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Direct Enantioselective Synthesis of Bicyclic Diels–Alder Products

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Dedicated to Prof. Jan-E. Bäckvall on the occasion of his 60th birthday.

Abstract: The direct amine-catalyzed enantioselective Diels–Alder reaction between α,β-unsaturated cyclic ketones and nitroolefins is presented. A simple diamine catalyzes the asymmetric Diels–Alder reaction with high stereoselectivity and furnishes the corresponding Diels–Alder adducts in good to high yields with >25:1 *dr* and up to 86% *ee*. The study demonstrates a convenient entry to functionalized bicyclic molecules contaning four stereocenters that are formed with excellent diastreoselectivity and good to high enantioselectivity.

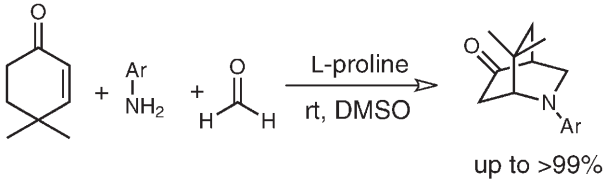
Keywords: asymmetric catalysis; Diels–Alder reaction; nitroolefins; organocatalysis; α,β-unsaturated cyclic ketones

Introduction

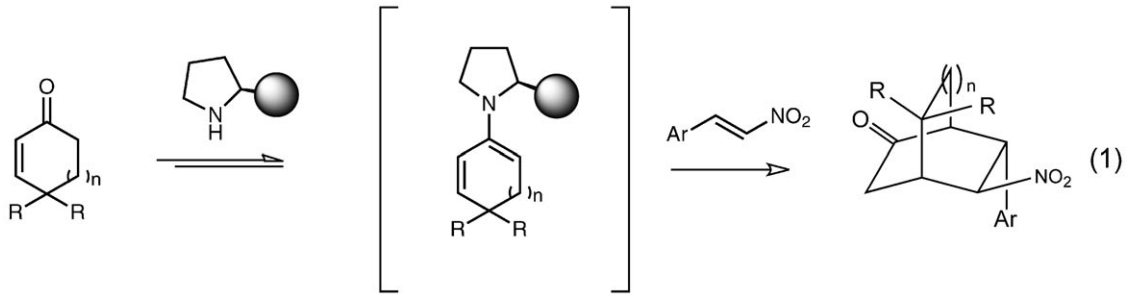
The Diels–Alder reaction is a fundamental carbon-carbon bond-forming reaction in organic synthesis. This cycloaddition protocol allows for the stereoselective construction of six-membered cyclic rings with up to four continuous stereocenters. Therefore, chemists have developed several catalytic asymmetric protocols for this important reaction.[1]

In recent years, an intense research effort has been made to find small chiral organic molecules as catalysts for enantioselective reactions.[2] In particular, amine catalysis has grown tremendously important within this research area. Amine catalysis relies on two fundamental mechanisms: enamine and iminium activation.[2] One of the first examples of this "new" generation of asymmetric synthesis was a Diels–Alder reaction published by MacMillan and co-workers in 2000.[3] In this reaction, a phenylalanine-derived imidazolium derivative catalyzes the enantioselective Diels–Alder reaction between α,β-unsaturated aldehydes and aliphatic dienes. The reactions proceed through an iminium activation pathway and the Diels–Alder products are isolated in high yields and *ee*s. Furthermore, Ishihara and co-workers have shown that primary chiral amine catalysts catalyze the Diels–Alder reaction between α-acyloxyacroleins and different dienes with high enantioselectivity.[4]

Asymmetric, organocatalytic methods for the generation of chiral dienes represent an attractive, but relatively undeveloped, alternative in the synthesis of enantioenriched cyclic systems.[5–7] In this context, Yamamoto and co-workers have developed an elegant organocatalytic, asymmetric pathway to the nitroso-Diels–Alder reaction.[6] Moreover, Barbas and co-workers published the first organocatalytic enamine-promoted Diels–Alder protocol between acyclic dienes and nitroolefins.[7] However, a moderate diastereoselectivity was achieved and only one example of modest asymmetric induction was reported. We recently found that proline and its derivatives catalyze one-pot three-component aza-Diels–Alder reactions between α,β-unsaturated cyclic ketones, anilines and formaldehyde that proceed *via* an asymmetric domino Mannich/aza-Michael pathway (Scheme 1).[5d] Based on this research and our interest in asymmetric cataly-



Scheme 1. The direct catalytic enantioselective aza-Diels–Alder reaction.

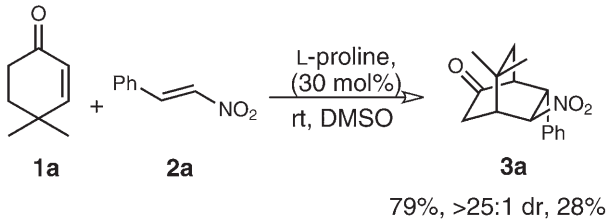


sis,[8] we became intrigued in whether chiral amines could catalyze the reaction between α,β-unsaturated cyclic ketones and nitroolefines *via in situ* generation of chiral enamines [Eq. (1)]. This potential reaction will be a highly challenging task since the formation of four new stereocenters has to be controlled.

Herein, we report the highly diastereoselective organocatalytic Diels–Alder reaction between α,β-unsaturated cyclic ketones and nitroolefins that gives the corresponding bicyclic adducts in high yields with >25:1 *dr* and up to 86% *ee*.

Results and Discussion

In an initial experiment, 4,4-dimethyl-2-cyclohexen-1-one (**1a**) and *trans*-β-nitrostyrene (**2a**) were mixed in the presence of a catalytic amount of L-proline (30 mol%). After 5 days of vigorous stirring, the desired Diels–Alder product **3a** was isolated in 79% yield with >25:1 *dr* and 28% *ee* (Scheme 2).

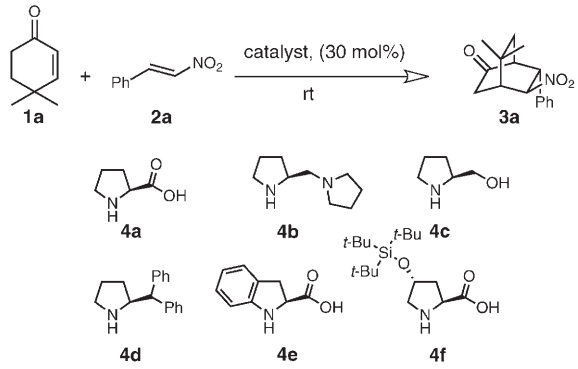


Scheme 2. The direct enatioselective synthesis of bicyclic Diels–Alder products.

Encouraged by this preliminary result, we decided to investigate different reaction conditions in order to optimize the reaction. An initial catalyst screen of the reaction between 4,4-dimethyl-2-cyclohexen-1-one (**1a**) and *trans*-β-nitrostyrene (**2a**) (Table 1), revealed that L-proline (30 mol%), the chiral amine (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (**4b**) and prolinol (**4c**) catalyzed the asymmetric formation of the corresponding bicyclic compound **3a**. The proline-catalyzed reaction was high-yielding whereas reactions mediated by the chiral amines **4b** and **4c** were not. For example, chiral amine **4b** catalyzed the assembly of Diels–Alder product **3a** in an asymmetric fashion with 4:1 *dr* and 78% *ee* but merely 15% yield (entry 2).

To our delight, in this case, the addition of a catalytic amount of 2,4-dinitrobenzenesulfonic acid (**5a**) significantly enhanced the rate of the reaction and the corresponding Diels–Alder product **3a** was isolated in 69% yield with >25:1 *dr* and 77% *ee* (entry 3). This is in accordance with previous chiral diamine **4b**-cata-

Table 1. Catalyst screen.[a]



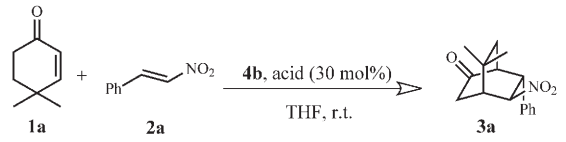
Entry	Catalyst	Time	Yield[b]	Dr[c]	Ee%[d]
1	**4a**	5 d	79	>25:1	28[e]
2	**4b**	8 d	15	4:1	78
3	**4b**	3 d	69	>25:1	77[f]
4	**4c**	9 d	15	9:1	76[f]
5	**4d**	5 d	N.R.[f]		
6	**4e**	10 d	N.R.[e]		
7	**4f**	5 d	N.R.		

[a] 4,4-Dimethyl-2-cyclohexen-1-one (60 μL, 0.45 mmol) was added to a stirred solution of catalyst (30 mol%) and *trans*-β-nitrostyrene (38 mg, 0.25 mmol) in THF (1 mL). The resulting reaction mixture was stirred for the time shown in the Table.
[b] Isolated yield of pure product **3a**.
[c] Determined by NMR analyses.
[d] Determined by chiral-phase HPLC analyses.
[e] Reaction performed in DMSO.
[f] Reaction performed with 30 mol% of 3,5-dinitrobenzene-sulfonic acid **5a**. (N.R. = no reaction).

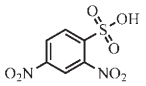
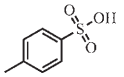
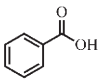
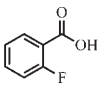
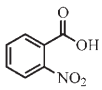
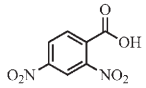
lyzed reactions involving nitroolefins where the addition of an organic acid additive improved the results.[5d,7,9] Chiral amines **4d–f** did not catalyze the formation of bicyclic product **3a** (entries 5–7). Only starting material was observed by NMR analysis. Thus, the presence of an acid additive in the reaction mixture seems to be crucial in order to obtain high yields. Next a series of different organic acids **5** was tested (Table 2). The screen revealed that chiral amine **4b** catalyzed the formation of bicyclic ketone **3a** with similar enantioselectivity 74–78% *ee* in the presence of the different acid additives **5**. Of the acids screened 2,4-dinitrobenzenesulfonic acid (**5a**) proved to be the most efficient.

Next, the solvent effect was investigated (Table 3).

Table 2. Selected examples of acid additive optimizations.[a]

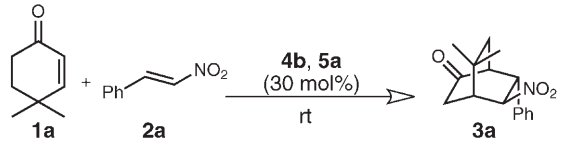


1a 2a 3a

Entry	Acid		Time	Yield[b]	d.r.[c]	ee%[d]
1		**5a**	3 d	69	>25:1	77
2		**5b**	3 d	15	>25:1	74
3		**5c**	3 d	18	>25:1	74
4		**5d**	3 d	34	25:1	78
5		**5e**	5 d	51	>25:1	78
6		**5f**	5 d	44	>25:1	78
7		**5g**	5 d	47	>25:1	74

[a] 4,4-Dimethyl-2-cyclohexen-1-one (60 μL, 0.45 mmol) was added to a stirred solution of catalyst **4b** (30 mol%), acid (30 mol%) and *trans*-β-nitrostyrene (38 mg, 0.25 mmol) in THF (1 mL). The resulting reaction mixture was stirred for the time shown in the Table.
[b] Isolated yield of pure product **3a**.
[c] Determined by NMR analyses.
[d] Determined by chiral-phase HPLC analyses.

Table 3. Solvent screen.[a]



1a 2a 3a

Entry	Solvent	time	Yield[b]	dr[c]	ee%[d]
1	THF	3 d	69	>25:1	77
2	1,4-Dioxane	4 d	40	>25:1	83
3	DMF	3 d	42	>25:1	80
4	$CHCl_3$	4 d	15	>25:1	66

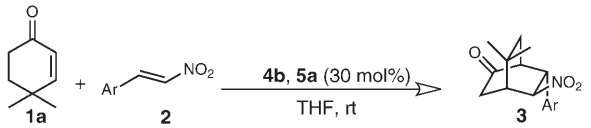
[a] 4,4-Dimethyl-2-cyclohexen-1-one (60 μL, 0.45 mmol) was added to a stirred solution of catalyst **4b** (30 mol%), acid **5a** (30 mol%) and *trans*-β-nitrostyrene (38 mg, 0.25 mmol)) in solvent (1 mL). The resulting reaction mixture was stirred for the time shown in the Table.
[b] Isolated yield of pure product **3a**.
[c] Determined by NMR analyses.
[d] Determined by chiral-phase HPLC analyses.

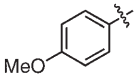
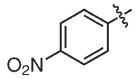
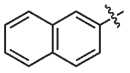
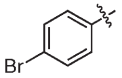
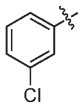
The screen revealed that diamine **4b** catalyzed the asymmetric formation of **3a** with excellent diastereoselectivity in all solvents investigated. The highest level of enantiomeric excess was obtained in dioxane or DMF and **3a** was assembled with 83 and 80% *ee*, respectively (Table 3, entries 2 and 3). However, the yield was significantly lower as compared to THF (entry 1). Consequently, we chose to probe the scope of the chiral diamine **4b**-catalyzed Diels–Alder reaction in THF (Table 4).

We found that the diamine **4b**-catalyzed reactions between cyclic ketone **1a** and nitrostyrenes **2** were highly diastereoselective and the corresponding products **3** were isolated in good to high yields with >25:1 *dr* and 65–86% *ee*. For example, product **3d** was isolated in 95% yield with >25:1 *dr* and 74% *ee* (entry 4). However, diamine **4b** failed to catalyze the formation of compound **3c**. Instead L-proline was used as catalyst and **3c** was obtained in 68% yield with >25:1 *dr* and 35% *ee* (entry 3). Moreover, the reaction with the aliphatic nitroolefin was sluggish and gave only traces of compound **3j** (entry 7). *ortho*- and *para*-substituted nitrostyrenes were also excellent substrates and the corresponding Diels–Alder products **3k** and **3l** were isolated in high yields and stereocontrol (>25:1 *dr* and 68–80% *ee*). Next, the enantioselective amine-catalyzed Diels–Alder reaction using a set of different α,β-unsaturated cyclic ketones **1** was investigated (Table 5).

We found that the chiral amine **4b**-catalyzed Diels–Alder reactions with α,β-unsaturated cyclohexenones **1** and cycloheptenone **1c** gave the corresponding

Table 4. The direct amine-catalyzed enantioselective Diels–Alder reaction between 4,4-dimethyl-2-cyclohexen-1-one and nitroolefins.

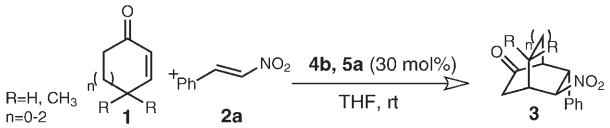


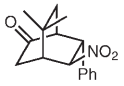
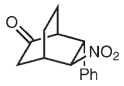
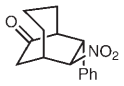
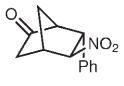
Entry	Ar		Time	Yield[b]	dr[c]	ee%[d]
1		**3a**	3 d	69	>25:1	77
			7 d	93	>25:1	78
2		**3b**	11 d	53	>25:1	65
			6 d	57	>25:1	75[e]
3		**3c**	7 d	68	>25:1	35[f]
4		**3d**	10 d	95	>25:1	74
5		**3e**	7 d	66	>25:1	86
6		**3i**	7 d	92	>25:1	77
7	Et	**3j**	3 d	trace	n.d.	n.d.
8		**3k**	3 d	76	>25:1	68
9		**3l**	3 d	66	>25:1	80

[a] 4,4-Dimethyl-2-cyclohexen-1-one (60 μL, 0.45 mmol) was added to a stirred solution of catalyst **4b** (30 mol%), acid **5a** (30 mol%) and nitroolefin (0.25 mmol) in THF (1 mL). The resulting reaction mixture was stirred for the time shown in the Table.
[b] Isolated yield of pure product.
[c] Determined by NMR analyses.
[d] Determined by chiral-phase HPLC analyses.
[e] 15% of acid **5a** was used.
[f] L-Proline (30 mol%) was used as the catalyst. N.d. = not determined.

products **3** in good yields with high *dr* >25:1 and high *ee*s. For example, the reaction between cycloheptenone **1c** and **2a** gave the corresponding bicyclic product **3g** in 80% yield with >25:1 *dr* and 71% *ee* (entry 4). In the case of enones **1b** and **1d**, the addition of dinitrobenzoic acid **5g** (30 mol%) gave the best results (entries 3 and 5). Cyclopentenone **1c** could also be used as a substrate for chiral amine **4b** catalysis and the corresponding product **3h** was

Table 5. The direct amine-catalyzed enantioselective Diels–Alder reaction between α,β-unsaturated cyclic ketones and nitroolefins.



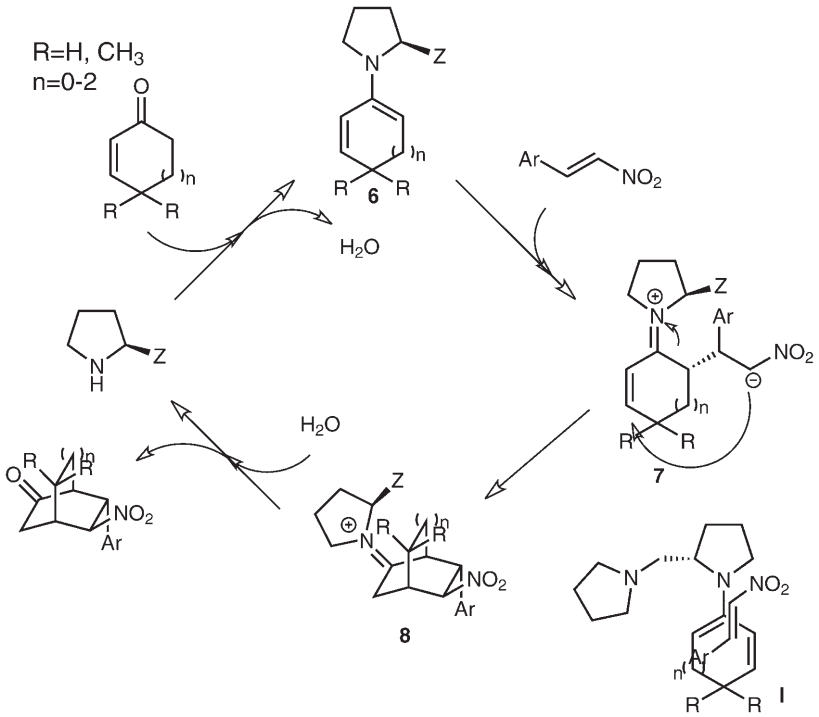
Entry	Product		Time	Yield[b]	dr[c]	ee%[d]
1		**3a**	3 d	69	>25:1	77
2		**3a**	7 d	93	>25:1	78
3		**3f**	4 d	61	>25:1	67[e]
4		**3g**	12 d	80	>25:1	71
5		**3h**	6 d	66	>25:1	32[e]

[a] To a stirred solution of catalyst **4b** (30 mol%), acid **5a** (30 mol%) and nitrostyrene (38 mg, 0.25 mmol) in THF (1 mL), was added α,β-unsaturated ketone (0.45 mmol). The resulting reaction mixture was stirred for the time shown in the Table.
[b] Isolated yield of pure product.
[c] Determined by NMR analyses.
[d] Determined by chiral-phase HPLC analyses.
[e] Reaction performed with 2,4-dinitrobenzoic acid **5g** (30 mol%) as the additive.

formed in high yields and excellent diastereoselectivity but modest enantioselectivity (entry 5).

Mechanism

The stereochemical outcome of the reaction was determined by X-ray structure analysis of **3i** (Figure 1).[10] The X-ray structure analysis revealed that compound **3i** had the absolute stereochemistry (1*S*, 4*R*, 7*S*, 8*S*). Based on the absolute stereochemistry of **3i** and previous experience with reactions involving chiral amine-derived dienes,[5d,6,7] the following stepwise domino double Michael reaction mechanism was proposed to account for the stereochemical outcome of the reaction (Scheme 3). Thus, the diamine catalyst **4b** forms a chiral enamine intermediate **6** with the α,β-unsaturated ketone **1**. Next, the nitroolefin adds to the *Re*-face of the chiral diene *via* transition state **I** to form the activated iminium species **7**, the anion of which performs a subsequent intramolecular *6-endo-trig* cyclization to furnish the corresponding Diels–Alder-bicyclic compound **8**. Hydrolysis by



Scheme 3. Proposed catalytic cycle and transition state for the amine-catalyzed Diels–Alder reaction.

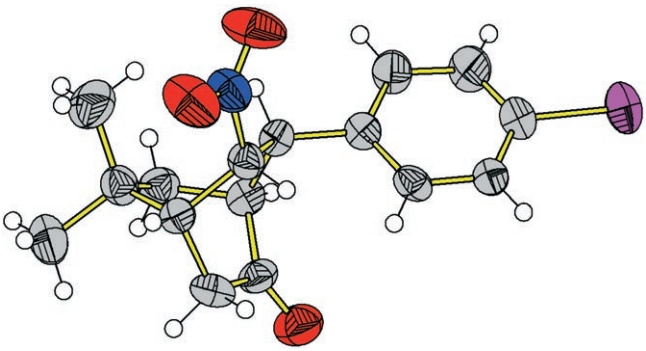


Figure 1. X-ray structure of Diels–Alder product **3i** (ORTEP picture).

water forms the corresponding bicyclic product **3** and releases the catalyst.

Conclusions

An asymmetric enantioselective protocol for the formation of bicyclic Diels–Alder products has been developed. The catalytic procedure furnishes bicyclic compounds with four stereocenters that are formed in high yields with excellent diasteroselectivity and good to high enantioselectivity. Moreover, this one-pot procedure gives access to highly functionalized bicyclic molecules with different useful functionalities for synthetic manipulations. Further elaboration of this novel transformation, its synthetic application and mechanistic studies are ongoing in our laboratory.

Experimental Section

Typical Experimental Procedure for the Preparation of the Diels–Alder Bicyclic Products

To a stirred solution of catalyst **4b** (13 μL, 0.075 mmol), acid **5a** (20 mg, 0.075 mmol) and nitrostyrene (38 mg, 0.25 mmol) in THF (1 mL), was added 4,4-dimethyl-2-cyclohexen-1-one (60 μL, 0.45 mmol). The reaction mixture was stirred at room temperature until complete conversion was established by NMR monitoring. The reaction mixture was filtered through a plug of silica and the volatiles were evaporated under reduced pressure to furnish the desired pure bicyclic Diels–Alder products.

5,5-Dimethyl-8-nitro-7-phenylbicyclo[2.2.2]octan-2-one (3a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (s, 3H), 1.13 (s, 3H), 1.75 (dd, $J = 14.2$, 2.6 Hz, 1H), 2.01 (dd, $J = 14.2$, 3.3 Hz, 1H), 2.35 (dd, $J = 19.7$, 2.9 Hz, 1H), 2.61 (q, $J = 2.6$ Hz, 1H), 2.86 (dd, $J = 19.7$, 3.4 Hz, 1H), 2.97 (q, $J = 2.8$ Hz, 1H), 4.58 (dd, $J = 2.0$, 1.0 Hz, 1H), 4.60 (dd, 2.0, 1.0 Hz, 1H), 6.17 (m, 1H), 7.26–7.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.5$, 30.6, 30.9, 40.3, 40.9, 43.2, 44.3, 51.0, 90.1, 127.2, 127.6, 129.1, 141.2, 211.9; HR-MS (ESI): $m/z = 296.1269$, calcd. for $[M+Na]^+$ ($C_{16}H_{19}NNaO_3$): 296.1257; $[\alpha]_D^{25}$: −57.3 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an AD column (*i*-hexane:*i*-PrOH = 98:2, $\lambda = 254$ nm, 1 mL min^{-1}): t_R major enantiomer = 19.2 min, minor enantiomer = 22.6 min.

7-(4-Methoxyphenyl)-5,5-dimethyl-8-nitrobicyclo-[2.2.2]octan-2-one (3b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (s, 3H), 1.12 (s, 3H), 1.73 (dd, J = 14.3, 2.6 Hz, 1H), 1.99 (dd, J = 14.2, 3.5 Hz, 1H), 2.33 (dd, J = 19.5, 2.7 Hz, 1H), 2.58 (q, J = 2.6 Hz, 1H), 2.84 (dd, J = 19.7, 3.1 Hz, 1H), 3.00 (q, J = 2.7 Hz, 1H), 3.77 (s, 1H), 4.16 (dd, J = 8.0, 1.4 Hz, 1H), 4.53 (dd, 8.0, 1.1 Hz, 1H), 6.83 (d, 8.8, 2H), 7.08 (dd, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4, 30.6, 30.9, 40.3, 40.9, 42.4, 44.3, 51.2, 55.3, 90.4, 114.4, 128.2, 133.4, 158.9, 212.1; HR-MS (ESI): m/z = 326.1347, calcd. for $[M+Na]^+$ ($C_{17}H_{21}N_1NaO_4$): 326.1363; $[\alpha]_D^{25}$: −64.3 (c 1.2, $CHCl_3$). The enantiomeric excess was determined by HPLC with an ODH column (i-hexane:i-PrOH = 90:10, λ = 254 nm, 1 mL min^{-1}): t_R minor enantiomer = 39.9 min, major enantiomer = 43.7 min.

5,5-Dimethyl-8-nitro-7-(4-nitrophenyl)-bicyclo-[2.2.2]octan-2-one (3c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 4.54–4.50 (m, 1H), 4.34–4.31 (m, 1H), 3.03–3.00 (m, 1H), 2.94–2.85 (m, 1H), 2.63–2.60 (m, 1H), 2.40–2.34 (m, 1H), 2.06–2.00 (m, 1H), 1.81–1.75 (m, 1H), 1.16 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.0, 148.2, 147.4, 128.3, 124.2, 89.3, 50.4, 44.0, 43.1, 40.8, 39.9, 30.7, 30.6, 29.5. 126.8, 91.2, 47.5, 45.0, 42.3, 34.4, 23.4, 18.2; HR-MS (ESI): m/z = 319.1293, calcd. for $[M+Na]^+$ ($C_{16}H_{19}N_2O_5$): 319.1288; $[\alpha]_D^{25}$: −3.6 (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with i-hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL min^{-1}; t_R minor isomer = 72.4 min, major isomer = 67.1 min.

5,5-Dimethyl-7-(naphthalen-2-yl)-8-nitrobicyclo-[2.2.2]octan-2-one (3d): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 6H), 1.79 (dd, J = 14.3, 2.7 Hz, 1H), 2.07 (dd, J = 13.9, 3.1 Hz, 1H), 2.44 (d, J = 2.5 Hz, 1H), 2.72 (q, J = 2.6 Hz, 1H), 2.90 (dd, J = 20.0, 2.9 Hz, 1H), 3.02 (q, J = 2.7 Hz, 1H), 4.40 (dd, J = 8.0, 1.6 Hz, 1H), 4.70 (dq, 1.0, 0.7 Hz, 1H), 7.27 (m, 2H), 7.47 (m, 2H), 7.65 (d, J = 1.8, 1H) , 7.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.5, 30.7, 30.9, 40.4, 41.0, 43.3, 44.4, 51.1, 90.0, 125.0, 126.1, 126.3, 126.5, 127.6, 129.1, 129.1, 132.6, 133.4, 138.5, 211.9; HR-MS (ESI): m/z = 346.1425, calcd. for $[M+Na]^+$ ($C_{20}H_{21}NNaO_3$): 346.1414; $[\alpha]_D^{25}$: −59.7 (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an AD column (i-hexane:i-PrOH = 95:5, λ = 254 nm, 0.5 mL min^{-1}): t_R major enantiomer = 20.7 min, minor enantiomer = 24.6 min.

7-Furan-2-yl-5,5-dimethyl-8-nitrobicyclo[2.2.2]octan-2-one (3e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 3H), 1.10 (s, 3H), 1.74 (dd, J = 14.3, 2.9 Hz, 1H), 1.94 (dd, J = 14.3, 3.3 Hz, 1H), 2.29 (dd, J = 19.5, 2.7 Hz, 1H), 2.68 (q, J = 2.7 Hz, 1H), 2.77 (dd, J = 19.6, 3.4 Hz, 1H), 3.0 (q, J = 2.8 Hz, 1H), 4.34 (dd, J = 7.2, 1.9 Hz, 1H), 4.67 (ddd, 7.2, 2.2, 0.7 Hz, 1H), 6.16 (d, 3.3, 1H), 6.27 (dd, J = 3.3, 1.9 Hz, 1H), 7.29 (dd, J = 1.8, 0.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.3, 30.4, 30.8, 37.0, 40.4, 44.2, 49.0, 87.0, 106.5, 110.4, 142.6, 153.1, 210.6; HR-MS (ESI): m/z = 286.1061, calcd. for $[M+Na]^+$ ($C_{14}H_{17}NNaO_4$): 286.1050; $[\alpha]_D^{25}$: −14.5 (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an AD column (i-hexane:i-PrOH = 95:5, λ = 254 nm, 0.5 mL min^{-1}): t_R major enantiomer = 24.3 min, minor enantiomer = 31.7 min.

5-Nitro-6-phenylbicyclo[2.2.2]octan-2-one (3f): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 3H), 7.10–7.05 (m, 2H), 4.84–4.80 (m, 1H), 4.17–4.13 (m, 1H), 2.98–2.92 (m, 1H), 2.70–2.67 (m, 1H), 2.54–2.50 (m, 2H), 2.30, 2.20 (m, 1H), 2.04–1.86 (m, 2H), 1.76–1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.8, 141.1, 129.2, 127.7, 126.8, 91.2, 47.5, 45.0, 42.3, 34.4, 23.4, 18.2; HR-MS (ESI): m/z = 268.0941, calcd. for $[M+Na]^+$($C_{14}H_{15}NO_3Na$): 268.0944; $[\alpha]_D^{25}$: −13.2 (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with i-hexane/i-PrOH (95:5) as the eluent. Flow: 0.5 mL min^{-1}; t_R minor isomer = 64.9 min; major isomer = 50.1 min.

8-Nitro-9-phenylbicyclo[3.2.2]nonan-6-one (3g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (m, 1H), 1.79–2.05 (m, 5H), 2.62 (d, J = 8.7 Hz, 2H), 2.83 (t, J = 4.5 Hz, 1H), 3.14 (m, 1H), 4.29 (d, J = 7.3 Hz, 1H), 4.74 (dd, J = 7.4, 4.2 Hz, 1H), 7.07 (d, 8.4, 2H), 7.22–7.31 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 26.6, 32.7, 35.0, 42.1, 46.5, 53.5, 92.4, 126.7, 127.5, 129.3, 143.5, 211.2; HR-MS (ESI): m/z = 282.1104, calcd. for $[M+Na]^+$ ($C_{15}H_{17}NNaO_3$): 282.1101; $[\alpha]_D^{25}$: −25.5 (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an AD column (i-hexane:i-PrOH = 94:6, λ = 210 nm, 0.5 mL min^{-1}); t_R minor enantiomer = 24.8 min, major enantiomer = 31.2 min.

6-Nitro-5-phenylbicyclo[2.2.1]heptan-2-one (3h): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.18 (m, 5H), 5.16–5.11 (m, 1H), 3.95–3.90 (m, 1H), 3.48–3.44 (m, 1H), 2.99 (s, 1H), 2.30–2.22 (m, 2H), 2.06–1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.6, 139.3, 129.3, 127.7, 126.7, 92.6, 55.5, 44.9, 41.8, 38.9, 35.4; HR-MS (ESI): m/z = 254.0786, calcd. for $[M+Na]^+$ ($C_{13}H_{13}NO_3Na$): 254.0788; $[\alpha]_D^{25}$: −2.4 (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD-H with i-hexane/i-PrOH (95:5) as the eluent, flow: 0.5 mL min^{-1}; t_R minor isomer = 52.2 min; major isomer = 65.6 min.

7-(4-Bromophenyl)-5,5-dimethyl-8-nitrobicyclo-[2.2.2]octan-2-one (3i): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 3H), 1.13 (s, 3H), 1.74 (dd, J = 14.3, 2.7 Hz, 1H),1.99 (dd, J = 14.3, 3.5 Hz, 1H), 2.32 (dd, J = 19.9, 3.0 Hz, 1H), 2.85 (dd, J = 19.8, 3.2 Hz, 1H), 2.96 (q, J = 2.8 Hz, 1H), 4.18 (dd, J = 8.1, 1.5 Hz, 1H), 4.49 (ddd, 8.1, 2.1, 1.0 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4, 30.6, 30.8, 40.1, 41.0, 42.7, 44.2, 51.0, 89.9, 121.7, 128.9, 132.2, 140.2, 211.6; HR-MS (ESI): m/z = 374.0373, calcd. for $[M+Na]^+$ ($C_{16}H_{19}NBrNaO_3$): 374.0362; $[\alpha]_D^{25}$: −57.3 (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an AD column (i-hexane:i-PrOH = 98:2, λ = 254 nm, 1 mL min^{-1}); t_R major enantiomer = 28.5 min, minor enantiomer = 47.3 min.

6-(2-Bromophenyl)-8,8-dimethyl-5-nitrobicyclo-[2.2.2]octan-2-one (3k): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (s, 3H), 1.25 (s, 3H), 1.72 (dd, J = 14.4, 2.4 Hz, 1H), 2.07 (dd, J = 14.4, 3.6 Hz, 1H), 2.37 (dd, J = 19.6, 2.8 Hz, 1H), 2.43 (q, J = 1.6 Hz, 1H), 2.85 (dd, J = 19.6, 2.8 Hz, 1H), 3.06 (q, J = 2.4 Hz, 1H), 4.75 (d, J = 8.0 Hz, 1H), 4.85 (dd, J = 8.0, 1.6 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.24–7.27 (m, 1H), 7.63 (d J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6, 30.6, 30.8, 39.4, 40.6, 42.0, 44.0, 50.9, 87.2, 125.3, 126.4, 128.0, 129.1, 133.8, 138.9, 210.6; HR-MS (ESI): m/z = 374.0366, calcd. for $[M+Na]^+$ ($C_{16}H_{18}BrNNaO_3$): 374.0362; $[\alpha]_D^{25}$: −44.2 (c 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an AD column (i-hexane:i-PrOH = 93:7, λ = 230 nm, 1 mL min^{-1}); t_R minor enantiomer = 11.2 min, major enantiomer = 15.9 min.

6-(3-Chlorophenyl)-8,8-dimethyl-5-nitrobicyclo-[2.2.2]octan-2-one (3l): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.11 (s, 3H), 1.13 (s, 3H), 1.76 (dd, $J = 14.4$, 2.4 Hz, 1H), 1.99 (dd, $J = 14.4$, 3.2 Hz, 1H), 2.35 (dd, $J = 19.6$, 2.4 Hz, 1H), 2.59 (m, 1H), 2.86 (dd, $J = 19.6$, 3.2 Hz, 1H), 2.97 (q, $J = 2.4$ Hz, 1H), 4.18 (d, $J = 8.4$ Hz, 1H), 4.54 (d, $J = 8.0$, 1H), 7.00–7.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 29.4, 30.6, 30.8, 40.1, 40.8, 42.9, 44.2, 50.7, 89.6, 125.1, 127.7, 127.9, 130.4, 134.9, 143.1, 211.4; HR-MS (ESI): $m/z =$ 330.0872, calcd. for $[M+Na]^+$ ($C_{16}H_{18}ClNNaO_3$): 330.0867; $[\alpha]_D^{25}$: −31.2 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC with an AD column (*i*-hexane:*i*-PrOH = 95:5, $\lambda = 230$ nm, 1 mL min^{-1}); t_R minor enantiomer = 12.5 min, major enantiomer = 13.9 min.

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[10] CCDC 642488 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

