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Enantioselective Organocatalytic Michael Addition of Cyclobutanones to Nitroalkenes

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Abstract: Synthetic applications of cyclobutanones other than ring expansion and fragmentation reactions are rare. Herein, highly efficient diastereo- and enantioselective organocatalytic Michael additions of 2-substituted cyclobutanone derivatives to nitroalkenes are reported allowing the stereocontrolled creation of 'all-carbon' quaternary centers. The approach relies on both the use of Brønsted base/hydrogen-bond donor bifunctional organocatalysts, and importantly, the specific stabilization and activation of cyclobutanone with a secondary amide moiety. The reaction was found to nicely accommodate a broad scope of substrates, allowing the control of up to three contiguous stereogenic centers. This work has opened new synthetic opportunities.

Keywords: asymmetric catalysis; C–C bond formation; Michael addition; organic catalysis; strained molecules

Introduction

The bending found in small-ring molecules and particularly cyclobutane derivatives has for long attracted the interest of chemists due to their occurrence in natural products (Figure 1[1]),[2] together with the theoretical aspects associated with the unusual bond angles and the ring strain in these compounds.[3] Of particular interest is cyclobutanone, the smallest stable saturated cyclic ketone, cyclopropanone being an unstable compound. When compared to larger ring ketones, cyclobutanone exhibits a relatively high strain energy, which results in a significantly enhanced carbonyl electrophilicity (comparable to that of an aldehyde) and a higher acidity of its enolizable protons (Figure 2).[4] Because of these constitutive features, synthetic applications of cyclobutanone derivatives have so far essentially concentrated on thermodynamically favored fragmentation and ring expansion reactions, other reaction types being far less studied.[3,5] However, with the advent of organocatalysis,[6] new opportunities have emerged in the past decade, and a limited number of methodologies have now been made available for the non-destructive functionalization of cyclobutanone derivatives in the optically active series (essentially aldol-type reactions), but rarely combining good reactivity with high levels of selectivity.[7] Despite the recent progresses made in this area, the construction of chiral all-carbon quaternary centers[8] from cyclobutanone derivatives remains an unsolved, but highly desirable (see Figure 1), synthetic issue.

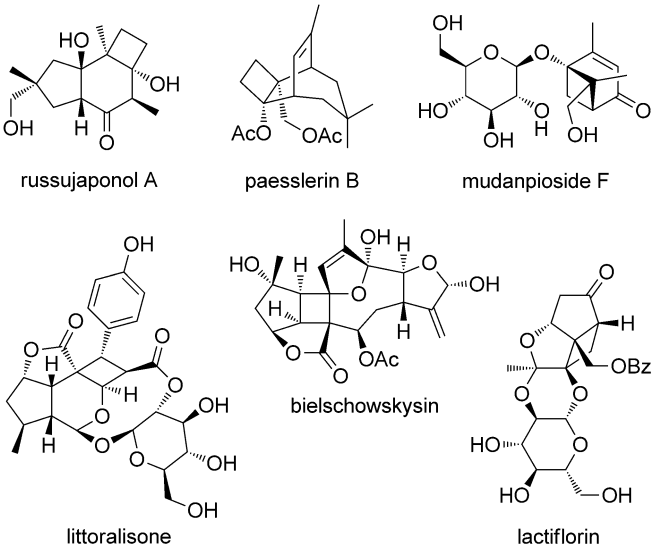


Figure 1. Selected examples of cyclobutane-containing natural products.[1]

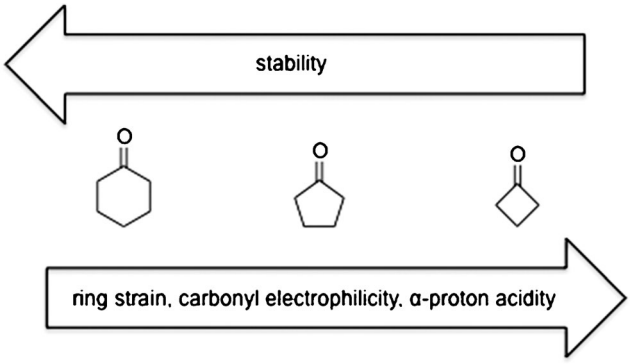
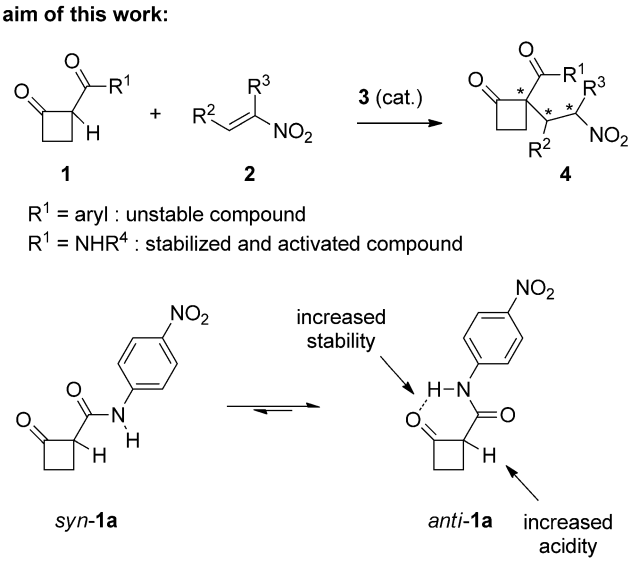


Figure 2. Reactivity scale of cyclic ketones.

It was anticipated that a regio- and stereoselective Michael addition of 2-substituted cyclobutanones would be an appropriate transformation for such a synthetic endeavor. Indeed, the Michael addition is one of the most important and useful reactions for the creation of carbon–carbon bonds, and a number of organocatalytic enantioselective Michael additions of carbonyl compounds to reactive electron-deficient olefins have been described.[6] Among these, regio- and stereoselective asymmetric Michael additions of 1,3-dicarbonyl compounds to nitroolefins have been studied, essentially from acyclic, and to a lesser extent, five- and six-membered cyclic, β-keto esters and 1,3-diketones.[9]

Based on these precedents, we surmised that such Michael additions would also be possible in the cyclobutanone series, providing that soft organocatalytic regioselective enolization conditions are compatible with the intrinsic instability of 1,3-dicarbonyl cyclobutanones (Scheme 1). In other words, the realization of this idea requires a subtle balance between the reactivity and the stability of the activated cyclobutanones. For example, as a serious obstacle to our plan, 2-acylcyclobutanones exhibit a very electrophilic ketone group and were found to be somewhat unstable in air,[10] precluding their use for our objective, and more generally hampering their applications. Based on recent work from our laboratory, it was proposed that the rationally designed secondary β-keto amide **1a** would provide a good starting point.[11] Indeed, this cyclobutanone derivative is stabilized in its *anti* conformation by an intramolecular hydrogen bond between the acidic N–H proton and the ketone carbonyl group (Scheme 1).[12] The electron-withdrawing 4-nitrophenyl amide substituent increases the acidic character of the N–H proton, thereby enhancing the strength of the stabilizing hydrogen bond. As a result, **1a** and its analogues are stable compounds. Another beneficial consequence of the intramolecular hydrogen bond found in secondary β-keto amides is the significantly increased acidity of the α-proton when compared to tertiary β-keto amides (*ca.* $pK_{a(DMSO)} = 18–21$ for tertiary β-keto amides). This facilitated formation of the corresponding enolates is expected to translate into an increased pronucleophilic character of secondary β-keto amides. It should be noted here that, because of their higher pK_a values and thus lower reactivity when compared to other 1,3-dicarbonyl compounds (*ca.* $pK_{a(DMSO)} = 13–18$), β-keto amides have rarely been used as pronucleophiles in organocatalytic transformations.[11] Stabilizing intramolecular hydrogen bonds are also expected to exist in the enolates derived from the cyclobutanone **1a** and its analogues, which should result in a rigidification of these reactive forms and thus, should induce high stereoselection.



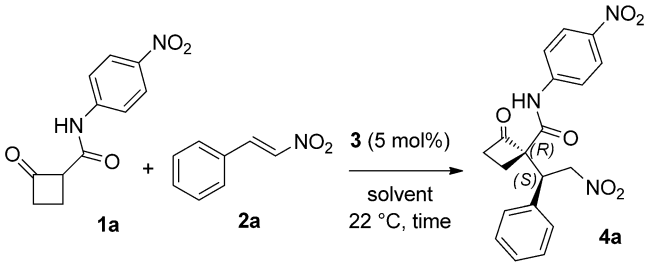
Scheme 1. Aim of this work, and conformations of secondary β-keto amides.

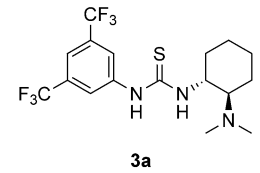
In this article, we report the first highly efficient and stereoselective Michael addition reactions of 2-substituted cyclobutanones **1** to substituted nitroalkenes **2** for the preparation of a new class of densely functionalized cyclobutanones **4** containing an all-carbon quaternary center adjacent to another stereogenic center.

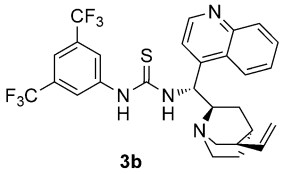
Results and Discussion

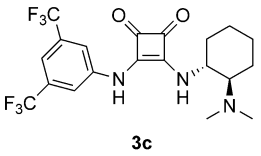
As a test ground for our hypothesis,[13] the Michael addition of cyclobutanone **1a** to *trans*-β-nitrostyrene (**2a**) was first attempted with the bifunctional organocatalyst **3a** introduced by Takemoto[9e] (Table 1, entry 1). Rewardingly, the adduct **4a** could be obtained in acceptable yield as a mixture of diastereomers ($dr = 1.7:1$), and interestingly, the major diastereomer was obtained with an excellent enantioselectivity ($er = 199:1$[14]). The practicability of the transformation being established, we looked for a more pro-

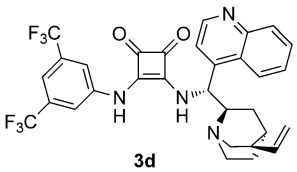
Table 1. Optimization of the catalytic system.

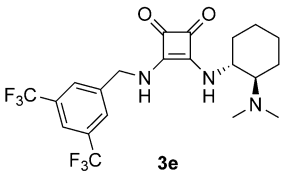


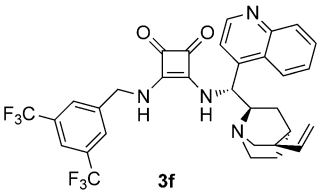












Entry	3	Solvent, time	Yield[a]	*dr*[b]	*er*[c]
1	**3a**	CH_2Cl_2, 7 h	71%	1.7:1	199:1
2	**3b**	CH_2Cl_2, 1 h	88%	4:1	>200:1
3	**3c**	CH_2Cl_2, 2 h	74%	2.2:1	2.9:1
4	**3d**	CH_2Cl_2, 6 h	76%	6:1	15:1
5	**3e**	CH_2Cl_2, 30 min	80%	13:1	11:1
6	**3f**	CH_2Cl_2, 20 min	95%	17:1	>200:1[e]
7[d]	**3a**	toluene, 7 h	71%	2.2:1	>200:1
8	**3f**	toluene, 24 h	62%	16:1	>200:1[e]
9	**3f**	$CHCl_3$, 30 min	94%	17:1	>200:1[e]
10	**3f**	$(ClCH_2)_2$, 2 h	93%	15:1	>200:1[e]
11	**3f**	AcOEt, 24 h	94%	11:1	>200:1[e]
12	**3f**	THF, 6 h	95%	13:1	>200:1[e]

[a] Isolated pure product obtained after chromatographic purification.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Determined by HPLC on a chiral stationary phase for the major diastereomer.
[d] Reaction performed with 10 mol% of **3a**.
[e] The minor enantiomer *ent*-**4a** was not detected.

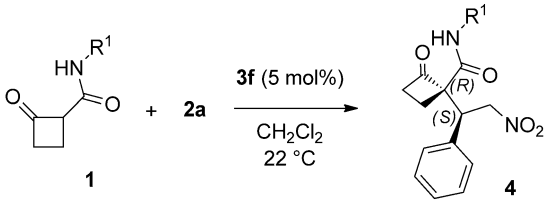
ductive and diastereoselective catalyst fitting with high standards. With catalyst **3b**,[15a] in which a 9-amino-9-*epi*-cinchonine unit replaces the diaminocyclohexyl moiety, the reaction proved to be faster and more efficient with improved although still not satisfactory diastereoselectivity, while keeping the excellent level of enantioselectivity for the major diastereomer (entry 2).

A few years ago, Rawal and co-workers have introduced squaramides as excellent hydrogen-bond donor moieties for applications in bifunctional organocatalysis,[9j,15b] and logically, a series of squaramide-containing organocatalysts **3c–f** was tested in the model Michael addition of the secondary β-keto amide **1a** to *trans*-β-nitrostyrene (**2a**). Catalysts **3c** and **3d**[15b,c] bearing *N*-arylsquaramide moieties were moderately productive and poorly selective in the studied transformation (entries 3 and 4). However, with the new *N*-benzylsquaramide catalyst **3e**, a net increase in the diastereoselectivity was observed, but accompanied by a significant decrease in the enantioselectivity when compared to the thiourea-containing catalysts **3a** and **3b** (entry 5). Finally, the best result could be obtained with catalyst **3f**[9j] combining a 9-amino-9-*epi*-cinchonine moiety with a *N*-benzylsquaramide hydrogen-bond donor unit, and the Michael adduct **4a** could be obtained with satisfying excellent yield, diastereo- and enantioselectivity (entry 6). From this screening of bifunctional catalysts **3a–f**, and within the limits of the studied transformation, it appears that the 9-amino-9-*epi*-cinchonine basic unit moiety is in every case superior to the diaminocyclohexyl moiety. Also, a subtle tuning of the hydrogen bonding and possible π-π interaction properties of the catalyst proved important to reach excellent yield and stereoselectivities.[16]

A screening of aprotic organic solvents with catalysts **3a** and **3f** (Table 1, entries 7–12) showed that the reaction is not much sensitive to the nature of the solvent, and confirmed that dichloromethane was optimum in terms of reaction time and stereoselectivities at room temperature. Interestingly, it revealed that the reaction can also be performed efficiently in a low toxicity solvent such as ethyl acetate albeit requiring 24 h for full conversion (entry 11).

With the optimum conditions in hand, the scope of the reaction was investigated. First, a series of secondary 2-carbamoyl cyclobutanone pronucleophiles **1**[17] was screened to evaluate the influence of the R^1 group (Table 2), including electron-demanding (entries 1 and 2), -neutral (entry 3), and electron-donating (entries 4 and 5) aryl, as well as bulky alkyl (entry 6) substituents. In all cases, the corresponding Michael adducts **4a–f** were obtained efficiently with good to excellent diastereoselectivities and enantioselectivities. Reaction times were however found to be significantly influenced by the nature of the R^1 substituent, electron-withdrawing groups allowing fast reactions (entries 1 and 2) while prolonged reaction times were required with electron-donating groups (entries 4–6). The superior reactivity of the secondary

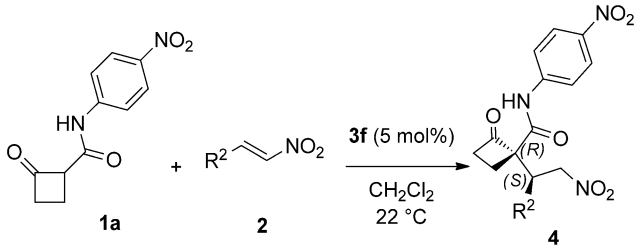
Table 2. Screening of 2-carbamoyl cyclobutanone pronucleophiles **1**.



Entry	**1**, time; R^1	**4**	Yield[a]	*dr*[b]	*er*[c]
1	**1a**, 0.3 h; 4-$(O_2N)C_6H_4$	**4a**	95%	17:1	>200:1[d]
2	**1b**, 0.5 h; 3,5-$(F_3C)_2C_6H_3$	**4b**	73%	15:1	35:1
3[e]	**1c**, 4 h; C_6H_5	**4c**	94%	14:1	20:1
4	**1d**, 4 h; 4-$(CH_3O)C_6H_4$	**4d**	82%	8:1	30:1
5	**1e**, 16 h; 4-BrC_6H_4	**4e**	84%	16:1	44:1
6	**1f**, 16 h; $C(CH_3)_3$	**4f**	85%	12:1	24:1

[a] Isolated pure product obtained after chromatographic purification.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Determined by HPLC on a chiral stationary phase for the major diastereomer.
[d] The minor enantiomer *ent*-**4a** was not detected.
[e] Reaction performed with 2.5 mol% of catalyst **3f**.

Table 3. Screening of nitroalkenes **2**.



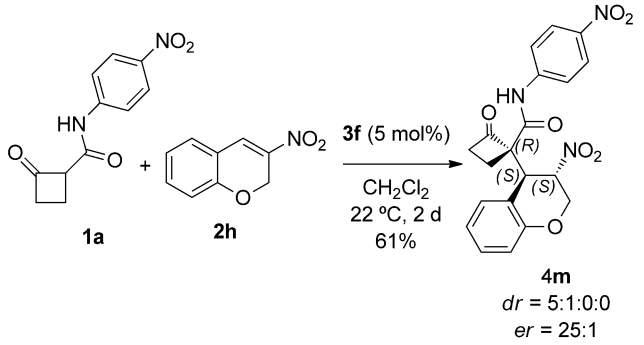
Entry	**2**, time; R^2	**4**	Yield[a]	*dr*[b]	*er*[c]
1	**2b**, 0.5 h; 4-$(O_2N)C_6H_4$	**4g**	62%	10:1	90:1
2	**2c**, 0.5 h; 4-$(CH_3O)C_6H_4$	**4h**	74%	15:1	>200:1[d]
3	**2d**, 7 d; 4-BrC_6H_4	**4i**	74%	17:1	>200:1
4	**2e**, 2 d; 3-furyl	**4j**	54%	15:1	35:1
5	**2f**, 2 d; 2-thienyl	**4k**	51%	13:1	90:1
6	**2g**, 24 h; $CH_2CH_2C_6H_5$	**4l**	36%	17:1	129:1

[a] Isolated pure product obtained after chromatographic purification.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Determined by HPLC on a chiral stationary phase for the major diastereomer.
[d] The minor enantiomer *ent*-**4h** was not detected.

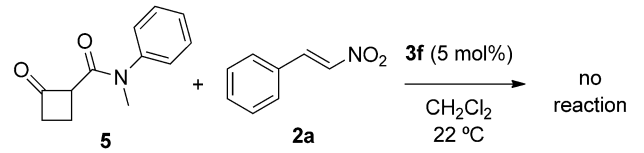
β-keto amides **1a** and **1b** exhibiting the more acidic amide protons (N−H) of the series reflects the better stabilization of their reactive enolate forms through intramolecular hydrogen-bonding interactions.

The reaction of β-keto amide **1a** with a variety of β-substituted nitroolefins **2** was then examined (Table 3). Excellent diastereo- and enantioselectivities were obtained regardless of the nature of the R^2 group, including electronically impoverished (entry 1) and enriched (entries 2 and 3) aryl groups as well as heteroaryl groups (entries 4 and 5), but also with the usually poorly reactive β-alkyl-substituted nitroolefin **2g** (entry 6).

The Michael addition of the secondary β-keto amide **1a** with an α,β-disubstituted nitroolefin was also briefly examined. The stereocontrol of the additional stereogenic center formed in the reaction is a difficult issue, as recently highlighted by Duschmalé and Wennemers.[18] Pleasingly, the reaction of **1a** with 3-nitro-2*H*-chromene (**2h**) under the optimized conditions furnished the adduct **4m** in acceptable yield and stereoselectivities (Scheme 2).



Scheme 2. Reaction with an α,β-disubstituted nitroolefin.



Scheme 3. Reactivity of a tertiary β-keto amide.

In order to confirm the crucial role of the acidic amide proton as an intramolecular activating and stabilizing group in the secondary β-keto amides **1a–f**, a control experiment was performed with the tertiary β-keto amide **5**[17] and the nitroolefin **2a** under the optimized reaction conditions. As anticipated, no reaction occurred and the starting material **5** could be recovered quantitatively (Scheme 3). The chemical inertness of the tertiary β-keto amide **5** in the Michael addition to nitroolefins is in sharp contrast with the excellent result obtained with its secondary β-keto amide analogue **1c** (Table 2, entry 3). This difference of reactivity can be clearly attributed to the increased acidity of secondary β-keto amides resulting from an intramolecular hydrogen bond.

The relative and absolute configurations of the cyclobutanone Michael adducts **4a–m** were determined to be as depicted herein by X-ray diffraction analysis of **4k** (Figure 3, *left*), which was confirmed by the complementary X-ray diffraction analysis of **4l** (Figure 3, *right*).[19] Importantly, from these structural data it appears that, as for the secondary β-keto amide substrates **1**, the products **4** are stabilized, at least in the solid state, by an intramolecular hydrogen bond between the acidic N–H amide proton and the cyclobutanone carbonyl group ($d_{O4–HN1}=2.234$ Å in **4k**, and $d_{O1–HN1}=2.607$ Å in **4l**). This highlights again the decisive role of the secondary 2-carbamoyl group in the transformation, here as a stabilizing unit for the reaction products.

The stereochemical outcomes of the reaction can be explained by invoking a preferred transition state in which the approach of both reaction partners is controlled by the bifunctional catalyst **3f** as depicted in Figure 4.[20] The squaramide hydrogen bond donor moiety of the catalyst would coordinate to the nitro group in **2**, both enhancing its electrophilicity and directing the reactive olefinic moiety out the most hindered part of the catalytic supramolecular complex in the direction of the *N*-benzyl moiety. Meanwhile, the deprotonation of 2-carbamoyl cyclobutanone **1** by the basic amine moiety of the catalyst would give the corresponding enolate stabilized and suitably rigidified by an intramolecular hydrogen bond, and coordinated to the ammonium moiety of the catalyst with the bulky amido group pointing out to the less sterically-demanding area. It can be noted that, consistently with the proposed model, the catalysts **3a–f** all afforded the same major enantiomer (−)-**4a** during their evaluation (Table 1).

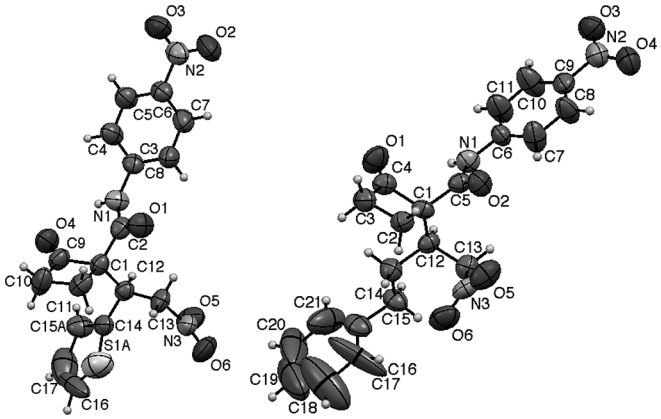


Figure 3. Representations of **4k** (left) and **4l** (right) obtained by X-ray diffraction analysis. Ellipsoids are drawn at 50% probability level and hydrogen atoms are represented as fixed-size spheres of radius 0.15 Å. See the Supporting Information for details (ref.[19]).

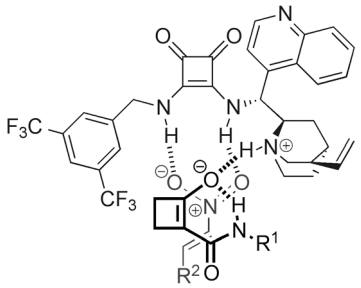
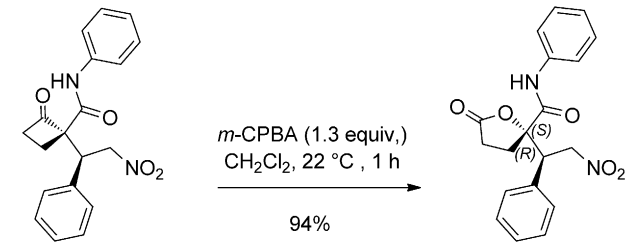


Figure 4. Proposed approach in the transition state with catalyst **3 f**.



4c
dr = 14:1, *er* = 20:1

6
dr = 14:1, *er* = 20:1

Scheme 4. Enantioselective synthesis of a γ,γ-difunctionalized butanolide.

The densely functionalized cyclobutanones **4** are expected to be versatile starting points for the synthesis of optically active well-defined chiral small molecules otherwise difficult to prepare. One example is given in Scheme 4 with the regio- and stereoselective Baeyer–Villiger oxidative ring-expansion[21] of cyclobutanone **4c** to give the γ,γ-difunctionalized butanolide **6** in high yield with complete retention of configuration as confirmed by NMR and X-ray diffraction analysis.[19] Similar butanolide moieties are found, for example, in the natural products spiculisporic and lycoperdic acids (Figure 5, *top*),[22] and only a few catalytic methods are available for the efficient enantioselective synthesis of this substitution pattern.[23] It should also be noted that, at least in the solid state, the secondary amide unit contributed to the stabilization of the product **6** through an intramolecular hydrogen bond between the acidic N–H proton of the amide and the intracyclic oxygen atom of the butanolide ($d_{O1–HN1}=2.195$ Å, Figure 5, *bottom*).

Conclusions

Overall, we have developed the first practical and efficient enantioselective synthetic route to functionalized cyclobutanones displaying an 'all-carbon' chiral quaternary center adjacent to an additional controlled stereocenter. The reaction nicely accommodates a large scope of substrates, allowing the control of up to three contiguous stereogenic centers. Of importance, the specific activation/stabilization of the cyclo-

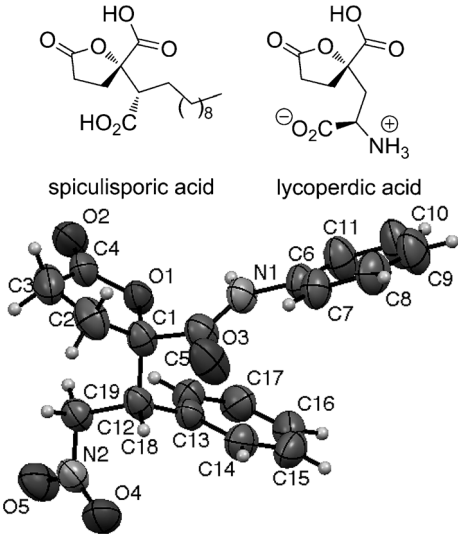


Figure 5. Example of naturally occurring γ,γ-difunctionalized butanolides (*top*), and representation of **6** obtained by X-ray diffraction analysis (*bottom*). Ellipsoids are drawn at the 50% probability level and hydrogen atoms are represented as fixed-size spheres of radius 0.15 Å. See the Supporting Information for details (ref.[19]).

butanones with a secondary amide was found crucial to the success of the approach. The reactivity associated with the ring strain in cyclobutanones and the functional group density found in the products described herein are expected to lead to simplified stereoselective synthetic approaches to useful chiral small molecules, and more generally expand the applications of cyclobutanones in organic synthesis.

Experimental Section

General Information

Unless otherwise stated, all commercially available reagents were used without further purification. All reagents were weighed and handled in air at room temperature. All reactions were performed in oven-dried glassware under argon atmospheres. Anhydrous solvents were obtained from a solvent purification system, or alternatively for methanol by refluxing over magnesium turning and distillation under an argon atmosphere. Reactions were monitored by TLC performed on Merck 60F254 plates, visualized by UV (254 nm) and/or ethanolic solutions of *p*-anisaldehyde/H_2SO_4 or phosphomolybdic acid. Flash chromatography was performed with Merck 40–63 μm silica gel eluted with ethyl acetate/petroleum ether. Petroleum ether (PE) refers to the fraction that was distilled at 40–60 °C. Melting points were determined on a Büchi B-450 apparatus. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at the specified temperature and concentration (g/100 mL). Enantiomeric ratios were determined by HPLC on chiral stationary phase at Chirbase (http://chirbase.u-3mrs.fr/). NMR data were recorded at 300 or 400 MHz (Bruker Avance spectrometers), and chemical shifts (δ) are reported in ppm relative to residual non-deuterated solvent signals for ^{1}H NMR ($CHCl_3$: 7.26 ppm, DMSO-d_6: 2.50 ppm), or to deuterated solvent signals for ^{13}C NMR ($CDCl_3$: 77.16 ppm, DMSO-d_6: 39.52 ppm, acetone-d_6: 206.26 and 29.84 ppm). Coupling constants (*J*) are in Hertz, and the classical abbreviations are used to describe the signal multiplicity. High-resolution mass spectra were obtained at Spectropole (http://www.spectropole.u-3mrs.fr/).

Preparation of Organocatalyst 3e

See Supporting Information.

General Procedure for the Synthesis of (−)-4a–m and (±)-4a–m

To a solution of β-keto amide **1** (*ca.* 0.24 mmol) and nitroalkene **2** (*ca.* 0.20 mmol) in anhydrous CH_2Cl_2 (*ca.* 1.0 mL) was added catalyst **3** (5 mol%). The reaction mixture was stirred at 22 °C until consumption of the nitroalkene **2** as monitored by TLC, whereupon it was concentrated under vacuum and directly purified by flash chromatography to give the pure product (−)-**4**. The racemic products (±)-**4a–m** were obtained using a catalytic amount of polystyrene-supported catalyst PS-PEMB.[24]

Compound 4a: Following the general procedure with catalyst **3f** (3.1 mg, 0.005 mmol), compounds **1a** (28.1 mg, 0.12 mmol) and **2a** (14.9 mg, 0.10 mmol) afforded compound **4a** as a light yellow solid; yield: 26.9 mg (95%, **4a**/*iso*-**4a** = 17:1); R_f = 0.34 (AcOEt/PE = 3:7); mp 169–171 °C (amorphous); $[\alpha]_D^{31}$: −184 (*c* = 1.0, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (br s, NH), 8.22 (d, *J* = 9.0 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 2H), 7.39–7.35 (m, 3H), 7.29–7.26 (m, 2H), 4.97 (dd, *J* = 14.1, 10.0 Hz, 1H), 4.86 (dd, *J* = 14.1, 5.3 Hz, 1H), 4.25 (dd, *J* = 10.0, 5.3 Hz, 1H), 2.85 (ddd, *J* = 18.5, 10.2, 4.9 Hz, 1H), 2.61–2.53 (m, 1H), 2.42–2.23 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6): δ = 205.2 (C), 166.9 (C), 145.1 (C), 144.5 (C), 135.9 (C), 129.7 (2CH), 129.7 (2CH), 129.2 (CH), 125.4 (2CH), 121.0 (2CH), 78.2 (C), 75.9 (CH_2), 47.4 (CH), 44.7 (CH_2), 18.3 (CH_2); HPLC (Chiralpak IA, hexane/EtOH = 70:30, 1.0 mL min^{-1}, 300 nm): t_{4a} = 11.1 min, $t_{ent\text{-}4a}$ = 17.8 min, **4a**/*ent*-**4a** > 999:1 (*ent*-**4a** was not detected); HR-MS (ESI+): *m/z* = 384.1190, calcd. for $C_{19}H_{18}N_3O_6^+$ $[M+H]^+$: 384.1190.

Compound 4b: Following the general procedure with catalyst **3f** (6.2 mg, 0.010 mmol), compounds **1b** (78.1 mg, 0.24 mmol) and **2a** (29.8 mg, 0.20 mmol) afforded compound **4b** as a yellow viscous liquid; yield: 68.1 mg (73%, **4b**/*iso*-**4b** = 15:1); R_f = 0.25 (AcOEt/PE = 15:85); $[\alpha]_D^{31}$: −92 (*c* = 1.0, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (br s, NH), 7.90 (s, 2H), 7.57 (s, 1H), 7.32–7.27 (m, 3H), 7.22–7.18 (m, 2H), 4.91 (dd, *J* = 14.0, 10.6 Hz, 1H), 4.78 (dd, *J* = 14.0, 5.0 Hz, 1H), 4.17 (dd, *J* = 10.6, 5.0 Hz, 1H), 2.81–2.73 (m, 1H), 2.53–2.46 (m, 1H), 2.35–2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.6 (C), 166.3 (C), 138.3 (C), 133.3 (C), 132.7 (q, *J* = 33.0 Hz, 2C), 129.6 (2CH), 129.3 (CH), 128.5 (2CH), 123.1 (q, *J* = 272.0 Hz, $2CF_3$), 120.1 (2CH), 118.6 (CH), 76.1 (C), 74.7 (CH_2), 47.0 (CH), 44.7 (CH_2), 17.9 (CH_2); HPLC (Chiralpak IB, hexane/EtOH = 90:10, 1.0 mL min^{-1}, 254 nm): t_{4b} = 7.2 min, t_{ent-4b} = 7.9 min, **4b**/*ent*-**4b** = 93.01:2.64; HR-MS (ESI+): *m/z* = 475.1087, calcd. for $C_{21}H_{17}F_6N_2O_4^+$ $[M+H]^+$: 475.1087.

Compound 4c: Following the general procedure with catalyst **3f** (12.3 mg, 0.020 mmol), compounds **1c** (151.4 mg, 0.80 mmol) and **2a** (119.4 mg, 0.80 mmol) afforded compound **4c** as a colorless foam; yield: 253.9 mg (94%, **4c**/*iso*-**4c** = 14:1); R_f = 0.37 (AcOEt/PE = 3:7); mp 48–50 °C (amorphous); $[\alpha]_D^{33}$: −116 (*c* = 1.0, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (br s, NH), 7.50 (d, *J* = 8.7 Hz, 2H), 7.43–7.28 (m, 7H), 7.20–7.11 (m, 1H), 4.99 (dd, *J* = 13.9, 10.9 Hz, 1H), 4.88 (dd, *J* = 13.9, 4.9 Hz, 1H), 4.23 (dd, *J* = 10.9, 4.9 Hz, 1H), 2.83 (ddd, *J* = 15.1, 10.3, 3.9 Hz, 1H), 2.67–2.49 (m, 1H), 2.42–2.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.9 (C), 165.4 (C), 136.9 (C), 133.5 (C), 129.3 (2CH), 129.2 (2CH), 129.0 (CH), 128.6 (2CH), 125.3 (CH), 120.3 (2CH), 76.1 (C), 74.8 (CH_2), 47.1 (CH), 44.3 (CH_2), 17.8 (CH_2); HPLC (Chiralpak AD-H, hexane/EtOH = 80:20, 1.0 mL min^{-1}, 220 nm): t_{4c} = 12.0 min, $t_{ent\text{-}4c}$ = 21.1 min, **4c**/*ent*-**4c** = 95.30:4.70; HR-MS (ESI+): *m/z* = 356.1607, calcd. for $C_{19}H_{22}N_3O_4^+$ $[M+NH_4]^+$: 356.1605.

Compound 4d: Following the general procedure with catalyst **3f** (3.1 mg, 0.005 mmol), compounds **1d** (21.9 mg, 0.10 mmol) and **2a** (14.9 mg, 0.10 mmol) afforded compound **4d** as a yellow viscous liquid; yield: 30.2 mg (82%, **4d**/*iso*-**4d** = 8:1); R_f = 0.30 (AcOEt/PE = 3:7); $[\alpha]_D^T$ not determined because of compound decomposition upon storage. ^{1}H NMR (400 MHz, $CDCl_3$, for **4d**): δ = 7.99 (br s, NH), 7.34 (m, 7H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.98 (dd, *J* = 13.9, 10.9 Hz, 1H), 4.88 (dd, *J* = 13.9, 4.9 Hz, 1H), 4.22 (dd, *J* = 10.9, 4.9 Hz, 1H), 3.80 (s, 3H), 2.89–2.76 (m, 1H), 2.65–2.46 (m, 1H), 2.39–2.20 (m, 2H); ^{1}H NMR (400 MHz, $CDCl_3$, for *iso*-**4d**): δ = 7.99 (br s, NH), 7.34 (m, 7H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.08 (dd, *J* = 13.9, 11.0 Hz, 1H), 4.93 (dd, *J* = 13.9, 4.9 Hz, 1H), 4.06 (dd, *J* = 11.0, 4.9 Hz, 1H), 3.79 (s, 3H), 3.16–2.97 (m, 1H), 2.65–2.46 (m, 1H), 2.39–2.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, for **4d**); δ = 209.0 (C), 165.3 (C), 157.2 (C), 133.6 (C), 129.9 (C), 129.4 (2CH), 129.0 (CH), 128.6 (2CH), 122.1 (2CH), 114.4 (2CH), 76.0 (C), 74.9 (CH_2), 55.6 (CH_3), 47.2 (CH), 43.6 (CH_2), 17.9 (CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, for *iso*-**4d**): δ = 208.8 (C), 164.8 (C), 157.2 (C), 134.0 (C), 129.9 (C), 129.4 (2CH), 129.0 (CH), 128.7 (2CH), 122.0 (2CH), 114.3 (2CH), 75.7 (C), 75.1 (CH_2), 55.6 (CH_3), 48.7 (CH), 44.3 (CH_2), 22.0 (CH_2); HPLC (Chiralpak IA, hexane/$CHCl_3$/*i*-PrOH = 80:10:10, 1.0 mL min^{-1}, 254 nm): t_{4d} = 10.0 min, $t_{ent\text{-}4d}$ = 14.3 min, **4d**/*ent*-**4d** = 96.77:3.23; HR-MS (ESI+): *m/z* = 369.1446, calcd. for $C_{20}H_{21}N_2O_5^+$ $[M+H]^+$: 369.1445.

Compound 4e: Following the general procedure with catalyst **3f** (6.2 mg, 0.010 mmol), compounds **1e** (64.3 mg, 0.24 mmol) and **2a** (29.8 mg, 0.20 mmol) afforded compound **4e** as a white solid; yield: 70.3 mg (84%, **4e**/*iso*-**4e** = 16:1); R_f = 0.77 (AcOEt/PE = 1:4); mp 54–57 °C (amorphous); $[\alpha]_D^{27}$: −152 (*c* = 1.0, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (br s, NH), 7.46 (dd, *J* = 9.0, 2.4 Hz, 2H), 7.40–7.33 (m, 5H), 7.28 (dd, *J* = 9.0, 2.4 Hz, 2H), 4.96 (dd, *J* = 13.9, 10.6 Hz, 1H), 4.86 (dd, *J* = 13.9, 5.1 Hz, 1H), 4.21 (dd, *J* = 10.6, 5.1 Hz, 1H), 2.87–2.79 (m, 1H), 2.59–2.51 (m, 1H), 2.38–2.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0 (C), 165.6 (C), 136.0 (C), 133.5 (C), 132.3 (2CH), 129.5 (2CH), 129.2 (CH), 128.6 (2CH), 121.9 (2CH), 118.1 (C), 76.1 (C), 74.8 (CH_2), 47.1 (CH), 44.5 (CH_2), 17.9 (CH_2); HPLC (Chiralpak IA, hexane/EtOH = 90:10, 1.0 mL min^{-1}, 320 nm): t_{4e} = 19.62 min, $t_{ent\text{-}4e}$ = 34.61 min, **4e**/*ent*-**4e** = 97.80:2.20; HR-MS (ESI+): *m/z* = 417.0442, calcd. for $C_{19}H_{18}BrN_2O_4^+$ $[M+H]^+$: 417.0444.

Compound 4f: Following the general procedure with catalyst **3f** (6.2 mg, 0.010 mmol), compounds **1f** (40.6 mg, 0.24 mmol) and **2a** (29.8 mg, 0.20 mmol) afforded compound **4f** as a white solid; yield: 54.1 mg (85%, **4f**/*iso*-**4f** = 12:1); R_f = 0.33 (AcOEt/PE = 1:4); mp 90–93 °C (amorphous); $[\alpha]_D^{27}$: −35 (*c* = 1.0, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 5H), 6.13 (br s, NH), 4.89 (dd, *J* = 13.6, 11.2 Hz, 1H), 4.74 (dd, *J* = 13.6, 4.6 Hz, 1H), 4.05 (dd, *J* = 11.2, 4.6 Hz, 1H), 2.80–2.71 (m, 1H), 2.47–2.41 (m, 1H), 2.26–2.15 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2 (C), 166.3 (C), 133.9 (C), 129.2 (2CH), 128.8 (CH), 128.7 (2CH), 76.2 (C), 75.2 (CH_2), 52.0 (C), 47.7 (CH), 44.0 (CH_2), 28.6 (3CH_3), 17.7 (CH_2); HPLC (Chiralpak IC, hexane/*i*-PrOH/$CHCl_3$ = 85:5:10, 1.0 mL min^{-1}, 254 nm): t_{4f} = 10.81 min, $t_{ent\text{-}4f}$ = 14.71 min, **4f**/*ent*-**4f** = 95.95:4.05; HR-MS (ESI+): *m/z* = 319.1655, calcd. for $C_{17}H_{23}N_2O_4^+$ $[M+H]^+$: 319.1652.

Compound 4g: Following the general procedure with catalyst **3f** (6.0 mg, 0.010 mmol), compounds **1a** (45.5 mg, 0.19 mmol) and **2b** (37.7 mg, 0.19 mmol) afforded compound **4g** as a yellow solid; yield: 50.5 mg (62%, **4g**/*iso*-**4g** = 10:1); R_f = 0.30 (AcOEt/PE = 2:3); mp 183–185 °C (amorphous); $[\alpha]_D^{31}$: −52 (*c* = 1.0, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37 (br s, NH), 8.25 (d, *J* = 8.7 Hz, 2H), 8.23 (d, *J* = 9.1 Hz, 2H), 7.69 (d, *J* = 9.1 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 4.98–4.94 (m, 2H), 4.36 (dd, *J* = 9.6, 5.9 Hz, 1H), 3.01 (ddd, *J* = 15.7, 9.4, 5.6 Hz, 1H), 2.71–2.28 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0 (C), 165.3 (C), 148.3 (C), 144.5 (C), 142.2 (C), 140.7 (C), 129.76 (2CH), 125.3 (2CH), 124.5 (2CH), 119.9 (2CH), 75.4 (C), 74.4 (CH_2), 46.6 (CH), 44.8 (CH_2), 18.4 (CH_2); HPLC (Chiralpak IA, hexane/$CHCl_3$/*i*-PrOH = 70:10:20, 1.0 mL min^{-1}, 300 nm): t_{4g} = 13.5 min, $t_{ent\text{-}4g}$ = 16.7 min, **4g**/*ent*-**4g** = 98.90:1.10; HR-MS (ESI+): *m/z* = 446.1305, calcd. for $C_{19}H_{20}N_5O_8^+$ $[M+NH_4]^+$: 446.1306.

Compound 4h: Following the general procedure with catalyst **3f** (6.2 mg, 0.010 mmol), compounds **1a** (56.2 mg, 0.24 mmol) and **2c** (35.9 mg, 0.20 mmol) afforded compound **4h** as a yellow solid; yield: 60.8 mg (74%, **4h**/*iso*-**4h** = 15:1); R_f = 0.33 (AcOEt/PE = 35:65); mp 143–145 °C (amorphous); $[\alpha]_D^{31}$: −176 (*c* = 1.0, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (br s, NH), 8.18 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.91 (dd, *J* = 13.8, 10.2 Hz, 1H), 4.82 (dd, *J* = 13.8, 5.1 Hz, 1H), 4.20 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.76 (s, 3H), 2.86–2.79 (m, 1H), 2.58–2.53 (m, 1H), 2.39–2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.7 (C), 166.2 (C), 160.0 (C), 144.1 (C), 142.7 (C), 129.6 (2CH), 125.1 (2 CH), 124.9 (C), 119.7 (2CH), 114.8 (2CH), 76.3 (C), 74.9 (CH_2), 55.4 (CH_3), 46.2 (CH), 44.6 (CH_2), 17.7 (CH_2); HPLC (Chiralpak IB, hexane/EtOH = 90:10, 1.0 mL min^{-1}, 310 nm): t_{4h} = 43.1 min, $t_{ent\text{-}4h}$ = 46.0 min, **4h**/*ent*-**4h** > 999:1 (*ent*-**4h** was not detected); HR-MS (ESI+): *m/z* = 414.1295, calcd. for $C_{20}H_{20}N_3O_7^+$ $[M+H]^+$: 414.1296.

Compound 4i: Following the general procedure with catalyst **3f** (6.1 mg, 0.010 mmol), compounds **1a** (56.2 mg, 0.24 mmol) and **2d** (45.6 mg, 0.20 mmol) afforded compound **4i** as a yellow solid; yield: 72.0 mg (74%, **4i**/*iso*-**4i** = 17:1); R_f = 0.53 (AcOEt/PE = 2:3); m.p = 159–161 °C (amorphous); $[\alpha]_D^{30}$: −179 (*c* = 1.06, chloroform). ^{1}H NMR (400 MHz,

$CDCl_3$): $\delta = 8.36$ (br s, NH), 8.24 (d, $J = 9.1$ Hz, 2H), 7.68 (d, $J = 9.1$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 4.91 (dd, $J = 14.0$, 10.1 Hz, 1H), 4.84 (dd, $J = 14.0$, 5.4 Hz, 1H), 4.20 (dd, $J = 10.1$, 5.4 Hz, 1H), 2.96–2.88 (m, 1H), 2.65–2.53 (m, 1H), 2.49–2.38 (m, 1H), 2.37–2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.5$ (C), 165.8 (C), 144.4 (C), 142.4 (C), 132.8 (2CH), 132.3 (C), 130.1 (2CH), 125.3 (2CH), 123.6 (C), 119.8 (2 CH), 75.9 (C), 74.5 (CH_2), 46.4 (CH), 44.8 (CH_2), 18.0 (CH_2); HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, 1.0 mL min^{-1}, 300 nm): t_{4i} = 14.37 min, $t_{ent\text{-}4i}$ = 19.52 min, **4i**/*ent*-**4i** = 99.72:0.28; HR-MS (ESI+): m/z = 479.0561, calcd. for $C_{19}H_{20}BrN_4O_6^+$ $[M+NH_4]^+$: 479.0561.

Compound 4j: Following the general procedure with catalyst **3f** (6.2 mg, 0.010 mmol), compounds **1a** (56.2 mg, 0.24 mmol) and **2e** (27.8 mg, 0.20 mmol) afforded compound **4j** as a light brown solid; yield: 39.8 mg (54%, **4j**/*iso*-**4j** = 15:1); $R_f = 0.34$ (AcOEt/PE = 35:65); mp 149–151 °C (amorphous); $[\alpha]_D^{31}$: −90 ($c = 1.0$, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.42$ (br s, NH), 8.23 (d, $J = 9.0$ Hz, 2H), 7.71 (d, $J = 9.0$ Hz, 2H), 7.48–7.42 (m, 2H), 6.39 (s, 1H), 4.70 (dd, $J = 13.6$, 5.3 Hz, 1H), 4.63 (dd, $J = 13.6$, 9.9 Hz, 1H), 4.19 (dd, $J = 9.9$, 5.3 Hz, 1H), 2.99 (ddd, $J = 18.1$, 11.0, 5.8 Hz, 1H), 2.70–2.57 (m, 1H), 2.34–2.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.9$ (C), 165.9 (C), 144.6 (2 CH), 144.4 (C), 142.5 (C), 141.5 (2CH), 125.3 (CH), 119.8 (CH), 118.2 (C), 109.6 (CH), 75.7 (C), 75.1 (CH_2), 45.0 (CH), 38.8 (CH_2), 18.0 (CH_2); HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, 1.0 mL min^{-1}, 310 nm): t_{4j} = 15.3 min, $t_{ent\text{-}4j}$ = 17.8 min, **4j**/*ent*-**4j** = 97.25:2.75; HR-MS (ESI+): m/z = 374.0983, calcd. for $C_{17}H_{16}N_3O_7^+$ $[M+H]^+$: 374.0983.

Compound 4k: Following the general procedure with catalyst **3f** (6.2 mg, 0.010 mmol), compounds **1a** (56.2 mg, 0.24 mmol) and **2f** (31.0 mg, 0.20 mmol) afforded compound **4k** as a light yellow solid; yield: 39.7 mg (51%, **4k**/*iso*-**4k** = 13:1); $R_f = 0.35$ (AcOEt/PE = 3:7); mp 161–163 °C (recrystallized from $CHCl_3$/PE); $[\alpha]_D^T$: not determined because of compound decomposition upon storage. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.46$ (br s, NH), 8.24 (d, $J = 9.2$ Hz, 2H), 7.71 (d, $J = 9.2$ Hz, 2H), 7.33 (dd, $J = 4.9$, 0.8 Hz, 1H), 7.05–7.02 (m, 2H), 4.93–4.80 (m, 2H), 4.57 (dd, $J = 9.1$, 5.7 Hz, 1H), 2.95 (m, 1H), 2.66–2.61 (m, 1H), 2.55–2.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.3$ (C), 165.8 (C), 144.4 (C), 142.5 (C), 135.3 (C), 128.1 (CH), 127.8 (CH), 126.7 (CH), 125.3 (2CH), 119.9 (2CH), 76.2 (C), 75.9 (CH_2), 45.1 (CH), 42.7 (CH_2), 18.5 (CH_2); HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, 1.0 mL min^{-1}, 310 nm): t_{4k} = 14.9 min, $t_{ent\text{-}4k}$ = 19.9 min, **4k**/*ent*-**4k** = 94.97:1.06; HR-MS (ESI+): m/z = 390.0754, calcd. for $C_{17}H_{16}N_3O_6S^+$ $[M+H]^+$: 390.0754.

Compound 4l: Following the general procedure with catalyst **3f** (12.3 mg, 0.020 mmol), compounds **1a** (112 mg, 0.48 mmol) and **2g** (70.9 mg, 0.40 mmol) afforded compound **4l** as a yellow solid; yield: 55.9 mg (34%, **4l**/*iso*-**4l** = 17:1); $R_f = 0.40$ (AcOEt/PE = 3:7); mp 131–133 °C (recrystallized from $CHCl_3$/PE); $[\alpha]_D^{31}$: −81 ($c = 1.0$, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.35$ (br s, NH), 8.22 (d, $J = 9.2$ Hz, 2H), 7.69 (d, $J = 9.2$ Hz, 2H), 7.34–7.31 (m, 2H), 7.25–7.22 (m, 1H), 7.18–7.16 (m, 2H), 4.64 (dd, $J = 14.0$, 6.4 Hz, 1H), 4.42 (dd, $J = 14.0$, 5.5 Hz, 1H), 3.23–3.03 (m, 2H), 2.98–2.92 (m, 1H), 2.79 (ddd, $J = 14.4$, 9.5, 5.3 Hz, 1H), 2.67–2.57 (m, 2H), 2.17–2.06 (m, 1H), 2.03–1.96 (m, 1H), 1.82–1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 209.2$ (C), 165.7 (C), 144.3 (C), 142.5 (C), 139.9 (C), 129.0 (2CH), 128.5 (2CH), 126.9 (CH), 125.2 (2CH), 119.9 (2CH), 76.1 (C), 75.6 (CH_2), 44.2 (CH_2), 41.3 (CH), 33.6 (CH_2), 31.3 (CH_2), 19.7 (CH_2); HPLC (Chiralpak IC, hexane/$CHCl_3$/*i*-PrOH = 80:10:10, 1.0 mL min^{-1}, 230 nm): t_{4l} = 35.2 min, $t_{ent\text{-}4l}$ = 29.7 min, **4l**/*ent*-**4l** = 99.23:0.77; HR-MS (ESI+): m/z = 412.1500, calcd. for $C_{21}H_{22}N_3O_6^+$ $[M+H]^+$: 412.1503.

Compound 4m: Following the general procedure with catalyst **3f** (6.2 mg, 0.010 mmol), compound **1a** (56.2 mg, 0.24 mmol) and 3-nitro-2*H*-chromene (**2h**, 35.4 mg, 0.20 mmol) afforded compound **4m** as a white solid; yield: (50.0 mg (61%, dr = 5:1:0:0); $R_f = 0.50$ (AcOEt/PE = 3:7); mp 177–179 °C (amorphous); $[\alpha]_D^{31}$: −248 ($c = 1.0$, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.53$ (br s, NH), 8.26 (d, $J = 9.2$ Hz, 2H), 7.76 (d, $J = 9.2$ Hz, 2H), 7.29–7.25 (m, 1H), 7.01–6.92 (m, 3H), 4.98–4.90 (m, 1H), 4.75 (dd, $J = 5.6$, 2.9 Hz, 1H), 4.51 (dd, $J = 13.3$, 3.2 Hz, 1H), 4.45 (s, 2H), 2.98 (ddd, $J = 19.0$, 10.4, 6.1 Hz, 1H), 2.65 (ddd, $J = 11.9$, 10.5, 7.3 Hz, 1H), 2.52–2.39 (m, 1H), 2.18 (td, $J = 11.3$, 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 210.0$ (C), 165.6 (C), 153.8 (C), 144.6 (C), 142.4 (C), 130.7 (CH), 129.7 (CH), 125.3 (2CH), 122.2 (CH), 119.9 (2CH), 118.0 (CH), 115.0 (C), 78.8 (CH), 77.4 (C), 63.2 (CH_2), 45.9 (CH_2), 41.5 (C), 18.1 (CH_2); HPLC (Chiralpak IA, hexane/EtOH = 70:30, 1.0 mL min^{-1}, 310 nm): t_{4m} = 18.9 min, $t_{ent\text{-}4m}$ = 12.2 min, **4m**/*ent*-**4m** = 96.13:3.87; HR-MS (ESI+): m/z = 412.1138, calcd. for $C_{20}H_{18}N_3O_7^+$ $[M+H]^+$; 412.1139.

Compound 6

To a solution of compound **4c** (33.9 mg, 0.10 mmol, **4c**/*iso*-**4c** = 14:1, **4c**/*ent*-**4c** = 96:4) in anhydrous CH_2Cl_2 at 0 °C was added *m*-CPBA (22.5 mg, 0.13 mmol). The reaction mixture was stirred for 1 h at 0 °C and quenched with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to give the crude product. This material was purified by flash chromatography to give the pure butanolide **6** as a light pink solid; yield: 33.4 mg (94%, **6**/*iso*-**6** = 14:1); $R_f = 0.38$ (AcOEt/PE = 2:3); mp 106–108 °C (amorphous); $[\alpha]_D^{33}$: −21 ($c = 1.0$, chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$ (br s, NH), 7.29–7.16 (m, 7H), 7.14–7.08 (m, 2H), 7.05 (dt, $J = 7.3$, 1.2 Hz, 1H), 4.90 (dd, $J = 13.6$, 5.7 Hz, 1H), 4.85 (dd, $J = 13.6$, 9.3 Hz, 1H), 4.12 (dd, $J = 9.3$, 5.7 Hz, 1H), 2.85–2.73 (m, 1H), 2.50 (ddd, $J = 16.4$, 10.2, 7.4 Hz, 1H), 2.43–2.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.3$ (C), 168.2 (C), 135.9 (C), 133.8 (C), 129.2 (2CH), 129.1 (2CH), 129.1 (2CH), 129.1 (CH), 125.8 (CH), 120.9 (2CH), 88.2 (C), 75.2 (CH_2), 49.5 (CH), 28.6 (CH_2), 27.8 (CH_2); HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, 1.0 mL min^{-1}, 205 nm): t_6 = 8.2 min, $t_{ent\text{-}6}$ = 12.4 min, **6**/*ent*-**6** = 96.15:3.85; HR-MS (ESI+): m/z = 355.1288, calcd. for $C_{19}H_{19}N_2O_5^+$ $[M+H]^+$: 355.1288.

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[13] In a preliminary study, **1a** was allowed to react with methyl vinyl ketone in the presence of catalyst **3a**, but the corresponding Michael adduct was found to be unstable.
[14] It is our conviction that, when compared to *ee* [enantiomeric excess], *er* [enantiomers ratio] is better and importantly, more intuitively reflects enantioselectivity. An *er* of 199:1 corresponds to an *ee* of 99.0%. For an interesting discussion, see: B. C. Gibb, *Nature Chem.* **2012**, *4*, 237–238.
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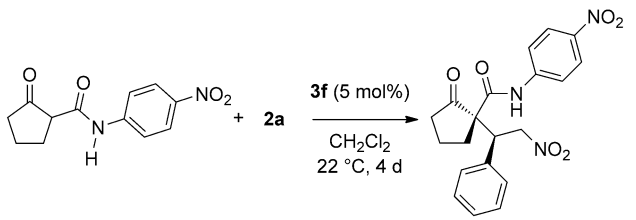

IV
93%, *dr* = 12:1
er = 8:1

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