of functionalized [2.2.1] bicyclic heptanes in a highly enantioselective manner from simple starting materials. The reaction features metal free, mild, and operationally simple conditions, providing synthetically useful bicyclo[2.2.1] heptane-1-carboxylates in good yields with excellent enantio-selectivity. Importantly, this method is amenable to large scale preparation, thus facilitating relevant drug discovery and pharmaceutical activities. Efforts aiming at the application of this newly developed method are pursued in our laboratory and will be reported in due course.

Acknowledgements

Notes and references

1 K. C. Nicolaou and T. Montagnon, *Molecules That Changed The World*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2008, p. 29.
2 H. Liang, *Beilstein J. Org. Chem.*, 2008, **4**, 31.
3 (*a*) T. Satou, Y. Ogawa and K. Koike, *Phytother. Res.*, 2015, **29**, 1246; (*b*) B. Lee, J. Bohmann, T. Reeves,

4 C. Levenson and A. L. Risinger, *J. Nat. Prod.*, 2015, **78**, 1357.
4 Y. Matsuo, H. Sakagami and Y. Mimaki, *Chem. Pharm. Bull.*, 2014, **62**, 1192.
5 R. M. Adibhatla, J. F. Hatcher and A. Gusain, *Neurochem. Res.*, 2012, **37**, 671.
6 A. Li, C. C. Yuan, D. Chow, M. Chen, M. G. Emery, C. Hale, X. Zhang, R. Subramanian, D. J. St. Jean, R. Komorowski, M. Véniant, M. Wang and C. Fotsch, *ACS Med. Chem. Lett.*, 2011, **2**, 824.
7 (*a*) W. Oppolzer, *Pure Appl. Chem.*, 1990, **62**, 1241; (*b*) W. Oppolzer, *Tetrahedron*, 1987, **43**, 1969; (*c*) B. H. Kim and D. P. Curran, *Tetrahedron*, 1993, **49**, 293.
8 T. Hayashi, K. Ueyama, N. Tokunaga and K. Yoshida, *J. Am. Chem. Soc.*, 2003, **125**, 11508.
9 K. Vandyck, B. Matthys, M. Willen, K. Robeyns, L. V. Meervelt and J. V. D. Eycken, *Org. Lett.*, 2006, **8**, 363.
10 (*a*) H. Sundén, R. Rios, Y. M. Xu, L. Eriksson and A. Córdova, *Adv. Synth. Catal.*, 2007, **349**, 2549; (*b*) X. Feng, Z. Zhou, R. Zhou, Q. Q. Zhou, L. Dong and Y. C. Chen, *J. Am. Chem. Soc.*, 2012, **134**, 19942; (*c*) R. Mose, M. E. Jensen, G. Preegel and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2015, **54**, 13630; (*d*) M. Hatano, Y. Goto, A. Izumiseki, M. Akakura and K. Ishihara, *J. Am. Chem. Soc.*, 2015, **137**, 13472; (*e*) M. Rueping, A. Kuenkel and R. Fröhlich, *Chem. – Eur. J.*, 2010, **16**, 4173; (*f*) B. Tan, Y. Lu, X. Zeng, P. J. Chua and G. Zhong, *Org. Lett.*, 2010, **12**, 2682; (*g*) M. Tsakos, M. R. J. Elsegood and C. G. Kokotos, *Chem. Commun.*, 2013, **49**, 2219.
11 A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713.
12 For selected examples of catalytic enantioselective conjugate addition reactions, see: (*a*) M. Bella and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2004, **126**, 5672; (*b*) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119; (*c*) H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906; (*d*) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman and L. Deng, *Angew. Chem., Int. Ed.*, 2005, **44**, 105; (*e*) Y. Chi, N. A. Kopf and S. H. Gellman, *J. Am. Chem. Soc.*, 2008, **130**, 5608.
13 Y.-Z. Li, J. Wang, W.-B. Sun, Y.-F. Shan, B.-F. Sun, G.-Q. Lin and J.-P. Zou, *Org. Chem. Front.*, 2015, **2**, 274 and references therein.
14 CCDC 1474474 (**3rb**) contains the supplementary crystallographic data for this paper.

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